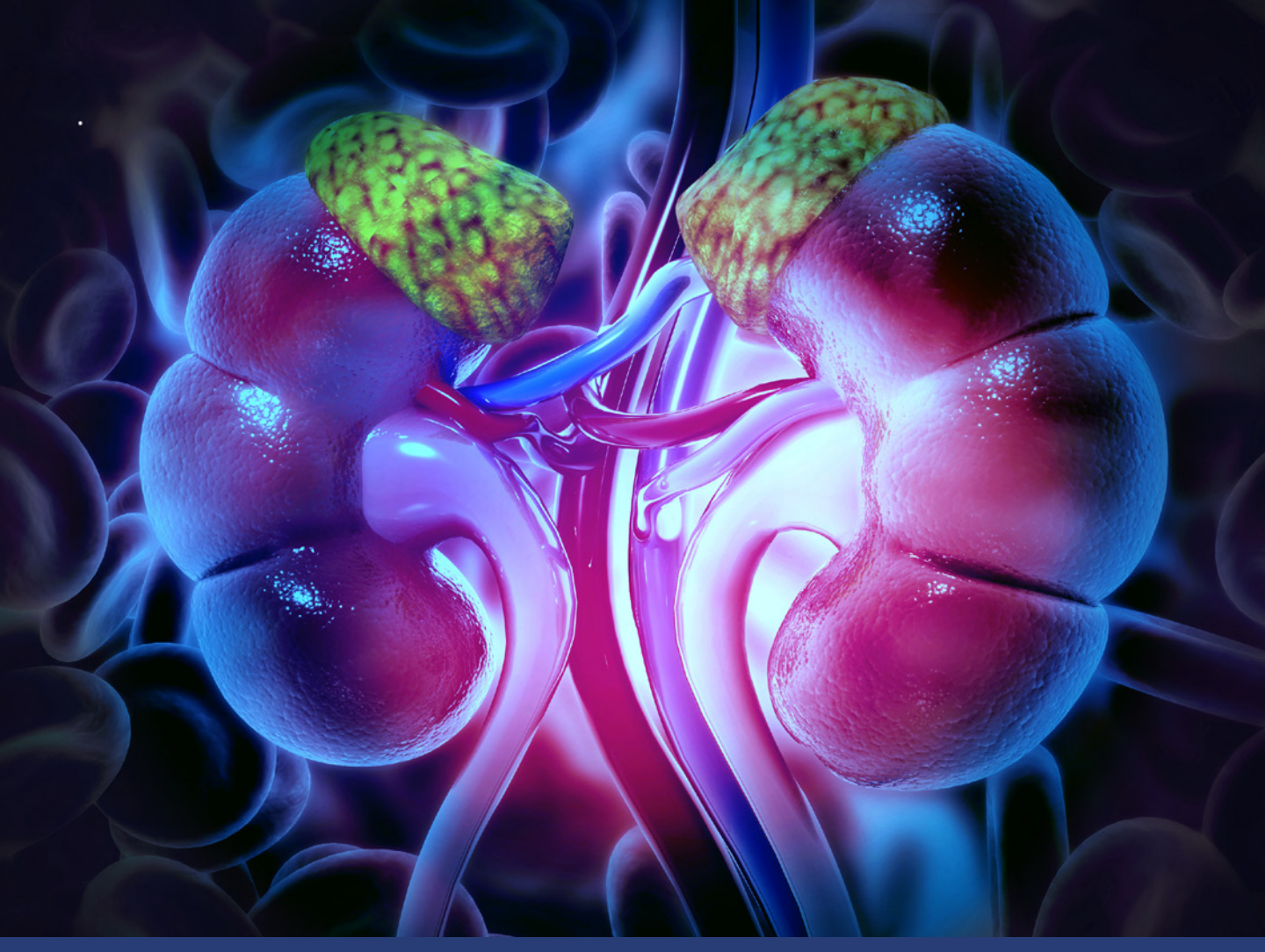

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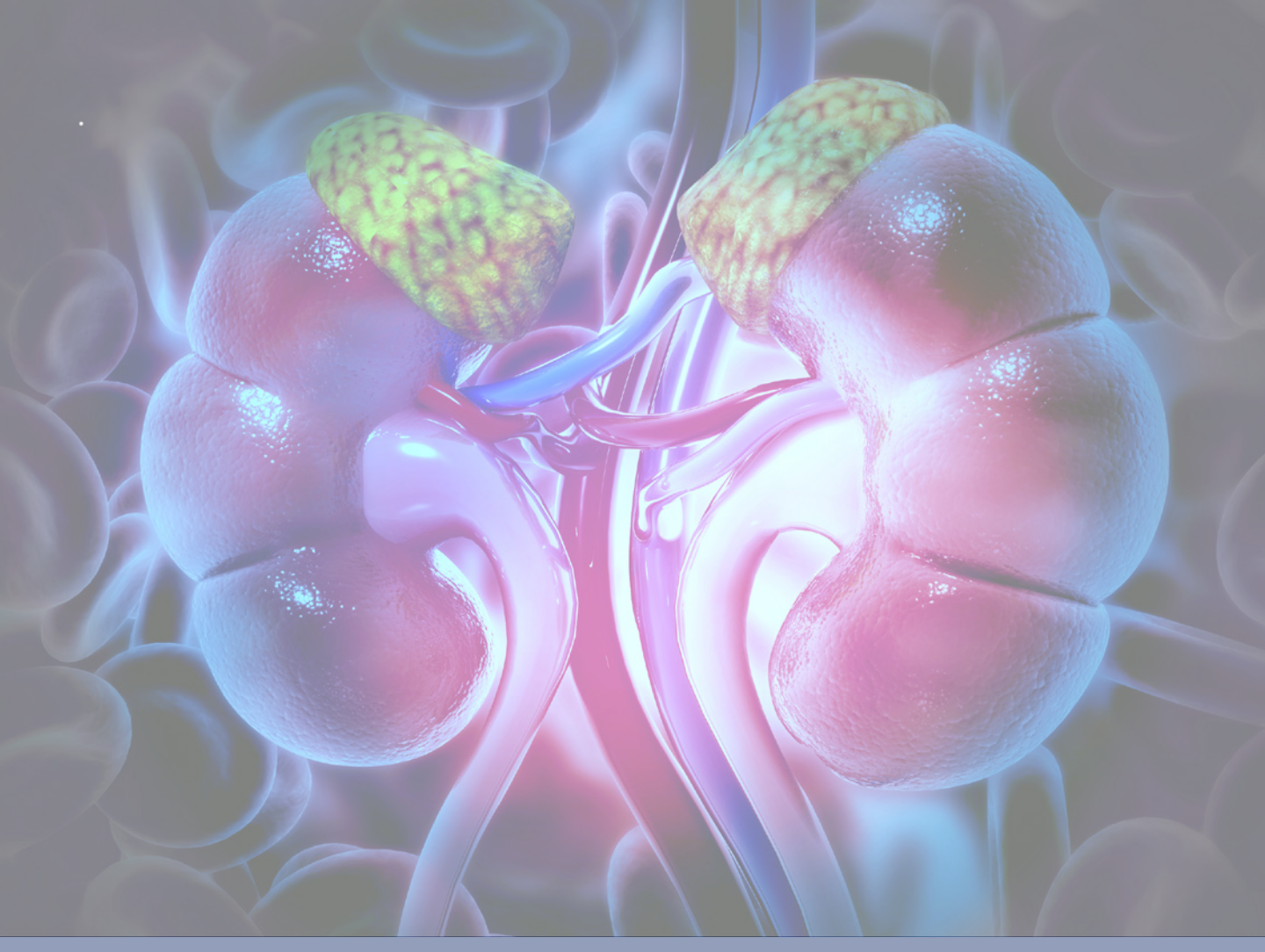

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We have made every attempt to ensure the information about trials and therapies is accurate at the time of publication of this book; however, it is possible that this data may have changed after publication. The reader is advised to review the latest results of the trials discussed in this book as well as the latest approved product information published by the manufacturers for the medications and medical devices mentioned in this book.

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International Consultation on Urological Diseases (ICUD)
Société Internationale d'Urologie
World Urologic Oncology Federation (WUOF)

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Preface

ICUD, the World Urologic Oncology Federation, and the Société Internationale d'Urologie

Laurence Klotz,
CM, MD, FRCSC

The International Consultation on Urologic Diseases (ICUD) is a 42-year-old organization that produces book-length overviews of major topics in urology. These have, in many cases, defined the state of the art of the topic and serve as important internationally recognized references. They have been widely read and highly respected as sources for reliable information and broadly based perspectives on disease management.

The chapters are prepared with input from diverse experts from around the world. The list of ICUDs is below. These texts have been major undertakings, involving scores of individuals as editors, chapter (or committee) chairs, and committee members.

The structure of the ICUD has evolved considerably. The initiative began in 1981 as a voluntary collaboration with support from international and national urological associations. The Consultations were supported, initially informally, by the World Health Organization (WHO) and the Union for International Cancer Control (UICC). The ICUD was formally established as a scientific, international non-profit NGO under Belgian law on June 28, 1994, to facilitate collaboration on an "organization to organization" basis with the WHO and UICC.

The principal aim of the ICUD has been consistent: to promote improvement in the management of urological diseases around the world by producing evidence-based recommendations. This is achieved by bringing together experts in urology and related fields to develop chapters based on a process that analyzes the available literature using an evidence-based approach. The recommendations must be suitable for adoption in all parts of the world, recognizing that resources and cultural influences differ widely between countries. The recommendations are not intended to be used as guidelines, although historically many ICUD recommendations have been incorporated into national guidelines.

The ICUD was for led many years by Prof Saad Khoury (Paris, France), and subsequently by Prof Paul Abrams (Bristol, UK). After many years the SIU became involved, initially as a collaborating partner. Eventually the SIU took over the management of the initiative. The World Urologic Oncology Federation (WUOF), an affiliate of the SIU, is the umbrella group for the 20 societies

of Urologic Oncology around the world. It was a perfect fit as the organizational partner for Oncology topics. Therefore, in 2018 the WUOF assumed the responsibility for the Oncology component of the ICUDs. The first WUOF-sponsored ICUD was the book entitled "Molecular Biomarkers in Urologic Oncology," released in November 2020. This comprehensive text is freely available as a downloadable PDF on the WUOF website, www.WUOF.org.

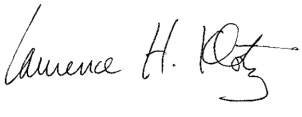
The ICUD differs from national guidelines in important ways. Most obviously, it represents a uniquely international perspective, drawing input from every region in the world. As such, the recommendations are less influenced by regional or national considerations.

The ICUD process has evolved. Historically, groups of experts responsible for specific chapters would meet face to face, often on multiple occasions and for several days at a time, to hammer out consensus and resolve disagreements. This approach was very resource-intensive. It is no longer practical, or necessary. The advent of virtual meetings has facilitated the ability to collaborate across oceans and continents. This has resulted in genuine and frequent consultation and collaboration between members of the chapter committees, unconstrained by resource limitations. This is reflected in the high quality of the chapters in this textbook. This edition will be published in digital form, which enables production of a high-quality document that is provided free of charge. It is freely available online, at www.WUOF.org, and on the SIU website.

This textbook represents input on the state of the art of kidney cancer from about 100 experts from every region in the world. Industry sponsorship was critical to the success of this initiative. We thank them for their support.

This textbook on kidney cancer is a significant achievement, and a testament to the talent and dedication of the 3 editors, Tony Choueiri, Grant Stewart, and Robert Uzzo, as well as the chapter chairs and committees. It has been a labor of love. We believe it will have a significant impact in improving the understanding of key issues in kidney cancer by clinicians around the world, and will improve the management of patients and their outcomes.

A textbook like this also requires a production team with diverse skills and talents. The production team, led by Areti Malapetsas of Medit Global, was superb. Ms. Malapetsas expertly managed the book production and was the senior medical copyeditor. The other members included Christian Bello and Nicholas Floratos, proofreaders, and Falasteen Alfranji, graphic designer. We are also grateful for the outstanding efforts of Ms. Patty Djan, who managed the ICUD sponsorship program. The quality of this book is a testament to their enthusiasm and expertise.



Laurence Klotz
Managing Editor, ICUD Oncology
Past Chairman, World Urologic Oncology Federation

List of Sponsors

Société Internationale d'Urologie	AVEO Oncology	Eisai Corporation

Past ICUD Consultations

2020 – 1st ICUD-WUOF International Consultation on Molecular Biomarkers in Urologic Oncology
Editors: Yair Lotan, Nathan Lawrentschuk, and Jack Schalken

2018 ICUD-SIU. Congenital Lifelong Urology: Caring for the Adolescent and Adult Patient with Congenital and Childhood GU Conditions
Seoul, South Korea
Chairs: Dan Wood and Hadley M. Wood

2017 ICUD-SIU. Bladder Cancer
Lisbon, Portugal
Chairs: Peter Black and Paulo Gontero

2016 ICUD-ISC. 6th International Consultation on Incontinence
Tokyo, Japan
Chairs: Paul Abrams, Linda Cardozo, Adrian Wagg, and Alan Wein

2016 ICUD-SIU. Urological Management of the Spinal Cord Injured Patient
Buenos Aires, Argentina
Chair: Shaun Elliott and Reynaldo Gomez

2015 ICUD-SIU. Image Guided Therapy in Urology
Melbourne, Australia
Chairs: Rafael Sánchez-Salas and Mihir Desai

2014 ICUD-EAU. Minimally Invasive Surgery in Urology
Stockholm, Sweden
Chairs: Walter Artibani and Jens Rassweiler

2014 ICUD. Men's Health (facilitated by AUA)
Orlando, United States
Chairs: Ajay Nehra, Ridwan Shabsigh, and Graeme Jackson

2014 ICUD-SIU. Stone Disease
Glasgow, Scotland
Chairs: John Denstedt and Jean de la Rosette

2014 ICUD-EAU. Medical Management of Urological Malignancy (MMUM)
Lisbon, Portugal
Chairs: Christian Stief and Christopher Evans

2013 ICUD-AUA. Topic Consultation on Anticoagulation in Urological Surgery
Chair: Stuart Wolf

2013 ICUD-SIU. Children's Congenital Anomalies
Vancouver, Canada
Chairs: Catherine de Vries and Rien Nijman

2013 ICUD-SIU. Upper Tract Transitional Cell Carcinoma
Vancouver, Canada
Chairs: Arnolf Stenzl, Shahrokh Shariat, and Serena Matin

2012 ICUD-EAU. 5th International Consultation on Incontinence
Paris, France
Chairs: Paul Abrams, Linda Cardozo, and Alan Wein

2012 ICUD-SIU. Male LUTS
Fukuoka, Japan
Chairs: Chris Chapple, Kevin McVary, and Claus Roehrborn

2011 – 2nd International Consultation on Bladder Cancer
Vienna, Austria
Chairs: Mark Soloway and Henk van der Poel

2011 – 4th International Consultation on Prostate Cancer
Berlin, Germany
Chairs: Manfred Wirth and Gerald Andriole

2010 – 1st ICUD-EAU International Consultation on Renal Cell Cancer
Barcelona, Spain
Chairs: Peter Mulders and Zya Kirkali

2010 – 1st ICUD-SIU International Consultation on Urethral Stricture
Marrakesh, Morocco
Chairman: Gerry Jordan

2010 – 1st ICUD-SIU International Consultation on Obstetric Vesico-Vaginal Fistula
Marrakesh, Morocco
Chairmen: Dirk de Ridder and Sherif Mourad

2009 – 3rd International Consultation on Sexual Medicine
Paris, France

2009 – 1st International Consultation on Genito-Urinary Infections
Stockholm, Sweden

2009 – 1st ICUD-SIU International Consultation on Testis Cancer
Shanghai, China

2008 – 4th International Consultation on Incontinence
Paris, France

2008 – 1st International Consultation on Penile Cancer
Santiago, Chile

2007 – 2nd International Consultation on Stone Disease
Paris, France

2006 – 1st Consultation on Congenital Anomalies
Cape Town, South Africa

2005 – 6th International Consultation on New Developments in Prostate Cancer & Prostate Diseases
Paris, France

2004 – 1st International Consultation on Incontinence
Monte Carlo, Monaco

2004 – 1st International Consultation on Bladder Tumors
Honolulu, Hawaii

2003 – 2nd International Consultation on Erectile and Sexual Dysfunctions
Paris, France

2002 – Consultation on Genitourinary Trauma
Stockholm, Sweden

2002 – 3rd International Consultation on Prostate Cancer New Treatment Modalities
Paris, France

2001 – 2nd International Consultation on Incontinence
Paris, France

2001 – 1st International Consultation on Stone Diseases
Paris, France

2000 – 5th International Consultation on Benign Prostatic Hyperplasia
Paris, France

2000 – 1st International Consultation on Nosocomial Infections in Urology
Paris, France

1999 – 2nd International Consultation on Prostate Cancer
Paris, France

1999 – 1st International Consultation on Erectile Dysfunction
Paris, France

1998 – 1st International Consultation on Incontinence
Monte Carlo, Monaco

1997 – 4th International Consultation on Benign Prostatic Hyperplasia
Paris, France

1996 – 1st Consultation on Prostate Cancer
Monte Carlo, Monaco

1995 – 3rd International Consultation on Benign Prostatic Hyperplasia
Monte Carlo, Monaco

1994 – 4th International Symposium on Recent Advances in Urological Cancer Diagnosis & Treatment
Paris, France

1993 – 2nd International Consultation on Benign Prostatic Hyperplasia
Paris, France

1991 – 1st International Consultation on Benign Prostatic Hyperplasia
Paris, France

1990 – 3rd International Symposium on Progress Urinary Tumors
Paris, France

1989 – 2nd International Symposium on Progress Urinary Tumors
Paris, France

1987 – 1st International Symposium on Progress Urinary Tumors
Paris, France

1986 – Prostate Cancer
Paris, France

1985 – Bladder Tumors
Paris, France

1984 – 1st International Symposium on Testicular Cancer
Paris, France

1983 – Kidney Tumors
Paris, France

1981 – Prostate Cancer
Paris, France

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Abbreviations Used in the Text

Abbreviation	Full Term	COMMITTEE #
2OG	2-oxoglutarate	4
2SC	S-(2-succino)-cysteine/2-succinocysteine	3, 5
3D-CRT	3-dimensional conformal radiotherapy	9
4D-CT	4-dimensional CT	9
18F-FDG	18F-Fluorodeoxyglucose	6
AAA	abdominal aortic aneurysm	2
ABC	Arterial Based Complexity	7
ACD-RCC	acquired cystic disease–associated renal cell carcinoma	3
ACE	angiotensin-converting enzyme	15
ACGM	American College of Medical Genetics and Genomics	3
ACR	American College of Radiology	6
ADL	activities of daily living	15
AEs	adverse events	12
AI	artificial intelligence	2
AJCC	American Joint Committee on Cancer	3, 6, 7, 11, 12
AKI	acute kidney injury	8, 15
ALARA	amount of radiation dose is as low as reasonably achievable	9
ALK	anaplastic lymphoma kinase	3
ALK-RCC	anaplastic lymphoma kinase–rearranged renal cell carcinoma	3
ALT	alanine transaminase	15
AMACR	alpha-methylacyl-CoA racemase	3
AML	angiomyolipoma	6, 7, 10
angio-CT	abdominal CT	8
aPTT	activated partial thromboplastin time	11
AQP1	aquaporin 1	7
ARE	antioxidant response element	4
AS	active surveillance	9, 10
ASCO	American Society of Clinical Oncology	9, 10, 15
ASR	age-standardized rate	2
AST	aspartate transaminase	15

AUA	American Urological Association	6, 9, 10
AUC	area under the curve	2
BAF47	BRG1-associated factor 47	4
BAL	bronchoalveolar lavage	15
BAP1	BRCA1-associated protein 1	6, 16
BAP1-TPDS	BAP1 tumour predisposition syndrome	5
BEMPEG	bempegaldesleukin	14
BHD	Birt-Hogg-Dubé	2, 3, 5, 10
BHP RCC	biphasic hyalinizing psammomatous renal cell carcinoma	3
BICR	blinded independent central review	12
BMI	body mass index	2, 8
BP	blood pressure	15
BRRS	Bannayan-Riley-Ruvalcaba syndrome	5
BSA	body surface area	15
CA	cryoablation	9
CAIX	carbonic anhydrase IX	3, 6, 7, 12
ccDNA	cell-free DNA	7
CCF	Cleveland Clinic Foundation	16
CCPRCT	clear cell papillary renal cell tumour	3
ccRCC/CCRCC	clear cell RCC	2, 3, 4, 5, 6, 10, 11, 13, 17
CD	cluster of differentiation	3
CDC	collecting duct carcinoma	3
CDER	Center for Drug Evaluation and Research	12
CDK4/6	cyclin-dependent kinase 4/6	14
CE	cardiovascular event	8
CEUS	contrast-enhanced ultrasound	6, 7
cfMeDIP–seq	cell-free–methylated DNA immunoprecipitation and high-throughput sequencing	2
CHMP	Committee for Medicinal Products for Human Use	12
chRCC	chromophobe renal cell carcinoma	2, 3, 4, 6, 7, 10, 17
CI	confidence interval	2, 9, 10, 12, 15, 16
C index	Centrality Index	7, 8
CIMP	CpG island methylator phenotype	3, 4
CK	cytokeratin	3

CKD	chronic kidney disease	8, 9, 10
CLAMP	Coefficient-Location-Anterior, Multi, and Posterior boundary	7
CN	cytoreductive nephrectomy	4, 12, 16
CNS	central nervous system	5
CPD	cardiopulmonary bypass	11
CPI	immune checkpoint inhibitor	12, 15
CPS	combined positive score	17
CRP	C-reactive protein	17
CRT	conventional external beam RT	13
CSA	Contact Surface Area	7, 8
CSF	cerebrospinal fluid	7
CS	Cowden syndrome	5
CSS	cancer-specific survival	7, 8, 9, 10
CT	computed tomography	2, 5, 6, 7, 8, 9, 10, 11, 12
CTC	circulating tumour cell	7
CTCAE	Common Terminology Criteria for Adverse Events	12, 14, 15
ctDNA	circulating tumour DNA	2
CTLA-4	cytotoxic T-lymphocyte antigen 4/cytotoxic T-lymphocyte associated protein 4	7, 12, 13, 14, 15, 17, 18
CXR	chest X-ray	10
CYP3A4	cytochrome P450 3A4	15
DAP	Diameter-Axial-Polar	7
DCE	dynamic contrast enhanced	9
DFS	disease-free survival	12
DFSI	disease-free survival interval	13
DISSRM	Delayed Intervention and Surveillance for Small Renal Masses	9, 10
DWI	diffusion-weighted imaging	6, 7
EAU	European Association of Urology	6, 9, 10, 12, 16
EBL	estimated blood loss	8
ECOG	Eastern Cooperative Oncology Group	7, 9, 12, 16
EDP	early disease progression	7
EEA	European Economic Area	12
eGFR/GFR	estimated glomerular filtration rate/glomerular filtration rate	6, 8, 9, 10, 12, 15, 16
EGFR	epidermal growth factor receptor	17

EMA	European Medicines Agency	12
EORTC	European Organisation for Research and Treatment of Cancer	8, 16
EPIC	European Prospective Investigation into Cancer and Nutrition	2
ESC	eosinophilic solid cystic	5
ESC RCC	eosinophilic solid and cystic renal cell carcinoma	3
ESMO	European Society of Medical Oncology	9, 10, 16
ESRD	end-stage kidney disease	2, 9
ETC	electron transport chain	17
EU	European Union	12
EVT	eosinophilic vacuolated tumour	3
FDA	US Food and Drug Administration	12, 13, 14, 16
FDG-PET	fluorodeoxyglucose positron emission tomography	5
FDG PET/CT	fluorodeoxyglucose–positron emission tomography/computed tomography	7
FH	fumarate hydratase	4, 5, 17
FH-RCC	fumarate hydratase–deficient renal cell carcinoma	3
FISH	fluorescence in situ hybridization	3, 17
FNA	fine needle aspirations	7
GBCA	gadolinium-based contrast agent	12
GEMM	genetically engineered mouse model	4
GETUG-AFU	Genitourinary Group and French Association of Urology/Group d'etude des tumeurs urogenitalies	13, 16
GIST	gastrointestinal stromal tumour	3, 4, 5
GLS	glutaminase	14
GR	growth rate	10
GTV	gross tumour volume	9
GUPS	Genitourinary Pathology Society	3
HA3D	hyper-accuracy three-dimensional	8
HBV	hepatitis B virus	15
HCF-1	host cell factor-1	4
HERV-E	human endogenous retrovirus type E	14
HFS	hand foot syndrome	12
HIF	hypoxia-inducible factor	3, 4, 13, 14, 15, 16
HLA	human leukocyte antigen	4, 14
HLRCC	hereditary leiomyomatosis and renal cell carcinoma	2, 3, 4, 5, 10, 17

HOCT	hybrid oncocytic-chromophobe tumour	3, 5
HPFB	Health Products and Food Branch	12
HPRC	hereditary papillary renal cancer	2, 4, 5, 10
HPT-JT	hereditary hyperparathyroidism jaw tumour syndrome	5
HR	hazard ratio	2, 12, 16, 17
HRQoL	health-related quality of life	8, 15
HU	Hounsfield units	7
IARC	International Agency for Research on Cancer	2
ICA1	urothelial cancer associated 1	17
ICB	immune checkpoint blockage	4
ICI	immune checkpoint inhibitor	13, 14, 16
ICRU	International Commission on Radiation Units and Measurements	9
IDO	indoleamine 2,3-dioxygenase	14
IFN-α	interferon-α	7, 12, 16
IFN-γ	interferon-gamma	14
IHC	immunohistochemistry	3, 5, 12
IL-2	interleukin-2	7, 12, 14, 16
IMDC	International Metastatic RCC Database Consortium	6, 13, 16, 17
IMRT	Intensity-modulated radiation therapy	9
INI1	Integrase interactor 1	4
IO	immuno-oncology/immunotherapy	4, 11, 12, 13, 15, 16
IQR	interquartile range	10
irAEs	immune-related adverse events	12, 15
IRI	ischemia-reperfusion injury	8
IROCK	International Radiosurgery Oncology Consortium for Kidney	9
ISUP	International Society of Urological Pathology	3, 5, 6, 7, 17
ITH	intratumoural heterogeneity	3, 4
ITV	internal target volume	9
IVC	inferior vena cava	3, 6, 8, 11, 12, 16
KCCure	Kidney Cancer Research Alliance	12
KDM5C	lysine demethylase 5C	6
KIM-1	kidney injury molecule-1	2, 7, 12
KM	Kaplan–Meier	7

KRAS/AKT	Kirsten rat sarcoma virus/protein kinase B	16
LAD	locally advanced disease	12
LAG3	lymphocyte activating gene 3	14
LAK	lymphokine-activated killer	16
LC	local control	9
LDH	lactate dehydrogenase	16
LEVF	left ventricular ejection fraction	15
lncRNA	long noncoding RNA	17
LOE	level of evidence	10
LOH	loss of heterozygosity/heterogeneity	3, 4
LOT	low-grade oncocytic tumour	3
LPN	laparoscopic partial nephrectomy	8
LTD	longest tumour diameter	10
LuFT	lung function test	15
LVI	lymphovascular invasion	3
MA	minimal access	11
MAMS	multi-arm multistage	12
MAP	Mayo Adhesive Probability	7, 8
MCL-1	myeloid cell leukemia-1	16
MCN	multilocular cystic nephroma	7
MCNLMP	multilocular cystic renal neoplasm of low malignant potential	3
MCUL	multiple cutaneous and uterine leiomyomatosis	5
MDT	metastasis-directed therapy	16
MFS	metastasis-free survival	7
MHC-1	major histocompatibility complex class I	14
miRNA	microRNA	7
MiT	microphthalmia transcription	3
MITF	micropthalmia-associated transcription factor/ micropthalmia transcription factor	3, 5
MM	malignant mesotheliomas	5
mRCC	oligometastatic/metastatic RCC	7, 13, 16
MRgRT	MR-guided radiotherapy	9
MRI	magnetic resonance imaging	5, 6, 7, 8, 9, 10, 11, 12
m-RNS/RNS	modified R.E.N.A.L nephrometry score/R.E.N.A.L nephrometry score	9

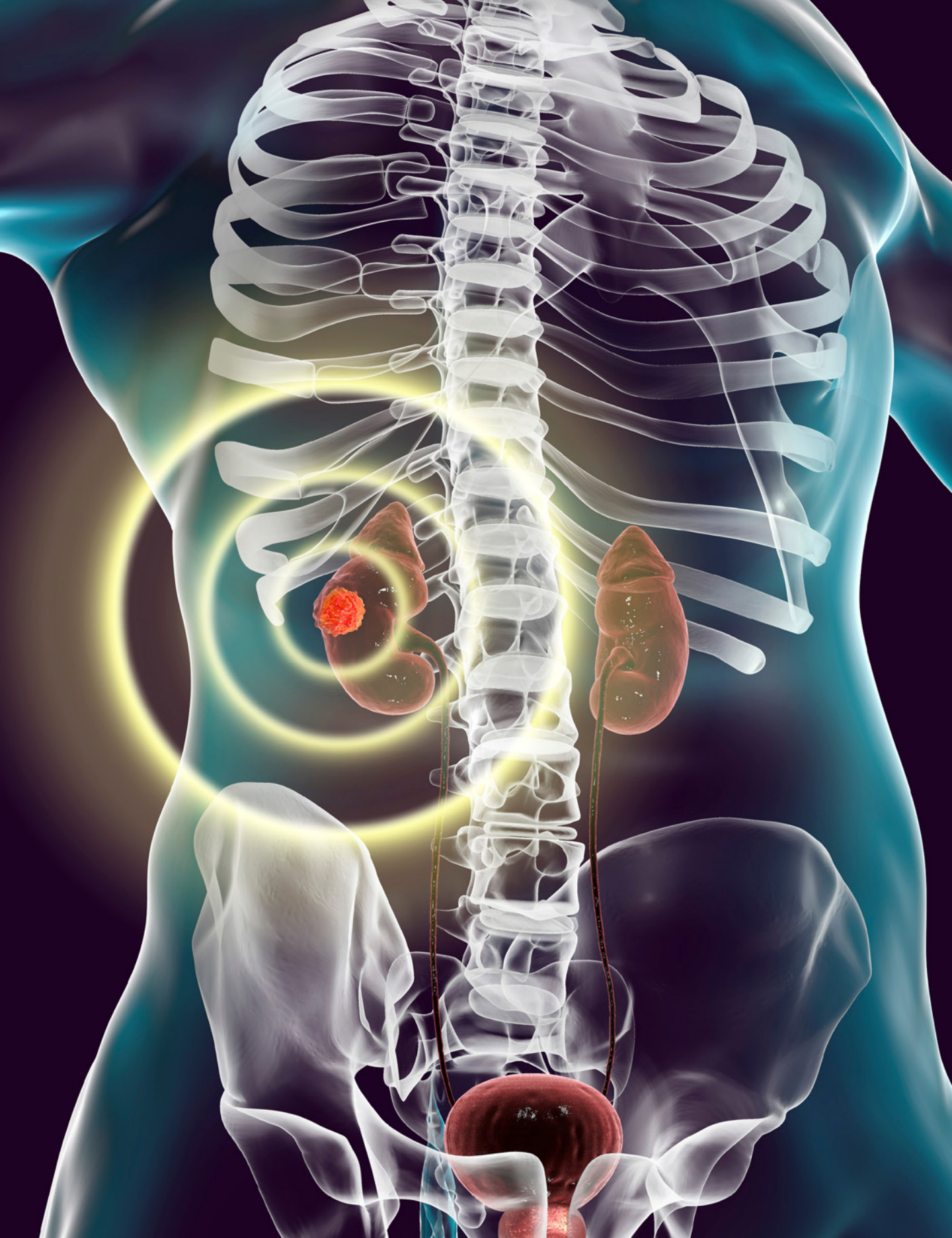
MSCT	contrast-enhanced multislice computed tomography	7
MSKCC	Memorial Sloan Kettering Cancer Center	16
mtDNA	mitochondrial DNA	4
mTOR	mammalian target of rapamycin	5, 12, 13, 17
mTORI	mTOR inhibitor	15
MTS RCC	mucinous tubular and spindle cell carcinoma	3
MTV	metabolic tumour volume	6
MUC4	mucin 4	6
MWA	microwave ablation	9
NCDB	National Cancer Data Base	10
NCCN	National Comprehensive Cancer Network	3, 5, 6, 9, 10, 13, 15
nccRCC	non-clear cell renal cell carcinoma	17
NCT	National Clinical Trial	14
NED	No Evidence of Disease	12, 13, 16
NePhRO	Zonal Nearness-Physical-Radius-Organization	7
NICE	National Institute for Health and Care Excellence	12
NIP	noninfectious pneumonitis	15
NPV	negative predictive value	6
NRF2	nuclear factor-erythroid factor 2-related factor 2	16
NSAIDs	nonsteroidal anti-inflammatory drugs	2
NSS	nephron-sparing surgery	8, 12
NV	nonvisible	2
NYHA	New York Heart Association	8
OARs	organs at risk	9
ODAC	Oncologic Drugs Advisory Committee	12
OPN	open partial nephrectomy	8
OR	odds ratio	15
ORR	objective response rate	13, 16
OS	overall survival	6, 7, 8, 9, 12, 13, 16, 17
PADUA	Preoperative Aspects and dimensions used for an anatomical classification	7, 8
PASS	Peritumoral artery scoring system	7
PBRM1	Polybromo 1	16
PBMRT1	prothymosin alpha pseudogene 1	3
PBS	Pharmaceutical Benefits Scheme	12

PCI	progression criteria for intervention	10
PD	progressive disease	12
PD-1	programmed cell death 1 receptor	7, 12, 13, 14, 15, 17, 18
PDC	pyruvate dehydrogenase complex	17
PDGFR	platelet-derived growth factor receptor	15, 16
PD-L1	programmed cell death 1 ligand 1	6, 7, 13, 14, 16, 17
PDX	patient-derived xenograft	4
PET	positron emission tomography	6, 12
PFS	progression-free survival	5, 6, 9, 10, 13, 16, 17
PGL	paraganglioma	4
PGL/PHEO	familial paraganglioma-pheochromocytoma	3
Pheo	pheochromocytoma	4
PHTS	*PTEN* hamartoma tumour syndrome	5
PIM	proviral integration site for Moloney murine leukemia virus	14
PN/PNx	partial nephrectomy	7, 8, 9, 10, 12
PPV	positive predictive value	6
PR	partial response	11
pRCC	papillary RCC	2, 3, 4, 6, 7, 10, 17
PRV	planning organ at risk volume	9
PS	performance status	7, 12, 16
PSM	positive surgical margin	8
PSMA	prostate-specific membrane antigen	6
PT	prothrombin time	11
PTEN	phosphatase and tensin homolog	16
PTFE	polytetrafluoroethylene	11
PTV	planning target volume	9
QoL	quality of life	2, 8
RAIV	Renal and Ischemic Volume	7
RAPN	robot-assisted partial nephrectomy	8
RCC	renal cell carcinoma	2, 3, 5, 6, 7, 9, 10, 11, 12, 14, 15, 16, 18
RCC FMS	renal cell carcinoma with fibromyomatous stroma	3
RCC NOS	renal cell carcinoma, not further specified	3

RCT	randomized controlled trial	8, 12
RECIST	Response Evaluation Criteria in Solid Tumours	9, 12
RENAL	Radius-Exophytic-Nearness-Anterior/ posterior-Location	7
RFA	radiofrequency ablation	9
RFS	recurrence-free survival	7, 8, 12
RMB	renal mass biopsy	7, 10
RMC	renal medullary carcinoma	3, 4
RN/RNx	radical nephrectomy	7, 8, 9, 12
ROCSS	renal oncocytoma	3, 10
ROTEM	rotational thromboeleastometry	11
RPS	Renal Pelvic Score	7
RT	radiotherapy	13
RTB	renal tumour biopsy	10
RTII	Renal Tumor Invasion Index	7
SABR	stereotactic ablative radiotherapy	9
SARR	Surgical Approach Renal Ranking	7
SBRT	stereotactic body radiation therapy	13
scMC	single-cell mass cytometry	4
SCNA	somatic copy number alterations	3, 4
scRNA-seq	single-cell RNA sequencing	4
SD	stable disease	11, 12
SDH	succinate dehydrogenase	3, 4, 5, 10
SEER	Surveillance, Epidemiology, and End Results	2, 8, 10
SETD2	SET domain containing 2	16
SIB	Surface Intermediate Base	8
SIR	Society of Interventional Radiology	9
SITC	Society for Immunotherapy of Cancer	15
SMARCB1	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1	4
SNF5	Sucrose Non-Fermenting 5	4
SNPs	single-nucleotide polymorphisms	15
SOB	shortness of breath	15
SPARE	Simplified Padua Renal	7
SPECT/CT	technetium-99m sestamibi single-photon emission computed tomography	10
SRM	small renal mass	2, 4, 7, 9, 10

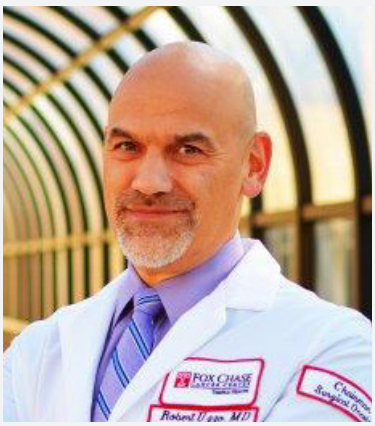
SRS	stereotactic radiosurgery	13, 16
ssGSEA	single gene set enrichment analyses	4
STORM	Salvage Treatment of OligoRecurrent Nodal Prostate Cancer	16
S-TRAC	Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of Renal Cell Carcinoma Following Nephrectomy	13
SUL	standardized uptake normalized to lean body mass	6
SUVmax	maximum standardized uptake value	6
SWOG	Southwest Oncology Group	16
TA	thermal ablation	10
TAM	tumour-associated macrophage	4
TCA	tricarboxylic acid cycle	14
TCGA	The Cancer Genome Atlas	4, 5, 10, 17
TCR	T-cell receptor	4, 14
TC RCC	tubulocystic renal cell carcinoma	3
TDO	tryptophan 2,3-dioxygenase	14
TEE	transesophageal echocardiography	11
TEG	thromboelastographic	11
TET	ten-eleven translocation methylcytosine dioxygenase	4
TFE3	transcription factor E3	3
TFEB	transcription factor EB	3
TGA	Therapeutic Goods Administration	12
Th2	T-helper subtype 2	4
TIGAR	TP53-inducible glycolysis and apoptosis regulator	6
TIL	tumour-infiltrating T lymphocyte	4
TIM-3	T-cell immunoglobulin and mucin-domain containing-3	14
TLF RCC	thyroid-like follicular carcinoma	3
TLG	total lesion glycolysis	6
TKI	tyrosine kinase inhibitor	4, 6, 13, 14, 15
TMB	tumour mutational burden	17
TME	tumour microenvironment	4
TNF	tumour necrosis factor	17
TNM	tumour-node-metastasis staging system/The TNM Classification of Malignant Tumours	3, 7, 11, 12
TP	tumour program	4

TRACERx	TRAcking Non-small Cell Lung Cancer Evolution Through Therapy (Rx)	4, 10
TRAEs	immune-related adverse events	15
tRCC	translocation carcinoma	3, 17
Treg	regulatory T cell	4, 14
TSC	tuberous sclerosis complex	2
TSG	tumour suppressor gene	5
TSH	thyroxine stimulating hormone	15
TT	targeted molecular therapy	16
UCS	urinary collecting system	8
UISS	University of California LA Integrated Staging System	7, 12
unRCC	unclassified renal carcinoma	17
uPLIN2	urinary perilipin 2	7
US	ultrasound	7, 10
VEGF/R	vascular endothelial growth factor/receptor	3, 4, 13, 14
VEGFR-2	vascular endothelial growth factor receptor-2	16
VEGFR-TKI	VEGFR tyrosine kinase inhibitor	11, 12, 15, 16, 17
VHL	von Hippel-Lindau	2, 3, 5, 8, 10, 13, 14, 15, 16
VSTM2A	V-set and transmembrane domain containing 2A	3
WBRT	whole brain radiotherapy	16
WHO	World Health Organization	3, 5, 6, 7, 17
WIT	warm ischemia time	8
VMAT	volumetric-modulated arc therapy	9
VTT	venous tumour thrombus	11
XIAP	X-linked inhibitor of apoptosis protein	16
ZII	Zero Ischemia Index	7
ZS	Zhongshan Score	7



COMMITTEE 1

Introduction: Evolution of the Management of Kidney Cancer



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Kidney cancer is among the 10 most common cancers in Europe and the United States. The 5-year survival is less than 80% overall, with a significant decrease as the stage of disease advances. Kidney cancer is also a malignancy that is projected to have an increase in incidence over the next 15 years, which is unusual, as the incidence for most cancers is either stable or declining. With an aging population prone to hypertension and obesity (two major risk factors in kidney cancer), this malignancy takes the stage as a public health problem.

The last International Consultation on Urological Diseases (ICUD) Consultation on renal cancer was in 2010, and the only one prior to that was in 1983. Now is absolutely the right time for a further ICUD Consultation on kidney cancer for multiple reasons. Until a couple decades ago, the only treatment available for most patients with kidney cancer was surgery, which was undertaken whether the patient had localized disease or had developed metastatic disease, as there was evidence that cytoreductive nephrectomy was beneficial in the advanced setting. However, there have been a slew of advances across all stages of renal cancer, which need substantial unpacking in a document such as the ICUD Consultation.

In the localized disease setting there are developments around early detection, baseline imaging, renal mass biopsy, surgical approaches, thermal ablation, trials of neoadjuvant therapies, and developing new treatments such as stereotactic radiotherapy. Bridging the gap between surgery and active therapy, and localized and metastatic disease, are the exciting developments around the use of adjuvant treatment for higher-risk localized disease to prevent recurrence. Convincing data is accumulating regarding such a role for immunotherapy using certain immune checkpoint blockers in this setting.

In the metastatic setting there have been myriad advances. Management has moved from cytokine therapy in the late 1990s, to which less than ~15% of patients showed any benefit, through to tyrosine kinase inhibitors in the mid-2000s, which had benefits for more than 60% of patients. We are now in a new era of immunotherapy, where checkpoint inhibitors and combinations with tyrosine kinase inhibitors have enhanced further the proportion of patients that show a response, including those with a long-term response. Kidney cancer oncology is truly one of the areas advancing most rapidly across all malignancies because of insights into the fascinating biology that underlies the disease. Indeed, both the 2018 and 2019 Nobel Prizes in Physiology or Medicine addressed important findings in the PD-(L)1, CTLA-4, and VEGF/HIF2 pathways, each of which is a validated target with at least one approved therapy in kidney cancer.

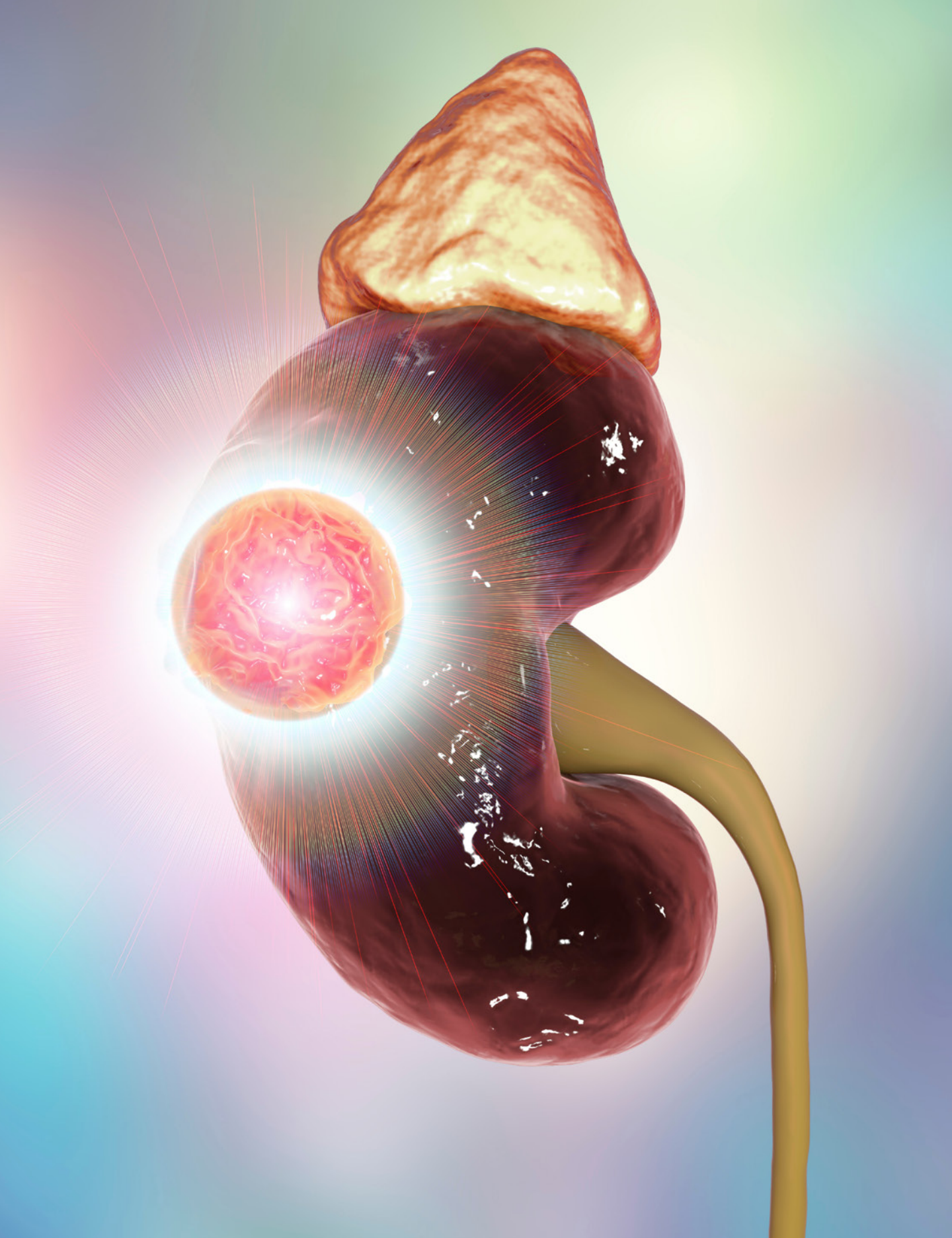
One of the key facets that marks out progress over the past two decades has been an increased emphasis on engaging a diverse multispecialty team to look after patients. Close working among urologists, oncologists, radiologists, pathologists, and nursing colleagues has enabled multimodal treatment strategies to be evaluated and introduced. No longer is care simply assigned as localized disease being the realm of the urologist and metastatic disease that of the oncologist.

Despite these clear improvements, we still have substantial work to do in curing more people with kidney cancer. Across all cancers over the past 50 years, there has been a 27% improvement in cancer-specific survival, but the improvement has been much smaller in renal cancer at 4%. However, we are starting to see long-term

survivors in kidney cancer and a corresponding increase in research into addressing the early toxicities and quality of life of patients living with kidney cancer. With an excellent multidisciplinary international kidney cancer research community, many of whom are authors of the ICUD Consultation, such advances are tractable.

It is important to note what our efforts are not. They are not guidelines like you might find written by professional societies such as the American Urological Association (AUA), American Society of Clinical Oncology (ASCO), or European Association of Urology (EAU). Each chapter here presents the reader with a timely overview of the topic that is evidence based. The format is by committee collaboration emphasizing international input across disciplines. In this regard, the end product outlines more than just an algorithm for care across stages, types, and other prognostic aspects of kidney cancer. It is a snapshot in time that summarizes where we are and provides insights into where we hope to go in the field.

This is a very exciting time in oncology. Nowhere is this better exemplified than in the field of kidney cancer. In the past one to two decades, the options for management of advanced renal cell carcinoma have expanded exponentially, improving response rates more than five-fold and quadrupling median overall survival times. As always, foundational science has led the way. Our improved understanding of the molecular underpinnings of renal cancers have led to the ability to perturb aberrant pathways for therapeutic benefit. These advances have led to incremental improvements in many other solid tumours and represent a triumph of decades' worth of investment in the scientific process. To paraphrase President Nixon's 1971 famous "War on Cancer" initiative—the battle has just begun in earnest, with advances in kidney cancer leading the way.



COMMITTEE 2

Epidemiology and Screening for RCC

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Epidemiology

Incidence and mortality

Data source and overview

Cancer incidence and mortality vary substantially worldwide. The International Agency for Research on Cancer (IARC) was established in 1965 by the World Health Assembly to provide comprehensive data on global cancer epidemiology as an independently financed organization within the framework of the World Health Organization.[1] According to a recent publication, the international cancer registry produced by the IARC encompasses 343 regional registries.[1] The registry data is currently available online at the Global Cancer Observatory as the GLOBOCAN database.[2,3] The data cover 185 countries and 36 cancers, including kidney cancer, and are regularly updated.[4] In this chapter, the data on incidence and mortality of kidney cancer are primarily based on the GLOBOCAN database and related publications by the IARC.[1–4] The key statistics of the GLOBOCAN report includes numbers, crude rate, age-standardized rate (ASR), and cumulative risk of incidence or mortality. Age is a key determinant for the risk of developing most types of cancer. The age structures vary according to countries or registries and also change over time. Therefore, GLOBOCAN calculates ASR and cumulative risk to provide meaningful comparisons of incidence and mortality across multiple populations or time points.[2,3] The ASR is the summary rate that would have been observed, given the age-specific rates in that area, in a population with an age composition of a reference population.[1] The Segi–Doll world standard is used as the reference in the GLOBOCAN calculation. The cumulative risk is defined as the probability that an individual will develop or die from the disease in question during a certain age span (0–74 years for the GLOBOCAN) in the absence of other causes of death.[1–3]

According to the GLOBOCAN report in 2020, globally kidney cancer was the 9th most frequently diagnosed cancer in men and the 14th most common in women.[2] Patients newly diagnosed with kidney cancer accounted for 2.2% of all new cancer diagnoses. The crude mortality rate of kidney cancer was 13th in men and 14th in women.[2] The global ASRs and cumulative risks of kidney cancer incidence and mortality based on the most recent GLOBOCAN database 2020 are summarized in **Table 1**. Although there have been variabilities according to countries and areas, the incidence of kidney cancer has generally exhibited an increasing trend over time in both sexes.[3] Kidney cancer is also one of few cancers predicted to continue to increase in incidence over the next 15 years.[5] In terms of mortality, however, the ASR and the cumulative risk for kidney cancer death have been stabilizing in many countries, and declined particularly in Europe and Northern America (United States and Canada) during the past one or two decades in both sexes.[3,6] Limitations of the GLOBOCAN database include the limited data available for evaluating renal cell carcinoma (RCC) and renal pelvic cancer separately, although RCC generally accounts for the majority of kidney cancer, i.e.,~95% in the United States. Staging information is limited and not available for kidney cancer. Missing data and allocation bias are also limitations.[1]

Geographic variability

The GLOBOCAN database highlights the geographic variabilities of kidney cancer incidence and mortality (**Table 1** and **Figures 1** and **2**). According to the GLOBOCAN 2020 report, the age-standardized incidence of kidney cancer was highest in Northern America, followed by Europe, Oceania, Latin America and the Caribbean, Asia, and Africa. As for the mortality, Europe had the highest age-standardized rate, which was followed by Northern America/Oceania, Latin America and the Caribbean, Asia, and Africa, reflecting that Northern America presented a relatively lower mortality rate in contrast to the incidence. The following sections summarize the characteristics of the epidemiology of kidney cancer in each global area.

Europe

In Europe, kidney cancer is the 5th most frequently diagnosed cancer in men and the 11th in women, while its mortality ranks 9th in men and 13th in women among all malignancies.[2] The recent data shows that Europe has the highest ASR of mortality in the world. It should be noted that the incidence and mortality of kidney cancer are particularly high in Eastern Europe countries, i.e., Lithuania (ASR of incidence/mortality, 14.5/4.2 per 100,000 in both sexes), the Czech Republic (14.4/4.3), Estonia (13.7/4.1), Slovakia (13.5/4.7), Latvia (13.5/4.3), and Belarus (12.2/3.7).[2] While in the other areas in Europe, Ireland has the highest incidence (12.1) and mortality (3.3). The trends of kidney cancer incidence and mortality were analyzed using the GLOBOCAN platform during the available period (1998–2010) in the top five countries within Europe regarding the number of annual new cases: Germany, France, United Kingdom, Italy, and Spain. This demonstrated that the incidence steadily increased from 1998 (ASRs, 7.8 and 3.8 per 100,000 in men and women, respectively) to 2010 (10.1 and 5.4, respectively). In contrast, the mortality slightly decreased in the same period (ASRs, 4.0 and 1.7 per 100,000 in men and women, respectively, in 1998; 3.4 and 1.4, respectively, in 2010).[3] Similar trends of incidence and mortality are observed in the Eastern Europe countries mentioned above.

Northern America

Northern America (United States and Canada) exhibited the highest ASR of kidney cancer incidence according to the GLOBOCAN 2020 report.[2] In this region, the incidence of kidney cancer is 6th in men and 9th in women across all cancer types, while mortality is 11th in men and 14th in women.[2] The annual changes of incidence and mortality from 1983 to 2012 are available in the GLOBOCAN database. In this period, the incidence gradually increased until 2008 (ASRs, 7.6 and 3.5 per 100,000 in men and women, respectively, in 1983; 12.8 and 6.9, respectively, in 2008) and has since stabilized.[3] In contrast, the mortality moderately increased until 1994 (ASRs, 3.5 and 1.7 per 100,000 in men and women, respectively, in 1983; 3.9 and 1.8, respectively, in 1994) and then started to decrease. The opposing trends of incidence and mortality after the mid-1990s are consistent with European countries.

Latin America and the Caribbean

In Latin America and the Caribbean, kidney cancer is the 6th most common cancer in men and the 13th in women, while its mortality is 11th in men and 13th in women.[2] Although the kidney cancer incidence is relatively low (ASR of incidence/mortality, 4.7/2.0 per 100,000 in both sexes overall) when compared to Europe and Northern America, Uruguay presents high incidence and mortality (14.3/4.4) similarly to Eastern

Europe countries. The number of annual new cases is largest in Brazil, followed by Mexico and Argentina. These countries exhibit a rising trend also in the mortality of kidney cancer to date.[3]

TABLE 1 Age-standardized rate and cumulative risk of kidney cancer incidence and mortality.

	Incidence		Mortality	
	ASR, per 100,000*	Cumulative risk, %†	ASR, per 100,000*	Cumulative risk, %†
Worldwide				
Male	6.1	1.45	2.5	0.81
Female	3.2	0.76	1.2	0.39
Both sexes	4.6	1.06	1.8	0.57
Europe				
Male	13.1	2.78	4.5	1.41
Female	6.4	1.36	1.7	0.58
Both sexes	9.5	1.96	2.9	0.91
Northern America				
Male	16.1	3.23	3.0	0.95
Female	8.6	1.69	1.3	0.45
Both sexes	12.2	2.39	2.1	0.67
Latin America and the Caribbean				
Male	6.3	1.37	2.8	0.79
Female	3.3	0.74	1.3	0.37
Both sexes	4.7	1.02	2.0	0.55
Oceania				
Male	12.4	2.83	3.0	1.05
Female	5.4	1.27	1.3	0.51
Both sexes	8.8	2.00	2.1	0.75
Asia				
Male	3.8	0.89	2.0	0.61
Female	1.9	0.45	0.90	0.30
Both sexes	2.8	0.65	1.4	0.44
Africa				
Male	2.1	0.48	1.4	0.43
Female	1.5	0.24	0.98	0.21
Both sexes	1.8	0.34	1.2	0.30

Abbreviations: ASR, age-standardized rate.*The age-standardized rate (ASR) was adjusted to the world standard population. †The cumulative risk was the probability of kidney cancer development or death in a lifetime defined as 0–74 years.

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Oceania

In Oceania, the kidney cancer incidence is 9th in men and 12th in women, and the mortality is 13th in men and 15th in women among all kinds of malignancy.[2] The majority (97%) of patients are diagnosed in Australia or New Zealand. In these countries, the incidence and mortality demonstrated similar trends to Europe and Northern America—the incidence increasing steadily and the mortality (ASR) decreasing particularly after the mid-1990s.[3]

Asia

Kidney cancer incidence and mortality are relatively low in Asian countries. The incidence is 12th in men and 16th in women, and the mortality is 13th in men and 16th in women among all kinds of malignancy.[2] The number of annual new cases is largest in China followed by Japan and India; kidney cancer patients newly diagnosed in these three countries account for 74% of all those in Asia. The incidence is particularly high in Japan, which is more prominent in the analysis of crude rate (19.9 in Japan vs. 3.4 in Asian countries overall) than in ASR (7.6 vs. 2.8, respectively),[2] suggesting that it is partially due to the biased age distribution. The incidence has been increasing in the three countries (China, Japan, and India). The mortality (ASR) has been decreasing since the mid-1990s in Japan similarly to Europe and Northern America. In contrast, a previous report showed that China had an increasing trend in mortality from 1990 to 2017.[7]

Africa

Africa has the lowest incidence and mortality of kidney cancer in the world (ASR of incidence/mortality, 1.8/1.2 per 100,000 in both sexes). It should be noted that cancer incidence is generally low in Africa, which is particularly highlighted in the comparison of crude rates. According to the GLOBOCAN estimate in 2020, the crude incidence of all cancers was 82.7 in Africa, which was notably lower than other areas described above (204.8–693.2). Among them, kidney cancer is the 12th most common cancer in men and the 16th in women, while the mortality is 13th in men and 14th in women among all kinds of malignancy.[2] No significant changes in incidence or mortality have been observed in Africa according to the previous report.[6]

Cancer stage and patient survival

Survival outcomes of kidney cancer patients largely depend on the stage at diagnosis. The most recent report based on the National Cancer Database in the United States showed that the 5-year survival rate was 93%, 70%, and 13% in patients with localized, regional, and distant diseases of kidney cancer, respectively.[8] Similar outcomes are also observed in the cancer statistics in the United Kingdom.[9] Previous studies analyzed the National Cancer Database in the United States and demonstrated that the clinical stage of kidney cancer significantly migrated toward earlier stages until 2007 and then stabilized through 2015.[10,11] Clinical stage I tumours accounted for 43% of all kidney cancers diagnosed in 1993; the percentage increased to 57% in 2004[10] and levelled off at around 70% after 2007, although the size of localized tumours continued to decline.[11]

Overall, between 1993 and 2004, 50.6%, 26.7%, and 22.7% of kidney cancer patients were diagnosed with stage I, stage II or III, and stage IV, respectively.[10] In contrast, between 2004 and 2015, 70.3%, 10.5%, 8.3%, and 11.0% of patients were diagnosed with stage I (including 47.5% of stage Ia and 22.8% of stage Ib), stage II, stage III, and stage IV, respectively, highlighting a significant increase of stage I as well as a decrease of stage IV.[11] A similar trend of stage migration was also reported from a single tertiary centre in Japan.[12] According to the study, the proportion of T1 tumours was 57% (T1a, 36%; T1b, 21%) in the period of 1989–1994, which increased to 75% (T1a, 52%; T1b, 23%) in the period of 2007–2012.

This shift in stage distribution may be at least partially related to increased early detection of kidney cancer, which may have been driven by recent technological advancements of imaging modalities and widespread use of cross-sectional imaging.[13–15] Such a shift in stage distribution may also in part explain the reduction in mortality observed in the context of an increase in incidence in most countries across the world. When the stage-specific changes in patient survival during 2004–2015 were assessed with the adjustment using potential confounders including age, sex, and comorbidities, a significant improvement was also observed particularly in stage IV patients, which could be related to recent advances in systemic therapy.[11,16]

FIGURE 1 Age-standardized rate of kidney cancer incidence.

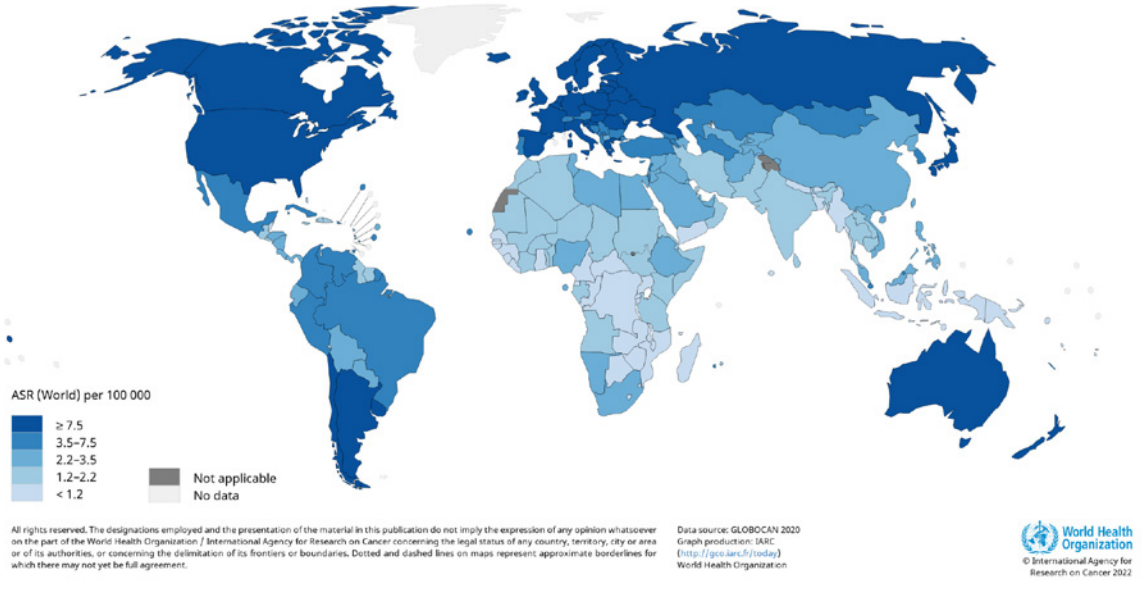

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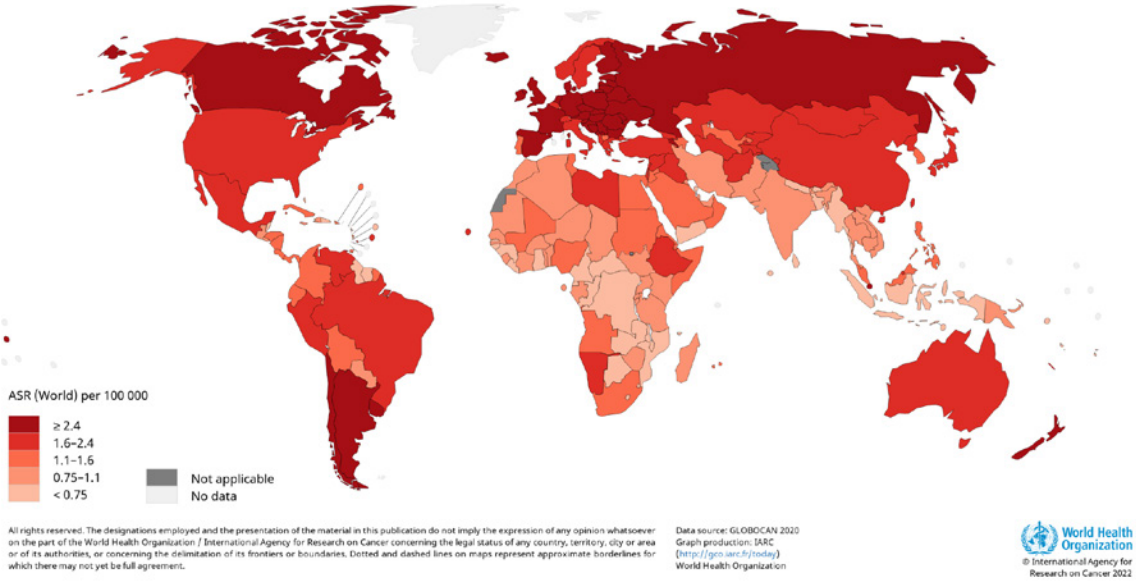
FIGURE 2 Age-standardized rate of kidney cancer mortality.



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Risk factors

The prior section reviewed the global incidence and mortality of kidney cancer, and also highlighted the vast variability of incidence and mortality among different countries and regions. Such disparities could be partially due to differences in underlying risk factors for the development of kidney cancer. Understanding the risk factors associated with development of kidney cancer is also important when developing preventive or screening strategies. Potential risk factors for RCC include smoking, obesity, comorbidities such as hypertension or diabetes, diet, and certain drug or occupational exposures. These factors could be modifiable and consequently possible targets for cancer prevention.[17] This section focuses first on the risk factors related to kidney cancer that are not modifiable, and then on those that are potentially modifiable.

Unmodifiable factors

Age

The incidence of RCC generally increases with increasing age.[6] According to the GLOBOCAN estimate in 2020, the global crude incidence rate of kidney cancer per 100,000 was 4.3 in population aged 40–49 years, 10.8 in 50–59 years, 20.3 in 60–69 years, and 29.6 in 70–79 years.[2] Similar correlations between age and incidence of kidney cancer are consistently observed worldwide for both sexes.[2,6,15] Kidney cancer mortality also increases

with age, which is at least partially a consequence of the increasing incidence by age.[3] Previous studies addressed the potential impact of age on survival outcomes in RCC patients.[18–21] Taccoen *et al.* analyzed 1,233 RCC patients undergoing surgery and investigated the characteristics of patients aged 40 years or less (n=93) in comparison to the other vast majority aged greater than 40.[18] They demonstrated that RCC in younger adults more often presented at a localized stage and less frequently with clear cell histology, and was also associated with improved cancer-specific survival compared with the older subjects. In the study by Karakiewicz *et al.* analyzing 3,595 patients with surgically managed RCC, the multivariable analysis revealed that cancer-specific mortality among young patients increases up to the age of 50 years and subsequently levels off until 75.[19] The age of 75 years appears to be another breakpoint, and the mortality again increases with age after this point. Another study explored age-related variations in gene expression patterns of clear cell RCC using the Cancer Genome Atlas and Cancer Genomics of the Kidney datasets, demonstrating age-associated decreases in stromal gene expression signatures and genes involved in extracellular matrix organization in tumours.[20] This genetic study suggested that different molecular characteristics may underlie the relationships between patient age and survival outcomes, although the impact of age may be more multifactorial and further studies will be required to investigate the clinical relevance of the findings.

Sex

Kidney cancer incidence is significantly higher in men than women.[2] As shown in **Table 1**, there is 2:1 male predominance regarding the incidence almost consistently across the world. The population-based mortality has an analogous trend by sex, with mortality higher in men.[2] Previous studies have suggested that this may in part be explained by disparities in stage and grade of RCC at diagnosis between men and women:[22,23] Aron *et al.* analyzed the Surveillance, Epidemiology, and End Results (SEER) database between 1973 and 2004 and reported that male patients presented with higher stage and higher grade of RCC than female patients.[22] Sex also has an impact on histological subtype of RCC: Lipworth *et al.* analyzed 1,532 patients with RCC who received nephrectomy at a single centre in the United States and reported that patients with chromophobe RCC were significantly more likely to be female in comparison to clear cell RCC after multivariable adjustment[24] and Casuscelli *et al.* showed that the proportion of female patients was significantly higher in chromophobe RCC (45.2%) than in clear cell RCC (33.7%).[25] Such differences by sexes may be related to various confounders including modifiable risk factors for RCC (smoking, obesity, or hypertension), or potential biases regarding diagnostic opportunities,[26,27] as well as intrinsic biological variances. There has been no clear consensus regarding the impact of sex on patient survival of RCC.[22,23] Fukushima *et al.* analyzed an international multi-institutional cohort of surgically managed clear cell RCC (n=2,055) and showed that female sex was significantly associated with favourable recurrence-free survival after the adjustment for age, race, type of surgery, and pathological T stage using the inverse probability of treatment weighting method.[28] This may suggest a possible positive impact of female sex on patient survival in localized RCC.

Race

Racial disparities of incidence and mortality of RCC have been widely studied, particularly the comparison between black and white patients in the United States. According to the GLOBOCAN database, the ASRs of kidney cancer incidence in 2016 were higher in black than white race for both sexes (black vs. white, per 100,000: 16.4 vs. 13.5 in men; 8.1 vs. 7.0 in women).[3] In contrast, there were no significant differences in

mortality between black and white race; the ASR of mortality (per 100,000) was 3.2 in men and 1.3 in women in the both races.[3] These results should, however, be interpreted in the context of racial differences in the stage and histology of RCC.[8,24,29,30] In a recent study analyzing the National Cancer Database in the United States, black patients exhibited significantly higher proportions for stage I and II (77.5% and 13.1%, respectively) and papillary (44%) RCC compared to white patients (stage I and II, 73.2% and 12.0%, respectively; papillary RCC, 17%).[29] Similar results were obtained in the study by Chow *et al.* based on the SEER database.[30] In that study, the investigators additionally compared patient survival by stage or histological subtype between black and white patients. That analysis demonstrated that black patients had consistently worse 5-year survival rates across all stages and subtypes. These findings suggest that those of black race have a worse survival from RCC even after accounting for differences in stage at diagnosis and histology.

Hereditary predisposition

Hereditary RCC accounts for 5–8% of kidney cancers.[31] Several hereditary RCC syndromes have been recognized to date, including von Hippel-Lindau (VHL) disease, hereditary papillary renal cell carcinoma (HPRC), Birt-Hogg-Dubé (BHD) syndrome, hereditary leiomyomatosis and RCC (HLRCC), and tuberous sclerosis complex (TSC). Shuch *et al.* analyzed 608 patients with hereditary RCC (most with VHL disease, n=387) in comparison to the SEER registry (1990–2008) and highlighted the early onset of hereditary RCC.[31] The median age of diagnosis of patients with hereditary RCC was 37 years and significantly lower than the SEER population. The lifetime risk for the development of RCC is reported to be approximately 70% in patients with VHL disease.[32,33] Patients may have synchronous or metachronous multiple RCCs in bilateral kidneys, which should be considered in the treatment and follow-up of RCC patients with VHL disease.

Although specific hereditary RCC syndromes are generally rare as described above, hereditary or familial predispositions are more common.[31] In a meta-analysis previously reported by Clague *et al.*, a family history of kidney cancer was associated with a 2.2-fold increased risk for sporadic RCC.[34] The investigators also conducted a case-control study, which demonstrated that a family history of kidney cancer in the first-degree relatives was associated with a 4.3-fold increased risk for RCC. Current advancements in understanding the genetic background of RCC may provide more accurate risk assessment in individual cases.

Modifiable factors

Smoking

Tobacco smoking is widely acknowledged one of the key modifiable risk factors for development of cancer.[17] The relationship between smoking habit and incidence of RCC has been also investigated in many previous studies and all support an association between smoking and RCC.[35–38] A recent meta-analysis reported that the pooled relative risks for RCC were 1.31 (95% confidence interval [CI], 1.22–1.40), 1.36 (1.19–1.56), and 1.16 (1.08–1.25) for all smokers, current smokers, and for former smokers, respectively.[35] Significant increased risks for RCC-specific mortality were also observed for all smokers and current smokers. Another study highlighted the impact of smoking intensity on RCC incidence, showing the highest risk for current smokers with 50-pack years or greater.[36] The preventive effect of smoking cessation for RCC development appears most likely for those who had quit smoking for longer than 10 years.[37]

Obesity

Obesity, defined as a body mass index (BMI) of 30 kg/m^2 or greater, is another established risk factor for RCC.[36,38–40] According to a previous meta-analysis, the pooled relative risks for RCC development were 1.28 (95% CI, 1.24–1.33) for preobesity (BMI ≥25 and <30) and 1.77 (1.68–1.87) for obesity (BMI ≥30), in comparison to normal weight.[40] Such impacts of BMI on the incidence of RCC were consistently observed for both sexes and across the areas including North America, Europe, and Asia.[40] Paradoxically, however, several studies have found that higher BMI is associated with earlier-stage disease and favourable survival outcomes in RCC patients.[41–44] Hakimi *et al.* analyzed 2,119 patients with clear cell RCC managed with surgery at a single institution.[42] In this study, obese and overweight patients had advanced-stage or high-grade disease less frequently compared with normal-weight patients. Although such variances in the stage and grade may partially affect the paradoxical relationship between BMI and patient survival, potential advantages of higher BMI in survival outcomes have been also reported in metastatic RCC.[43] Previous studies further explored differences in genomic expression or tumour microenvironment by BMI,[42–44] although the clinical relevance of those findings remains unclear.

Hypertension and diabetes

A number of prospective studies have been conducted during the past few decades investigating the potential impact of hypertension on kidney cancer incidence.[38,45–47] One of those studies analyzed 77,260 residents of Washington aged 50–76 years and explored risk factors for RCC.[38] In the multivariable model adjusted by all covariates related to lifestyles and comorbidities, hypertension was independently associated with the incidence of RCC (hazard ratio [HR], 1.70; 95% CI, 1.30–2.22). In a recent meta-analysis, a 67% increased risk for kidney cancer was observed among those with a history of hypertension, with each 10-mmHg increase in systolic and diastolic blood pressure associated with 10% and 22% increased risk for kidney cancer, respectively.[48] The biological mechanism underlying the relationship between hypertension and RCC development could be related to chronic renal hypoxia, although it remains largely unknown and further investigations will be required.[48,49]

Although diabetes may be also associated with an increased incidence of RCC, there have been controversies regarding whether diabetes is an independent risk factor for RCC.[15,50,51] The association between diabetes and RCC is often confounded by obesity and hypertension in cohort studies, as these conditions often coexist. In a large, prospective, cohort study that analyzed the associations between several lifestyles or comorbidities and RCC incidence, diabetes failed to show a statistical significance independently among covariates including smoking, obesity, and hypertension in the multivariable model.[38]

Diet

Previous studies suggest that specific nutritional intake may both negatively and positively affect the development of RCC.[52–57] Several studies have reported that meat intake may increase the risk for RCC, thought to be partially related to the carcinogens formed in the cooking process such as benzo(a)pyrene and polycyclic aromatic hydrocarbons.[52,53] In contrast, fruit and vegetable consumption, particularly that of cruciferous vegetables such as cabbage, broccoli, and cauliflower, may be protective against RCC development,[54,55] although the associations

between fruit and vegetable intake are inconsistent. For example, in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a prospective cohort study that includes more than 500,000 participants from 10 countries throughout Europe, no significant decrease of RCC risk was observed for fruit and vegetable intake.[56,57] The challenges related to this topic include the limited accuracy in quantification of ingestion, and further research is needed to develop consensus. As for alcohol consumption, previous studies suggested its protective effect on RCC, showing an inverse relationship between moderate alcohol intake (<60 g/day) and RCC risk.[58,59]

Occupation and drug exposure

Although the impact of occupation on RCC is generally considered limited, increased risks may be observed in specific occupations related to certain industrial agents.[15,51] Trichloroethylene has been most extensively examined from this aspect.[60–62] Trichloroethylene is a chlorinated solvent, widely used as a metal degreaser, extractant, and chemical intermediate.[60] Based on the large body of evidence, the Environmental Protection Agency in the United States has officially acknowledged the toxicity of trichloroethylene and concluded that it modestly increases the risks for several cancers including kidney cancer.[61] Previous studies have also suggested that occupational exposures to specific types of dust may be associated with an increased risk for RCC, although the results need further validation.[63]

The possible impact of analgesics has been also investigated. Choueiri *et al.* conducted a meta-analysis that revealed that the uses of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin were significantly associated with an increased incidence of kidney cancer, while the use of aspirin was not.[64] NSAID use may induce kidney injuries that can lead to carcinogenesis theoretically, although the biological mechanisms remain unclear.

Others: end-stage kidney disease and transplant

A higher incidence of RCC among patients with end-stage kidney disease (ESRD) has been well reported.[65] Approximately 4% of ESRD patients are diagnosed with RCC in the native kidneys and the lifetime risk of developing RCC is reported to be 10-fold higher compared to the general population.[66] ESRD patients also more often present with multiple or bilateral tumours. However, it has been also reported that RCCs in ESRD patients are generally less aggressive, exhibiting lower stage and grade than those in non-ESRD patients.[66,67] Such differences may be partially derived from the increased opportunities for imaging studies in ESRD patients, which lead to early diagnosis of RCCs. The differences may also be linked with different histological subtypes. Acquired cystic disease–associated RCC is a histological subtype almost exclusively observed in ESRD patients and accounts for 16.3% and 50.6% of RCCs in ESRD patients who have <10 and ≥10 years of dialysis, respectively.[68] The incidence of RCC in the allograft kidneys after transplant is much lower than in the native kidneys and a limited number of case series have been reported.[69,70] Leveridge *et al.* analyzed 3,568 patients who received kidney transplant and reported that 39 (1.1%) and 8 (0.2%) patients were diagnosed with RCC in native and allograft kidneys, respectively.[69]

Screening

Rationale for screening

The epidemiology of RCC highlights that despite a shift to lower stages of diagnosis, there remains a large proportion of individuals diagnosed each year with locally advanced or metastatic disease. Clearly, superior survival is noted in patients with earlier-stage compared to late-stage disease. Indeed, the 5-year survival rate is 87% in stage I compared to 12% in stage IV RCC.[71] Additionally, although for all cancers combined there has been a 27% improvement in all-cause mortality over the past 50 years, this improvement has not been seen in RCC treatment, where there has been only a 4% improvement in cancer survival since 1971. It should be noted that survival data varies between sources,[72] but it is likely that there have not been the same levels of improvements in survival for RCC that have been achieved in other cancer types. This has driven the desire to investigate the topic of screening for RCC, to enable earlier diagnosis and treatment of the disease, with the aim of improving survival outcomes.[144] Although this topic was initially investigated in the early 1990s and 2000s, there has been a resurrection in interest in the past few years, with an increasing number of publications on this subject.[73,74]

The research community has also identified screening and early detection of RCC as a key research priority in three independent priority setting initiatives over the past 5 years, highlighting the crucial importance of this topic.[75–78] Furthermore, patient groups have been vocal in their desire to champion this agenda.[79] The two main concerns from a patient perspective are: the frequent absence of symptoms in RCC even in advanced disease, and the relatively poor knowledge regarding this malignancy in the general population. Indeed, the majority of the public have a relatively low awareness of RCC: in a recent survey, 82% of individuals knew nothing about RCC or had only heard of the disease.[80] Initiatives to raise public awareness of hematuria have not been successful in improving detection of RCC,[81] suggesting that a more systematic identification approach may be necessary. Any screening program for RCC, however, must be evaluated with the Wilson and Jungner criteria in mind,[82] to minimize risks to the general population while maximizing benefits for individuals (**Table 2**).

TABLE 2 Wilson and Jungner criteria applied to screening for RCC,* highlighting key research questions

Criteria for screening	
1. The condition sought should be an important health problem.	• Screening for RCC is a key research priority. • RCC is the 7th most common cancer in Europe[142] and overall 5-year survival is 52%. • 11–23% of patients have metastases at diagnosis and 5-year survival in this group is 12%, suggesting early detection could improve survival.
2. There should be an accepted treatment for patients with recognized disease.	• Early detection of smaller tumours may preferentially allow minimally invasive techniques, reducing rates of open surgery and therefore associated morbidity and length of hospital stay, and improving quality of life and renal function.
3. Facilities for diagnosis and treatment should be available.	• Screening would increase disease incidence. Further research on cost and resource implications of this is key.
4. There should be a recognizable latent or early symptomatic stage.	• The natural history of small renal masses is not completely understood. However, as >50% of RCCs are detected incidentally, this suggests there is a latent asymptomatic stage at which to intervene.
5. There should be a suitable test.	• Currently, screening with ultrasound or low-dose abdominal CT, in combination with existing programs (such as AAA screening or lung cancer screening), seems the most viable option. Ideally, a screening approach would adopt a staged approach to increase efficiency and cost-effectiveness. First, a risk-stratification tool/prediction model would identify high-risk individuals from the general population. These individuals would be invited to have an initial urine or blood-based biomarker test (ideally, point-of-care test at home or in the community), followed by further imaging in secondary care.
6. The test should be acceptable to the population.	• Surveys demonstrate public acceptability and willingness to attend screening.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.	• This area is the highest research priority.

TABLE 2 Wilson and Jungner criteria applied to screening for RCC,* highlighting key research questions *(Cont'd)*

8. There should be an agreed policy on whom to treat as patients.	• Clear European Association of Urology Guidelines on the management of RCC have been published,[143] including active surveillance, ablative, and surgical options for localized disease.
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.	• A cost-effectiveness analysis of screening for RCC using ultrasound suggested that screening could potentially be cost-effective in men.[120] The low prevalence was a key determinant of cost-effectiveness, suggesting risk-stratified screening would be an ideal option.
10. Case finding should be a continuing process and not a "once and for all" project.	• It is unclear if screening should be performed as a one-off or repeated at regular intervals.

Abbreviations: AAA, abdominal aortic aneurysm; CT, computed tomography; RCC, renal cell carcinoma; SRM, small renal mass.

**Adapted from Rossi SH, T. Klatte J, Usher-Smith J, Stewart GD. Epidemiology and screening for renal cancer.* World J Urol. *2018;36(9):1341–1353. doi:10.1007/s00345-018-2286-7,[73] under the* Creative Commons License.

Screening modality

A successful screening strategy relies on a screening tool that is accurate, reliable, acceptable to the public, and scalable (i.e., can be rolled out on a population level by the existing health service). A number of screening approaches have been considered, each with advantages and disadvantages, although the ideal screening tool has yet to be identified.

Urinary tests

Urinary tests represent an ideal tool due to their noninvasive nature, ease of collection and storage, and acceptability by the general public.[80] This strategy could involve either a point-of-care test (such as dipstick for hematuria) or laboratory test (urinary biomarkers). Dipstick tests are cheap, readily available, and require minimal training; however, colour changes may be open to subjective interpretation. Nonvisible (NV) hematuria is defined as blood in the urine detected by urinary dipstick or microscopy, which is not visible to the naked eye (as opposed to visible hematuria, which is gross/macroscopic).[83] The main concerns are the nonspecific nature of NV hematuria for RCC, the high number of incidental findings, and the unacceptably high rate of false positives and false negatives.[74,84] Therefore, screening for RCC based around dipstick-detected NV

hematuria is not currently recommended (though there may be benefits for bladder cancer detection).[85] The vast majority of patients diagnosed with RCC will not have hematuria, meaning there would be a large number of false negatives. The prevalence of hematuria in RCC is 35% (prevalence 17.5% visible and 17.5% nonvisible hematuria), compared to 94% in bladder and ureter urothelial cancer.[86] The prevalence of NV hematuria may be as high as 20–30% in the general population; [84,87] however, <1% of individuals with NV hematuria are found to have RCC and 5% are found to have bladder cancer.[83] A meta-analysis suggests that in patients with NV hematuria, the prevalence of RCC was 0–10%, whereas the prevalence of bladder cancer may be as high as 16%.[88] Conversely, urinary dipstick may identify a large number of nonmalignant urological diseases that are associated with NV hematuria (including renal stones, cysts, etc.) as well as medical diseases associated with proteinuria or glycosuria (renal disease, diabetes, infection, etc.). The high volume of individuals requiring further investigation and the high number of incidental findings preclude this as a cost-effective screening strategy for RCC.

Urinary biomarkers would represent the ideal screening tool; however, to date nil are validated or approved for use in clinical practice.[89] A number of different analytes could be used, including urinary proteins, cell-free tumour DNA, microRNAs, and exosomes. Perhaps the most well-studied group is urinary proteins, including: aquaporin-1, perilipin-2, carbonic anhydrase-9, Raf-kinase inhibitory protein, nuclear matrix protein-22, 14-3-3 Protein β/α, and neutrophil gelatinase-associated lipocalin.[89] Aquaporin-1 and perilipin-2 have been evaluated in a prospective study of 720 patients undergoing screening CT, 80 healthy controls, and 19 patients with RCC. In this cohort, these two biomarkers used in combination achieved an area under the curve (AUC) >0.99 for RCC.[90] Although these two proteins may be good markers for ccRCC and pRCC, levels are low or negative in chRCC, meaning screening would miss the latter.[73] Further prospective validation in an independent cohort is warranted. Key considerations for urinary biomarker studies include: urinary collection and storage protocols to maximize analyte stability, standardization and establishment of gold standard methods for protein evaluation across international laboratories, high-quality study design, and comprehensive study reporting.

Blood tests

Blood-based tests represent another potentially useful option due their relative public acceptability and presumed relatively low cost. Analytes similar to those identified in urine may be used, such as: proteins, circulating tumour DNA (ctDNA), microRNAs, and exosomes. Kidney injury molecule-1 (KIM-1) is a glycoprotein that reflects injury to the proximal convoluted tubule of the kidney (from which ccRCC and pRCC are derived). KIM-1 levels are elevated in ccRCC and pRCC, and KIM-1 has therefore been investigated as a potential marker to improve early detection in these disease subtypes. Scelo *et al.*[91] demonstrated that KIM-1 blood levels may be elevated 5 years prior to a diagnosis of RCC. One of the main disadvantages is the low specificity of KIM-1 (levels may be elevated in kidney injury). Furthermore, KIM-1 levels are not elevated in patients with renal tumours derived from the distal nephron, therefore using this marker for screening would result in false negatives for patients with chRCC and collecting duct RCC. Although these challenges may limit the ability to use KIM-1 as a screening tool, KIM-1 may still be useful to monitor residual disease in patients with preoperatively raised KIM-1 levels, which would circumvent the challenges regarding low specificity.[92]

Cancer screening using ctDNA has recently received significant media attention and has entered large-scale validation studies. A number of studies have been published evaluating ctDNA for the simultaneous detection of multiple cancer subtypes with the aim of pan-cancer screening.[93,94] Although initial reports evaluating mutations[95] and methylation patterns[94] in ctDNA suggested patients with renal cancer may have lower levels of ctDNA than those with other malignancies, more recent reports evaluating DNA methylation appear more promising.[96] Nuzzo *et al.*[96] evaluated ctDNA methylation using cell-free–methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP–seq) in a case-control study. The study cohort included 99 ctDNA samples from patients with RCC (of which 33% were from patients with stage I-II disease), 21 samples from patients with stage IV bladder cancer, and 28 healthy controls. The overall AUC for the detection of RCC was 0.99, suggesting ctDNA may be detected in patients with RCC across the spectrum of disease severity, raising the possibility that in the future this could potentially be used to enable earlier disease detection. Further research on blood-based biomarkers as a screening tool, in prospective cohorts, is warranted.

Ultrasound

Ultrasound is perhaps the most well-studied screening method for RCC, with a number of observational studies published in the 1990s and 2000s.[97–104] The main drawback is that accuracy is dependent on operator experience, anatomical factors (including obesity and overlying bowel gas), and lesion size. There is a potential for false negatives, as ultrasound can detect 85–100% tumours >3 cm in size, but only 67–82% of tumours 2–3 cm in size.[105,106] Advantages of ultrasound include the relative acceptability by the general public, as it is pain-free and noninvasive (compared to blood tests). Ultrasound is widely available, does not involve ionizing radiation, and is relatively inexpensive compared to computed tomography (CT). Furthermore, focused renal ultrasound may be performed, imaging the kidneys alone rather than the entire abdomen, therefore reducing the time and cost of the scan and avoiding incidental detection of indeterminate lesions in other abdominal organs, which may require additional investigation with associated costs. Another potential advantage is the opportunity to combine screening for renal cancer with the existing abdominal aortic aneurysm (AAA) screening program, which would reduce the overall cost of the screening intervention and maximize cost-effectiveness. However, in some nations (such as the UK, France, and Sweden), the AAA screening program includes only men. To the best of our knowledge, Malaeb *et al.*[104] is the first and only study to explore this. Screening for AAA and kidney cancer using abdominal ultrasound was performed in 6,678 veterans, demonstrating this is a feasible approach that is well tolerated by patients. The study identified 22 patients with solid renal masses (prevalence, 0.32%): 5 individuals were lost to follow-up, 2 patients were not fit for operative management, and 15 patients underwent treatment. In patients undergoing treatment, survival was 80% (i.e., 12/15) at a median 55 months of follow-up.[104] Although this study is promising, none of the ultrasound studies were randomized in nature, meaning the impact of the intervention on survival remains unknown.

Computed tomography

Use of CT has increased in recent decades due to technological advances (enabling increased resolution, reduced scanning times, and lower radiation dose), increasing availability and reducing costs.[107,108] Contrast-enhanced CT is the gold standard diagnostic imaging technique to evaluate SRMs in patients with suspected

RCC (e.g., if a mass is identified on ultrasound or there is visible hematuria). Contrast uptake can enable the differentiation between benign and malignant disease, and visualization of tumour and vessel anatomy that can guide operative management approaches. However, the utility of contrast-enhanced CT as a screening tool in the general population is limited by the use of contrast (which may be nephrotoxic), relatively high radiation dose, and cost, particularly given the low prevalence of RCC. However, low-dose unenhanced CT has the advantage of providing less radiation dose and no contrast.

Whole-body CT has been proposed as a potential screening tool for the combined detection of multiple malignant and nonmalignant diseases (e.g., abdominal cancers, AAA, etc.).[109–111] Although a number of studies have been performed, the main drawback of performing whole-body scans is the high number of incidental findings, false positives, and findings of unknown clinical potential. For example, Millor *et al.*[112] reviewed 6,516 whole-body screening CTs (which included unenhanced chest CT, enhanced abdominal CT, cardiovascular, and bone assessments). Less than 2% of individuals had normal scans, meaning >98% had to undergo further investigations with significant costs, burden to the health service, and anxiety for the individual. 1.5% of individuals were found to have a malignancy (35/96 were RCC). As a result, whole-body CT to screen for kidney cancer as a standalone test in an unselected population is unlikely to be a cost-effective strategy at present.[113] It is postulated that in the future, machine learning and artificial intelligence (AI) may enable automated interpretation of imaging features, which will increase accuracy and reduce false positives. AI could additionally reduce the burden of interpreting large volumes of CT images by the health service, rendering this tool more feasible, and increase the utility of scans (e.g., by evaluating multiple features such as visceral fat for metabolic disease, aortic calcium for cardiovascular disease, and bone density for osteoporosis).[114]

Limiting screening to abdominal low-dose non-contrast CT alone may reduce the number of incidental findings, compared to whole-body CT screening.[109] The low prevalence of RCC remains a challenge, therefore an alternative approach is to add low-dose non-contrast abdominal CT scans to the low-dose unenhanced chest CT scans currently being investigated for lung cancer screening in high-risk members of the population. This would maximize cancer detection rates while reducing costs. A randomized controlled trial of lung cancer screening in the United States suggested that low-dose unenhanced chest CT may identify RCCs, despite imaging only the top section of the kidneys.[115] The Yorkshire Kidney Screening Trial (NCT05005195), currently underway, is a novel study and the first to evaluate the added benefit of screening for RCC by extending the low-dose chest CT to image the kidneys in 55–80 year-old smokers and ex-smokers undergoing lung cancer screening enrolled in the Yorkshire Lung Screening Trial.[116] It is postulated that combined screening may maximize cancer detection rates while reducing costs.

Screening population

The ideal population to whom screening for RCC should be offered is unknown. One of the main challenges is the relatively low prevalence of RCC. Meta-analyses have estimated that screening 1,000 individuals using ultrasound would identify between 1 and 2 patients with RCC,[97] while studies using CT have estimated this

number to be between 1 and 3 (pooled prevalence of RCC 0.17% [95% CI, 0.09–0.27%] and 0.21% [95% CI, 0.14–0.28%] in US and CT, respectively).[97,110] This means that a large number of individuals would have to undergo screening to detect only a small number of cancer cases. However, this is a challenge common to many screening programs, and these figures need to be interpreted in the context of existing screening interventions. For every 1,000 men screened in the UK National Health Service AAA screening program, 10 men are identified with a AAA ≥3 cm. Two of these individuals will undergo surgery at diagnosis, while a further 6 of these men will undergo surgery following active surveillance over a 20-year period.[117,118] For every 1,000 individuals undergoing guaiac-based fecal occult blood screening, 1.6 patients with colorectal cancer are detected (an additional 6 patients will be identified with high-risk adenomatous polyps requiring surveillance).[119] Screening for RCC may compare favourably with the established programs for AAA and colorectal cancer, although intrinsic differences underlying each screening program and the individual nature of each disease make direct comparisons artificial.[97] A health economic analysis of screening for RCC using ultrasound identified the prevalence of RCC as the greatest determinant of cost-effectiveness.[120] The higher the prevalence of the disease and the cheaper the screening modality, the greater the health economic benefit of any screening program.

Risk-stratified screening may enable more efficient identification of RCC, focusing on high-risk individuals and therefore maximizing benefits while reducing costs and harms for those at low risk. Risk-stratified screening is indeed likely to be the preferred option for future lung cancer screening programs as well as being investigated for established programs such as breast and colorectal cancers. A systematic review of risk-prediction models for RCC[121] identified 11 models that report performance measures and could potentially be used. Fewer than 20% (2/11) had been validated in an external population, highlighting one of the limitations of current models. The most commonly included factors were sex, age, smoking status, BMI, and hypertension, which is consistent with the known data on risk factors for RCC. However, none of these risk factors are specific for RCC. Only one study considered genetic risk (i.e., single-nucleotide polymorphisms) and biomarker studies were characterized by a high risk for bias. The models identified in the systematic review were externally validated in 450,687 participants within the UK Biobank cohort.[122] Five models had reasonable calibration and discrimination, with an area under the receiver operating characteristic curve between 0.61 and 0.72. All the models performed less well in women, compared with men. Additionally, although the models are better at identifying individuals at high risk for RCC than age and sex alone, the improvement was small. Future incorporation of biomarkers into risk scores could improve performance.

Screening implementation and public acceptability

If screening is demonstrated to improve disease-specific survival, it is crucial to consider implementation of the screening program and public acceptability. The program must be deliverable in the present health service, which may be stretched due to the provision of competing health interventions. The cost of screening is limited by not only the intervention itself (which may be imaging or a biomarker) but also the associated costs of investigating incidental findings and the cost of treatment of diagnosed conditions. For example, screening may identify benign renal and non-renal conditions (including simple cysts, congenital anomalies, renal stones, diabetes), which would need to be investigated, placing a burden on existing services. Other important

considerations are in regard to program delivery, including: optimal screening location (e.g., primary care, secondary care, screening vans in public spaces), training an adequate workforce to deliver screening (e.g., ultrasound delivered by technicians vs. sonographers), and quality control (e.g., audit for laboratories undertaking biomarker work or facilities offering imaging).

Public acceptability of the program will also be key to ensure high attendance rates. A survey has shown that members of the general public would be "very likely" or "likely" to undergo each of the following screening tests: urine test: 94%; blood test: 90%; ultrasound: 90%; low-dose CT: 79%; and low-dose CT offered as part of lung screening: 95%.[80] Although one cannot make assumptions about attendance based on survey data, the high anticipated intention to attend screening is promising. Furthermore, the public viewed risk-stratified screening positively. Most individuals (83%) reported that tailoring the starting age of RCC screening based on a risk score incorporating phenotypic or genetic risk was acceptable. Interestingly, risk scores were more acceptable than using sex alone to determine the age of screening (i.e., offering men earlier screening than women).[123] Additionally, 85% of participants reported they would be more likely to attend screening if the risk score suggested they were high risk, while being told they were low risk had no overall influence on intention to attend.[123]

Challenges and unknowns

Unknown survival benefit and stage shift

Perhaps the greatest unknown is whether screening for kidney cancer will translate to a survival benefit. Observational studies of screening for RCC using ultrasound published in the 1990s to 2000s suggested promising statistics; however, no randomized controlled trials have been performed to date. Mihara *et al.* screened >200,000 healthy individuals, and patients with screen-detected RCC had 5-year survival >97%.[100] An artificially inflated survival time may be seen in screen-detected cancers due to earlier detection in the absence of a true survival benefit (lead-time bias) or due to the detection of indolent, slow-growing cancers (length-time bias).[74] Only a randomized controlled trial would be able to elucidate whether increased survival observed among these screened individuals is a true benefit, rather than simply length- or lead-time bias. However, due to the low prevalence of RCC, a randomized controlled trial would need to recruit hundreds of thousands of participants to detect a survival benefit. Such a high-volume trial would be high cost and would require long-term follow-up, which are barriers to undertaking such a study.

Another unknown relates to whether screening would identify additional cancers over and above those diagnosed by the existing health service. Since the initial observational studies of screening for RCC were published,[97] nearly two decades have passed, and abdominal imaging using CT has become much more widely accessible. The incidence of RCC has increased dramatically (47% rise in incidence over 10 years). This is likely due to both a true rise in the disease and incidental detection during abdominal imaging for other complaints.[51]

Welch *et al.* estimated 43% of individuals aged 65–85 years on Medicare in the United States undergo either a CT chest or CT abdomen over a 5-year period,[108] meaning these individuals may not benefit from further screening. The "stage shift" refers to the detection of screen-detected cancers at an earlier and therefore treatable stage, compared to the existing standard of care. Further studies are needed to determine whether screening for RCC in the current climate will lead to increased detection and a stage shift.

The "sojourn time" or "preclinical period" refers to the length of time during which an individual with RCC has not yet received a diagnosis, and would therefore benefit from early detection via screening. Cancers with very short or very long sojourn times are not ideal screening candidates. For example, if the window to detect the malignancy is too short, it may not be possible to deliver a screening intervention, whereas if the window is too long, it suggests the cancer is indolent and may not impact survival. Imaging studies have suggested the sojourn time for RCC is between 3.7 and 5.8 years.[110] Scelo *et al.* demonstrated raised KIM-1 plasma levels up to 5 years prior to RCC diagnosis,[91] which is in keeping with the estimated sojourn time. Taken together, these studies suggest that there is a length of time during which asymptomatic patients might benefit from screening interventions. The optimal frequency of screening and target population have also yet to be identified. Thus far, studies have evaluated screening for RCC at a single time point rather than regular intervals.[73] This is akin to screening for AAAs, rather than the regular cancer screening that is currently performed for other malignancies (including breast, cervical, and colorectal). Further research into the natural history and epidemiology of renal masses will elucidate the ideal screening population (including age and gender of individuals) and screening interval.

False negatives, false positives, and overdiagnosis

As with any screening program, despite attempts to select a tool with high sensitivity and specificity, false negatives and false positives represent a true challenge. Imaging techniques (such as ultrasound) may miss small tumours, as may biomarkers. False negatives are damaging, as participants are falsely reassured of the absence of cancer, only to receive a positive diagnosis at a later date. Not only is this associated with real harms and anxiety to the individual, but it may also erode public trust in the screening program and could negatively affect attendance if the test is perceived to be inaccurate. As already mentioned, depending on the screening test (and especially with CT), a number of incidental findings may be identified that may have indeterminate clinical potential. These may require further investigation and there may be patient anxiety associated with the uncertainty surrounding the diagnosis.

One of the main challenges associated with screening for RCC relates to the identification of small renal masses (SRMs; defined as <4 cm in size), as improvements are still required to accurately diagnose and better understand the natural history of these lesions. SRM is a broad term that encompasses a mixture of potential diagnoses, including clear cell (ccRCC), papillary (pRCC), chromophobe (chRCC) RCC, or benign disease (including oncocytoma and fat-poor angiomyolipoma). Unfortunately, it is not possible to accurately differentiate benign from malignant SRMs using contrast-enhanced CT, the gold standard imaging investigation.[124,125] Recent studies suggest that magnetic resonance imaging or contrast-enhanced ultrasound could be useful

adjuncts for differentiating SRMs, although further research is required to validate the findings reported in the literature.[124,126–129] Renal biopsy is the gold standard approach to determine the histological diagnosis; however, it is often underused due to inadequate service provision, lack of expertise, or low perceived clinical benefit. Renal biopsy is also associated with risks: pain, bleeding, infection/sepsis, or accidental damage to adjacent structures (e.g., pneumothorax or abdominal organ injury).[130] Of these, the most common complication is bleeding, which tends to be self-limiting (e.g., perinephric hematoma or visible hematuria in ~10% cases) but may require blood transfusion (~1% cases) or intervention (0.3% cases).[130,131] The most worrying theoretical risk is tract seeding; this is generally considered rare, though a recent report suggests this may be as high as 1%.[132] Both bleeding and seeding risk may be mitigated via the use of a coaxial needle. Furthermore, biopsy may be difficult to perform due to small lesion size or difficult anatomy (difficult-to-access lesion or overlying bowel). On histopathological biopsy review, there may be difficulty differentiating benign from malignant diagnoses due to inadequate tissue sample or simply due to similarities between tumour types. Biopsy is nondiagnostic in ~10% of cases.[130] It can be particularly difficult to distinguish oncocytoma from eosinophillic variants of chRCC and ccRCC. A meta-analysis demonstrated approximately 25% of renal biopsies reported as oncocytoma are found to be malignant following excision.[133] Erring on the side of caution, patients with SRMs are often offered surgery and as a result, approximately 20 to 30% are found to have benign disease postoperatively, meaning they underwent unnecessary surgery, with associated morbidity and potential long-term effects on renal function.[134,135] Future research should focus on improving diagnostic techniques. Furthermore, at present it is not possible to determine which SRMs are aggressive and which are indolent, meaning that screening could identify a large number of individuals with SRMs who would not benefit from treatment. In patients with SRMs, annual growth rates are very variable and rates of metastases are generally low (0–2%).[136] Determinants of aggressive clinical course include: pathological subtype (where pRCC type 2 and ccRCC have the worse prognosis and chRCC and pRCC type 1 have the best), higher lesion grade, size, and tumour growth rate.[137] Increasing the use of active surveillance (which has been shown to be noninferior to primary intervention), especially in patients with comorbidities who may have a limited life expectancy, could reduce overtreatment.[138] Recently a growing number of observational studies are being performed that are increasing our understanding of the natural history of disease.[138] Ultimately, being able to clearly determine which SRMs require further investigation or treatment and developing pathways for the management of patients with SRMs based on competing risks is essential before any RCC population-based screening program can be implemented.

Impact of screening on quality of life

There are a number of ways in which screening can cause harm.[139–141] These include: physical harm, resulting from both the screening test and/or follow-up procedures; psychological harm, including increases in anxiety; treatment burden, including from subsequent invasive procedures and overdiagnosis; financial costs associated with travel and time off work to attend appointments and potential loss of earnings; social harm, resulting from social stigma or missing out on other activities; and dissatisfaction with health care.

As screening is offered to a large number of asymptomatic individuals in order to detect only a small number of cancers, it is crucial to understand any quality of life (QoL) detriment associated with screening itself. None of the observational studies evaluating ultrasound screening for RCC evaluated the impact on QoL. It is generally accepted that screening itself may be associated with a small but transient increase in anxiety and cancer worry. False negatives may lead to false reassurance and anxiety for patients. Incidental findings require further investigation, which may be invasive (such as transvaginal ultrasound for endometrial thickness identified on abdominal imaging, or biopsy of suspicious lesions), or regular follow-up, which may be associated with anxiety due to the identification of indeterminate lesions with unknown significance. Lastly, overdiagnosis of indolent SRMs or surgical removal of SRMs that are found to be benign may lead to associated anxiety and morbidity for patients. It is crucial that further studies evaluating screening focus not only on survival outcomes but also on patient reported outcomes and quality of life. The cost-effectiveness of any screening intervention needs to be demonstrated prior to the screening program being accepted into clinical practice. The gold standard represents a cost-utility analysis that evaluates the benefit and harms of the screening program in terms of the quality-adjusted life years gained by individuals due to the intervention. Future studies should focus on evaluating the QoL of patients undergoing all components of the screening pathway, including not only the screening intervention itself but also the QoL associated with diagnosis and management.

Future directions

In summary, the large proportion of patients with RCC who are diagnosed at a late, locally advanced or metastatic stage due to the absence of symptoms, and the risk of poor outcome in this group are the main drivers for the need to improve the early detection of RCC. Screening has therefore been recognized as a research priority by patients and clinicians alike. A number of potential candidate screening tools are currently being investigated, including urinary and blood biomarkers, ultrasound, and low-dose unenhanced CT, though it may be that a combination of these approaches may be optimal. Ultimately, the sensitivity and specificity of the chosen screening tool will determine the rate of false positives and false negatives, which must be minimized. One of the key challenges is the relatively low prevalence of the disease, which might be overcome by performing risk-stratified screening or screening for more than one condition (such as combined lung cancer and RCC screening). These options may maximize efficiency of screening while reducing harms. Preliminary research suggests that both these approaches may be acceptable to the general public. Whether screening for RCC will lead to a stage shift and the impact on cancer-specific survival are the decisive missing pieces of information that will determine whether the screening program might be adopted into clinical practice (along with feasibility, acceptability, and cost-effectiveness).

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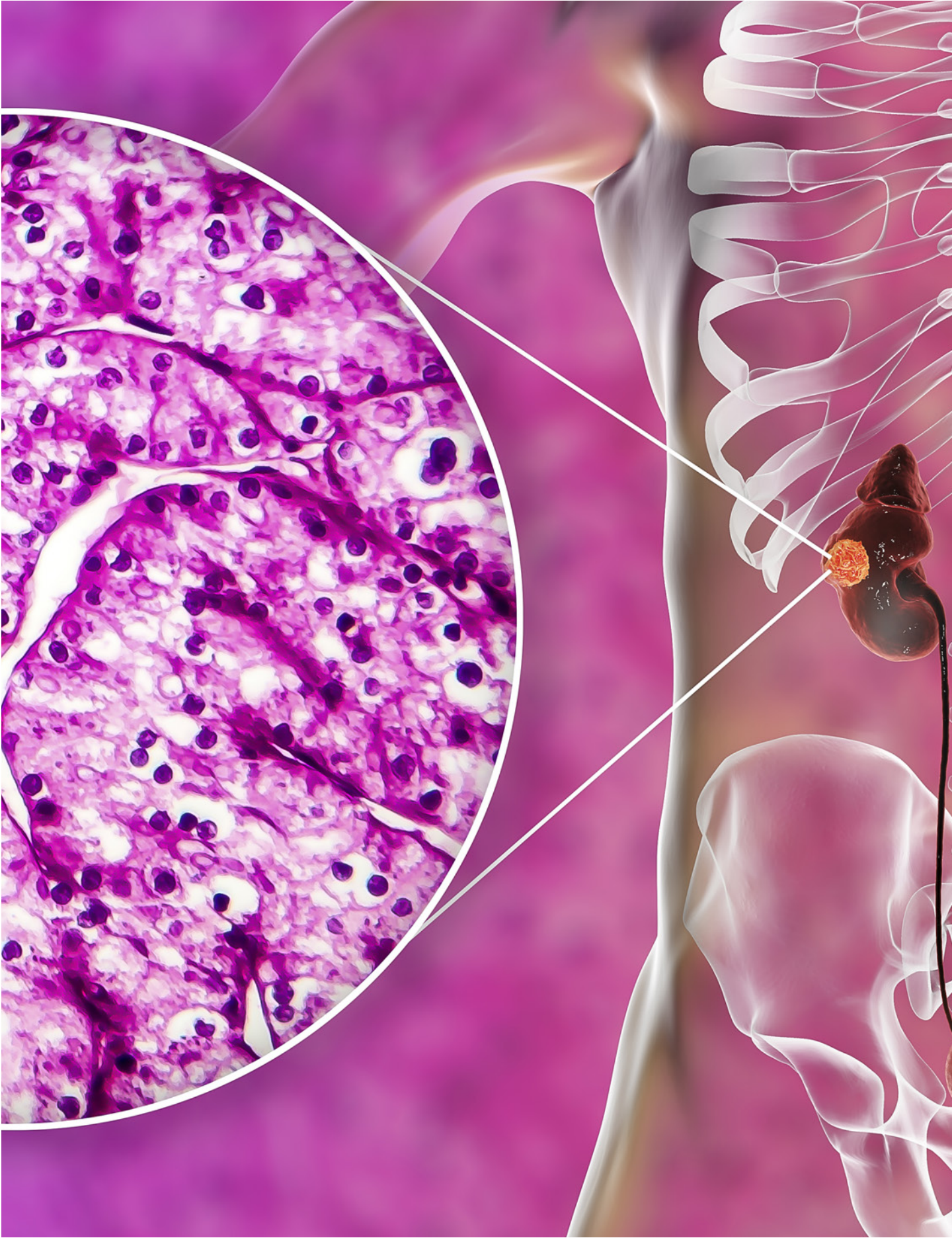

COMMITTEE 3

Recent Updates in Pathology of Renal Cell Carcinoma

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Table of Contents

Introduction

This chapter presents an overview of the morphologic characteristics, diagnostic immunohistochemistry (IHC), and molecular correlates of renal cell carcinoma (RCC). The authors provide their expert insights and synopsis of published literature, by critically evaluating the available evidence and data.

Histologic categorization of renal tumours is essential for: (i) accurate prognostication; (ii) appropriate management; and (iii) assessment of hereditary predisposition. For example, a patient with chromophobe RCC (ChRCC) is less likely to die from his disease compared to similar stage other common RCC subtypes such as clear cell RCC (CCRCC).[1] Additionally, histologic diagnosis may influence management including consideration for active surveillance or surgical resection in a patient with small renal mass. The histologic subtype (clear cell versus non clear cell) is incorporated into clinical decision-making (National Comprehensive Cancer Network [NCCN] guidelines),[2] and drives oncologic management. Furthermore, histology often serves as a marker for identification of hereditary predisposition syndromes (American College of Medical Genetics and Genomics [ACGM] Practice Guidelines).[3]

During the past two decades, knowledge of the underlying molecular biology has helped associate morphologies with specific molecular alterations, establish biologic subgroups, refine diagnostic features, and develop unique diagnostic ancillary profiles. These molecular studies have often led to the identification of novel histological and molecular subtypes. Another major contribution is the identification of subtypes previously regarded as RCC with benign or indolent behaviour. Despite these advances, histomorphology remains the fundamental driver of clinical diagnosis, prognosis, and management—a testimony to the power of morphology and the information embedded in spatial tissue organization.

Since the prior 2016 World Health Organization (WHO) classification (4th edition),[4] the Genitourinary Pathology Society (GUPS) published two manuscripts summarizing the advances.[5,6] In this chapter, we have adopted GUPS terminology and categories. Several new entities were described previously under different names, and we hope that unified GUPS terminology will resolve ambiguity.[5,6] In addition, many of these GUPS terms will be incorporated in the upcoming 2022 WHO classification (5th edition).[7] Herein, we highlight ongoing controversies in nomenclature, grading, staging, and clinical implications.

General Considerations for Macroscopic Examination

RCC are most frequently located in the renal cortex and grows as spherical masses with pushing margins. This contrasts with many other cancers that display infiltration with desmoplasia. Infiltrative growth patterns are

observed rarely, though more typically with collecting duct carcinoma (CDC), SMARCB1-deficient renal medullary carcinoma (RMC), or fumarate hydratase (FH)–deficient RCC.

Tumour stage, the most important prognostic parameter, is based on tumour size, invasion, and disease extent. The pathologic pT category is influenced by size and invasion. Tumours confined to the renal parenchyma with cutoffs of > 4, 7, and 10 cm are designated as pT1b, pT2a, and pT2b, respectively.[8] As illustrated by Bonsib, renal sinus invasion is one of the most frequent routes of extension, especially in CCRCC, the most common subtype. This emphasizes the importance of a thorough renal sinus gross examination.[9] The renal sinus contains the fat and lymphovascular supply surrounding the pelvicalyceal system, and sinus invasion warrants pT3a designation. Similarly, renal vein, segmental vein, perinephric fat, or pelvic/calyceal system warrants a pT3a designation. Renal sinus invasion can be subtle; at least 3 tissue blocks are recommended for examination, unless the invasion is grossly apparent.[9–14] This is because even subtle sinus or vascular invasion impacts prognosis.[15] As CCRCC grows, the likelihood of invasion of the renal sinus increases dramatically, such that CCRCC tumours over 7 cm usually invade these structures.[10] On the other hand, non-CCRCC (especially chromophobe or papillary RCC) may reach this size without such invasion.[16] Nevertheless, when the tumour size is greater than 5 cm, sampling the entire renal sinus interface is quite reasonable.[12]

RCC (especially CCRCC) has a predilection for intravenous growth. These tumour thrombi are finger-like outpouchings that grow into segmental veins, the main renal vein, and the inferior vena cava (IVC). They may even extend into the right atrium.[9–11] In addition, thrombi may grow in a retrograde fashion to the renal cortex when there is occlusion of the vein more proximally, creating satellite tumour nodules adjacent to main tumour (**Figure 1A**). Recognition that the satellite nodules are present along the venous outflow will prevent including them and overestimate the tumour size measurements or misinterpretation as tumour multifocality.[16–19]

The cut surface of renal tumours can be solid, cystic, and variegated. CCRCC classically has a golden yellow or orange cut surface[20] that often helps to differentiate it from non-clear RCC subtypes (**Figure 1B–D**). All macroscopically different appearing areas are sampled for microscopic examination. Other renal cancer types may vary in gross appearance, ranging from tan to hemorrhagic as described in more detail later.[21] Cholesterol deposition or foamy macrophages may also impart a yellow colour in non-clear cell tumours, especially papillary RCC (PRCC). When multiple tumours are present, sampling and measuring at least the 5 largest tumours and all heterogeneous tumours is recommended.[12] It is also recommended, when possible, to sample at least 1 or 2 additional sections away from the tumour to assess for medical renal disease.

Nephrectomies with thrombectomy specimens should be evaluated for tumour presence at the vein margin. Typically, the surgeon palpates the renal thrombus and ligates and/or resects the vein beyond it, without transecting the tumour thrombus. However, as the renal vein wall retracts, the tumour thrombus may be present within the lumen or beyond the vein margin. When the renal vein margin is stapled, the margin is almost always negative. The rim of the vein wall should be dissected and submitted for histologic examination. Current recommendations are for the margin to be considered positive only if the tumour is microscopically adherent to or invading the vein wall at the final tissue edge.[12,17]

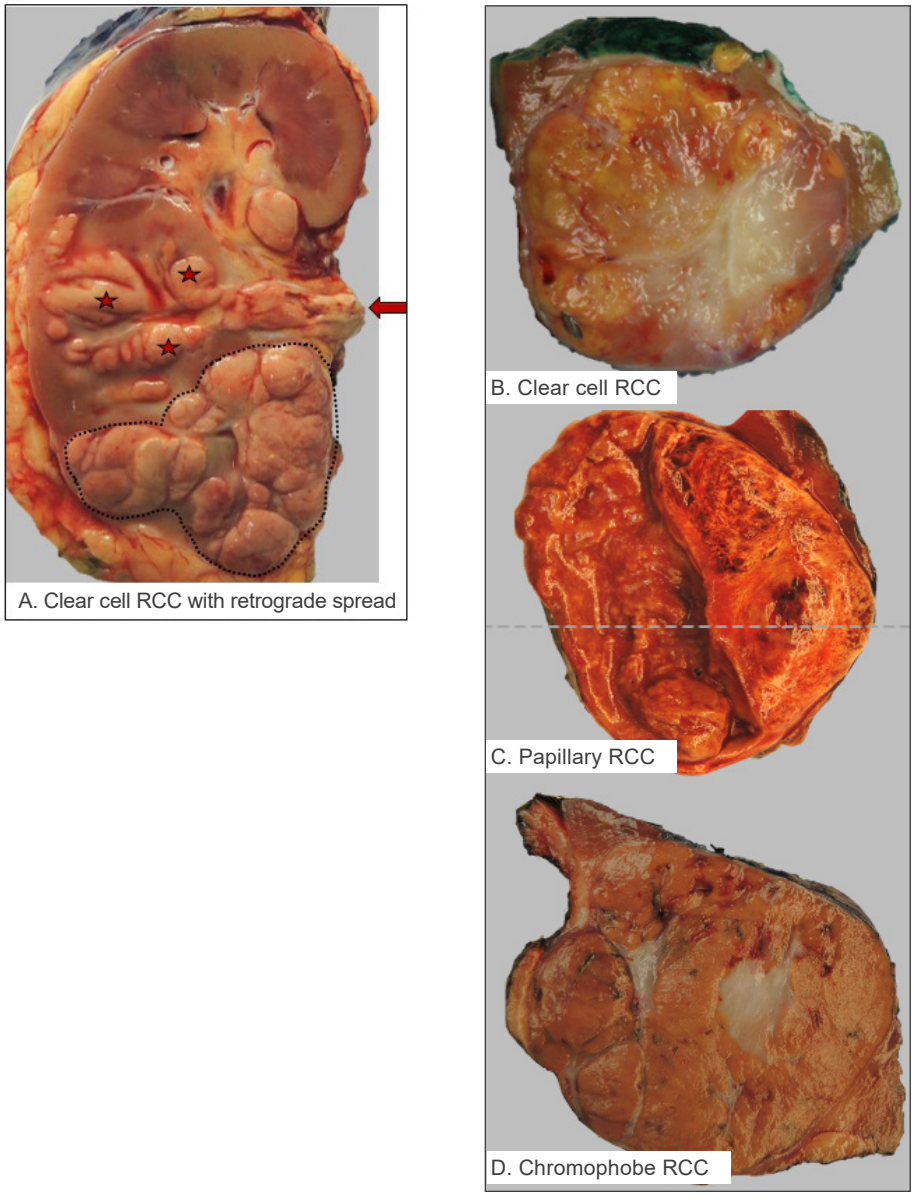
FIGURE 1 Gross photograph of the cut surface of kidneys with renal mass.

A. Gross photograph of a clear cell renal cell carcinoma (CCRCC) (encircled with dotted line) with retrograde spread and occlusive renal vein thrombus. The tumour extends into the renal vein (arrow). There are satellite nodules adjacent to the renal mass that represent retrograde spread (star) of tumour within renal vein branches.

B. Clear cell RCC with characteristic golden-yellow solid appearance. Central scar can be seen in CCRCC.

C. Papillary RCC with circumscribed mass composed of tan-to-necrotic and hemorrhagic areas.

D. Chromophobe RCC with solid-brown cut surface and a central scar, which can also be seen in oncocytoma.



Other parameters driving stage changes include direct invasion beyond Gerota fascia or directly into the adrenal gland (pT4), which is distinguished from discontinuous adrenal gland involvement (pM1). Lymph nodes are rarely palpable in conventional radical nephrectomy specimens without a separately performed lymph node dissection. Complete lymph node dissection is more frequently performed in younger patients with locally advanced disease and/or unfavourable clinical and pathologic features and offers limited survival benefit in patients with clinically node-negative RCC.[22,23] During macroscopic examination, search should be conducted for presence of grossly identifiable nodes and submitted when enlarged.[24]

Intraoperative consultation during nephrectomy is limited and largely restricted to margin assessment in partial nephrectomy and thrombectomy cases. Infrequently consultation may be obtained for diagnosis of uncharacteristic renal masses especially when multiple masses are present.[25]

Histopathologic Classification of Renal Cell carcinoma

The past four decades have witnessed significant developments in our understanding of RCC leading to a more precise histologic classification. As recently as 1975, RCC was limited to two subtypes—clear cell and granular cell RCC.[26] Increased use of molecular studies, better understanding of the biology, and careful histologic observations have expanded the classification of RCC to more than 15 entities.[5,6] Several additional novel, emerging, and evolving RCC types include eosinophilic solid and cystic renal cell carcinoma (ESC RCC), eosinophilic vacuolated tumour (EVT), low-grade oncocytic renal tumour (LOT), renal cell carcinoma with fibromyomatous stroma (RCC FMS), thyroid-like follicular renal cell carcinoma (TLF RCC), papillary neoplasm with reverse polarity, biphasic hyalinizing psammomatous renal cell carcinoma (BHP RCC) and anaplastic lymphoma kinase (ALK)-rearranged RCC. A summary of their key features is shown in **Table 1**. This updated classification will likely reduce the number of "unclassifiable renal carcinomas/tumors."

TABLE 1 Summary Features of Novel, Emerging, and Evolving Renal Entities

Type	Clinical features	Morphology	Immunohistochemistry	Molecular features
Eosinophilic solid and cystic renal cell carcinoma (ESC RCC)	Mostly in women, mostly sporadic and solitary, rare cases in TSC patients, indolent (great majority)	Solid and cystic, voluminous eosinophilic cells, cytoplasmic stippling	CK20+ CK7- CD117- Vimentin+ Cathepsin K+ (focal)	Somatic biallelic loss or mutations of *TSC1* and *TSC2*
Eosinophilic vacuolated tumour (EVT)	Broad age range, sporadic and solitary, rare cases in TSC patients, indolent	Solid, smaller tumour, tan-to-brown or grey, large vessels often found at the periphery, eosinophilic cells with frequent and prominent intracytoplasmic vacuoles, large nucleoli	Cathepsin K+ CD117+ CD10+ CK7- (only rare cells +) CK20- Vimentin-	*TSC/MTOR* mutations (all cases), deletions of chromosomes 19 and 1
Low-grade oncocytic tumour (LOT)	Older patients, sporadic and solitary, rare cases in TSC patients, indolent	Solid, smaller tumour, tan-to–mahogany brown, sharp transition to edematous areas with scattered individual cells, round to oval nuclei without irregularities and prominent nucleoli, often perinuclear halos	CK7+ (diffuse) CD117- (rarely weak +) GATA3+ (limited data) FOXI1- CK20- Vimentin-	*TSC/MTOR* mutations (almost all cases), lack of multiple chromosome losses, deletions of chromosomes 19p, 19q, and 1p (in some cases), no *CCND1* rearrangements
ELOC-mutated RCC	Mostly sporadic and solitary, indolent	Solid, smaller tumour, tan-to-brown, may have lobulated appearance, clear cells with voluminous cytoplasm forming nodules, separated, and encircled by fibromuscular stroma	CK7+ CAIX+ (membranous) CD10+ AMACR-	*ELOC* (*TCEB1*) mutation, monosomy chromosome 8

TABLE 1 Summary Features of Novel, Emerging, and Evolving Renal Entities *(Cont'd)*

Type	Clinical features	Morphology	Immunohistochemistry	Molecular features
Thyroid-like follicular renal cell carcinoma (TLF RCC)	Broad age range including children, solitary, mostly indolent	Thyroid-like follicular arrangement, follicles of variable size with eosinophilic luminal content, lining cells cuboidal to cylindrical	CK7+ Pax8+ Vimentin- TTF1- Thyroglobulin-	Fusion of *EWSR1-PATZ1* found in 3 cases, no other specific findings
Biphasic hyalinizing psammomatous renal cell carcinoma (BHP RCC)	Adult patients, about half of tumours with aggressive clinical course	Tubulo-papillary architecture, prominent fibrotic-to-hyalinized stroma and microcalcifications, heterogeneous morphology	CK7+ PAX8+ CD10+ HMB45- Melan-A-	*NF2* abnormalities in majority of cases, loss of chromosome 22 in some cases
Anaplastic lymphoma kinase rearrangement–associated renal cell carcinoma (ALK RCC)	Broad age range, solitary tumour, some in patients with sickle cell trait	Diverse (variable admixed patterns), often mucinous/myxoid background, medullary carcinoma-like morphology in children	ALK+ Other IHC nonspecific Rare cases TFE3+ (without translocation)	*ALK* rearrangement Fusion partners: *VCL, HOOK1, STRN, TPM3, EML4, PLEKHA7, CLIP1, KIF5B*, and *KIAA1217*

WHO updates and latest classification

Last decade witnessed a burgeoning categorization of renal tumours at the molecular level. Not surprisingly, some molecularly defined entities have associated morphological features. Recognizing the importance of genotype-phenotype correlations, a hybrid system for renal tumour classification has been adapted in the fifth edition of the WHO.[27] Traditionally defined entities by tumour morphology and IHC such as CCRCC, PRCC, ChRCC, etc., have been maintained. While these entities have been categorized as "morphologically defined," they all harbour characteristic molecular signatures.[28] In addition, a new category of molecularly defined RCCs such as TFE3-rearranged RCC, TFEB-altered RCC, ELOC (TCEB1)-mutated RCC, FH-deficient RCC, succinate dehydrogenase (SDH)-deficient RCC, ALK-rearranged RCC, and SMARCB1(INI1)-deficient RMC have been created, to underscore the significance of molecular testing for definite diagnosis. Most molecularly defined RCCs have morphologies and/or IHC features that raise the diagnosis, but they alone do not define them. Their accurate diagnosis requires strict genotypic-phenotypic analyses.

The developing entity of RCC FMS has been reported to harbour pathogenic/predicted to be pathogenic mutations in *TSC1*, *TSC2*, or *MTOR*. Unfortunately, it shares morphological features with ELOC-mutated RCC and a subset of CCRCC. Given their overlapping morphology but diverse biology, RCC FMS has been a subject of some debate. As such, it is considered by the WHO as a newly proposed emerging entity that needs further investigation.

Some entities previously classified as "type 2 PRCC" or "unclassified RCC" are now known to have unique molecular characteristics and morphologic correlates, such as FH-deficient RCC, TFE3-rearranged RCC, TFEB-altered RCC, and ESC RCC. In the fifth edition of WHO, "type 1 PRCC" is regarded as the classic PRCC and subtyping into type 1 and 2 is not recommended.

Lastly, the nomenclature of clear cell papillary RCC has been changed to clear cell papillary renal cell tumour (CCPRCT) to distinguish it from malignant renal tumours, as no metastasis have been reported since their initial description in 2006.

Microscopic considerations

RCCs are malignant tumours of renal tubular origin that represent a morphologically and biologically heterogeneous group of tumours. The RCC subtypes are discussed in some detail below.

Morphologically defined entities

Clear cell renal cell carcinoma

Making up 70% of all RCC and one of the more aggressive subtypes, CCRCC is molecularly characterized by biallelic *VHL* (3p25.3) inactivation.[29–31] The parietal epithelial cells of bowman capsule and adjacent proximal

nephron have been proposed to be the cell of origin of CCRCC.[32,33] The majority of CCRCC occurs sporadically in older adults with male predominance.[34] Rarely they occur in young adults except in syndromic settings (most commonly von Hippel-Lindau [VHL] syndrome), where they present as multiple tumours that are often bilateral.[35] NCCN guidelines now recommend evaluation for genetic predisposition in individuals diagnosed 46 years or younger (www.nccn.org/guidelines).

Macroscopically, CCRCC occurs as an expansile cortical mass that has a variegated cut surface and focal golden yellow colour due to the high intracytoplasmic lipid (**Figure 1B**). Degenerative changes, hemorrhage, and necrosis are often present at the centre, especially in large tumours. Firm white areas may represent high-grade or sarcomatoid differentiation and should always be sampled. CCRCC principally spreads through the vascular (hematogenous) route that often includes an extension into the renal sinus.[9,11,36]

Microscopically, CCRCC exhibits a wide spectrum of patterns.[37,38] The prototype is made up of small nests of tumour cells with clear cytoplasm surrounded by an intricate capillary network (**Figure 2A**). Large tumours often have morphologically heterogeneous areas, possibly correlating with subclones exhibiting different architectural and cytologic patterns (i.e., papillae formation, anaplasia, sarcomatoid or rhabdoid features, and adenocarcinoma-like morphology).[39,40] Presence of these patterns alone in needle biopsy specimens may necessitate ancillary testing for diagnosis.

Although there is no diagnostic IHC marker entirely specific for CCRCC, given the characteristic *VHL* inactivation and resulting activation of hypoxia-inducible factor (HIF), the downstream effector, carbonic anhydrase IX (CAIX), has been used to support the diagnosis. Diffuse membranous CAIX positivity is reported in up to 90% of CCRCC (**Figure 2B**).[41–44] However, focal or even diffuse CAIX staining can be seen in other tumours, especially when associated with hypoxia and necrosis.[45] CCRCC expresses both epithelial (low-molecular weight cytokeratin) and mesenchymal markers (vimentin). CK7 is usually negative or focal, but even diffuse staining does not exclude the diagnosis.[46]

Molecularly, CCRCC is characterized by large deletion of chromosome 3p, where *VHL* is located, and gain of 5q, through a process referred to as chromothripsis. Loss of 3p results in loss of one allele of several other tumour suppressor genes often mutated in CCRCC: *SETD2*, *BAP1*, and *PBRM1*. Other genes mutated in CCRCC include *KDM5C*, *TSC1, TSC2, MTOR*, *PIK3CA*, *PTEN*, *TP53*, and *KDM6A*.[30,47–49]

TABLE 2 Differentiating Characteristics and Immunohistochemistry for RCCs with Clear Cell Features

A. Tumours with prominent clear cytoplasm				
Histologic subtype	**Unique morphologic features**	**Characteristic positive markers**	**Pertinent negative markers**	**Molecular characteristics**
Clear cell RCC	Nested pattern surrounded with vascular network and cells with optically transparent cytoplasm	CAIX (diffuse membranous)	CD117	Loss of 3p25 and VHL inactivation
Chromophobe RCC (classic type)	Trabecular and sheets, clear and eosinophilic cells with thick cell border, wrinkled nuclear membrane	CD117 CK7	CAIX Vimentin	Chromosomal losses (1, 2, 6, 10, 13, 17, and 21)
TFE3- or TFEB-rearranged RCC	Solid, alveolar and papillary, psammoma bodies, clear and eosinophilic cells, often grade 3 nuclei	TFE3/TFEB Melan-A Cathepsin K	CK EMA	*TFE3, TFEB, MITF* rearrangement
Clear cell papillary RCT	Cystic and solid, papillary and branched glands, low-grade nuclei and clear cytoplasm, nuclei away from the basement membrane	CAIX (cup-like) CK7 (diffuse positive) HMWCK	CD10 AMACR	None
ELOC-mutated RCC	Tubulopapillary architecture, clear cytoplasm, prominent fibromyomatous stroma	CAIX CK7 CD10 HMWCK Vimentin	AMACR	*ELOC1 (TCEB1)* mutations, chromosome 8 monosomy
Papillary RCC	Papillary and tubular, psammoma bodies, foamy macrophages in fibrovascular stack, often with basophilic cytoplasm	CK7 (less in eosinophilic tumours) AMACR CD10 (luminal)	CAIX (not diffuse)	Gain of chromosomes 7 and 17, MET alterations

TABLE 2 Differentiating Characteristics and Immunohistochemistry for RCCs with Clear Cell Features *(Cont'd)*

B. Tumours with prominent papillary architecture				
Histologic subtype	**Unique morphologic features**	**Characteristic positive markers**	**Pertinent negative markers**	**Molecular characteristics**
Papillary RCC	Papillary and tubular, psammoma bodies	CK7 AMACR CD10 (luminal)	CAIX (not diffuse) CD117 BRAF (V600E)	Gain of chromosomes 7 and 17, MET alterations
Clear cell papillary RCT	Cystic and solid, papillary and branched glands, low-grade nuclei and clear cytoplasm, nuclei away from the basement membrane	CAIX cup-like CK 7-diffuse positive	CD10 AMACR	None
FH-deficient RCC	Papillary, tubulocystic architecture, prominent inclusion-like nucleoli	AMACR 2SC (cytoplasmic and nuclear) BAF47	FH loss	Germline and/or somatic inactivation of *FH*
TFE3- or TFEB-rearranged RCC	Solid, alveolar and papillary, psammoma bodies, clear and eosinophilic cells, often grade 3 nuclei	TFE3/TFEB Melan-A Cathepsin K	CK, EMA	*TFE3, TFEB, MITF* rearrangement
Mucinous tubular and spindle cell carcinoma	Cuboidal cells arranged in tubules, spindle cells arranged in whorls and streams, myxoid stroma	AMACR CK7 INI1 FH	CD10 AMACR	Multiple chromosomal losses (1, 4, 6, 8, 9, 13, 14, 15, and 22) and VSTM2A RNA expression
Collecting duct carcinoma	Infiltrative adenocarcinoma with tubulopapillary pattern, prominent desmoplastic stroma, necrosis	FH BAF47/INI1 PAX8 EMA	CAIX GATA3 p63 TTF1, CK20	None

TABLE 2 Differentiating Characteristics and Immunohistochemistry for RCCs with Clear Cell Features *(Cont'd)*

C. Tumours with prominent eosinophilic cytoplasm				
Histologic subtype	**Unique morphologic features**	**Characteristic positive markers**	**Pertinent negative markers**	**Molecular characteristics**
Chromophobe RCC (eosinophilic type)	Eosinophilic cells with thick cell border, wrinkled nuclear membrane	CD117 CK7 (often focal)	CAIX Vimentin	Chromosomal losses (1, 2, 6, 10, 13, 17, and 21)
Renal oncocytoma	Nested pattern, pink granular cytoplasm, round nuclei, smooth nuclear membrane, hypocellular stroma		CK7 (more than focal) Vimentin	Diploid, CCND1 rearrangement, chromosome 1, 14 and Y deletions
FH-deficient RCC	Papillary, tubulocystic architecture, prominent inclusion-like nucleoli	AMACR 2SC (cytoplasmic and nuclear) BAF47/INI1/hSNF5	FH	Germline and or somatic inactivation of *FH*
SDH-deficient RCC	Sheet or nests of cuboidal cells with fine eosinophilic cytoplasm, cytoplasmic inclusion with pale material		SDHB CD117	Germline and somatic mutations in *SDHB, SDHC, SDHA, SDHD*
Acquired cystic disease–associated RCC	Cribriform architecture, cells with eosinophilic cytoplasm, intracytoplasmic vacuoles, calcium oxalate crystals	AMACR CD10	CK7 GATA3 CD117	Chromosomal gains (3, 16), mutations in *KMT2C, TSC2*
Eosinophilic solid and cystic (ESC) RCC	Solid and cystic architecture, cells with abundant eosinophilic cytoplasm, coarse cytoplasmic granules/stippling	CK20 Cathepsin K Vimentin Melan-A	CD117 CK7	Biallelic loss of *TSC1* or *TSC2*
Eosinophilic vacuolated tumour (EVT)	Solid, eosinophilic cytoplasm with large vacuoles, large nucleoli	CD117 Cathepsin K	CK20 Vimentin CK7	*TSC2*, *MTOR* mutations and loss of chromosome 1

TABLE 2 Differentiating Characteristics and Immunohistochemistry for RCCs with Clear Cell Features *(Cont'd)*

C. Tumours with prominent eosinophilic cytoplasm *(Cont'd)*				
Histologic subtype	**Unique morphologic features**	**Characteristic positive markers**	**Pertinent negative markers**	**Molecular characteristics**
Low-grade oncocytic tumour (LOT)	Solid, uniform eosinophilic cells with low-grade nuclei and subtle perinuclear halos, sharp transition to lose edematous areas	CK7 (diffuse)	CD117 FOX1	TSC1, MTOR, RHEB mutations, loss of chromosome 19
Papillary RCC (eosinophilic)	Papillary and tubular, psammoma bodies	CK7 (less in eosinophilic tumours) AMACR CD10 (luminal)	CAIX (not diffuse) CD117	Gain of chromosomes 7 and 17, MET alterations
TFE3- or TFEB-rearranged RCC	Solid, alveolar and papillary, psammoma bodies, clear and eosinophilic cells, often grade 3 nuclei	TFE3/TFEB Melan-A/HMB-45 (in TFEB-RCC) Cathepsin K (less often in TFE3-RCC)	CK EMA	*TFE3, TFEB, MITF* rearrangement

TABLE 2 Differentiating Characteristics and Immunohistochemistry for RCCs with Clear Cell Features *(Cont'd)*

D. Tumours with poorly differentiated histology			
Histologic subtype	**Unique morphologic features**	**Characteristic positive markers**	**Pertinent negative markers**
Clear cell RCC (high grade)	Any component of classic nested pattern surrounded with vascular network	PAX8 CAIX (diffuse membranous) CK AE1/AE3 Vimentin	p63 CK20 HMB45/Melan-A Inhibin, TTF-1, GATA3
SMARCB1-deficient RMC	Infiltrative adenocarcinoma with prominent rhabdoid morphology, desmoplastic stroma, necrosis and neutrophils, sickled RBCs in vascular spaces	CK7 (focal) AMACR (focal) Oct3/4	BAF47/INI1/hSNF5
Collecting duct carcinoma	Infiltrative adenocarcinoma with tubulopapillary pattern, prominent desmoplastic stroma, necrosis	FH BAF47/INI1/hSNF5 PAX8 EMA	CAIX GATA3 p63 TTF1, CK20
Anaplastic lymphoma kinase (ALK)–rearranged RCC	Heterogeneous morphology with areas of medullary carcinoma–like areas and mucinous background	ALK TFE3 BAF47	
Epithelioid angiomyolipoma	Disintegrating epithelioid cells, thick-walled vessels	HMB45/Melan-A Cathepsin K SMA (positive in some cases)	PAX8 CK
Metastatic carcinoma	Variable	Variable	PAX8/PAX2 (except thyroid, urothelial, female genital tract)

TABLE 2 Differentiating Characteristics and Immunohistochemistry for RCCs with Clear Cell Features *(Cont'd)*

D. Tumours with poorly differentiated histology *(Cont'd)*			
Histologic subtype	**Unique morphologic features**	**Characteristic positive markers**	**Pertinent negative markers**
Adrenal cortical carcinoma	Sheets of clear to eosinophilic cells with bubbly cytoplasm, patchy pleomorphic nuclei	Inhibin alpha Calretinin SF-1 Melan-A/MART-1 Synaptophysin	PAX8 CK
Urothelial carcinoma	Papillary architecture or keratinization	GATA3 p63 HMWCK (34βE12) CK20 CK7	PAX8 (can be positive)

The differential diagnosis for low-grade CCRCC includes CCPRCT, multilocular cystic renal neoplasm of low malignant potential (MCNLMP), ELOC-mutated RCC, and PRCC with clear cytoplasm. CK7, CD10, and CAIX can help in this differential diagnosis (**Table 2A**).[50] High-grade CCRCC can sometimes be difficult to differentiate from MiT family translocation RCC, ChRCC, epithelioid angiomyolipoma, metastasis from other epithelial tumours, as well as urothelial and adrenal cortical tumours (**Table 2D**). Focal areas with typical CCRCC morphology in otherwise high-grade cases can be helpful in the diagnosis. In VHL syndrome, multiple tumours, tumourlets, and cysts lined by similar clear cells may be observed.[51]

Multilocular cystic renal neoplasm of low malignant potential

MCNLMPs (previously called multilocular cystic RCCs) are multiloculated cysts lined by few layers of low-grade clear cells and may include small clusters (without expansion of the septae) of similarly clear cells within fibrous septae.[52,53] They are often small cystic masses that are diagnosed incidentally and constitute about 10% of all cystic renal tumours.[54] Akin to CCRCC, MCNLMPs have *VHL* gene alterations, can occur in VHL syndrome patients, and have similar IHC profile.[55,56] MCNLMPs are indolent tumours with no reported metastasis and could be managed by active surveillance.[57,58]

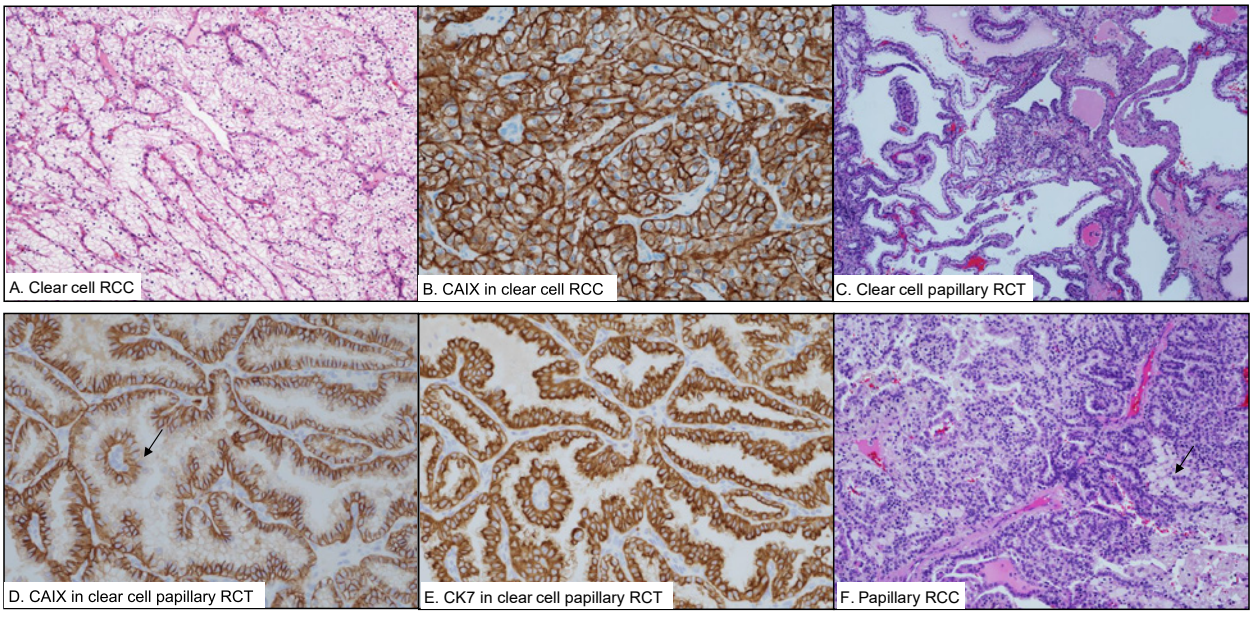
The differential diagnosis includes predominantly cystic CCRCC, tubulocystic (TC) RCC, CCPRCT, cystic nephroma, and localized renal cystic disease. CCRCC with prominent cystic change may be sometimes difficult to distinguish from MCNLMP. In this context, CCRCC is characterized by distinct and expansile solid tumoural nodules that exceed 1 mm (and are typically grossly visible), often with features suggestive of tumour regression/hyalinization. A definite diagnosis by biopsy is therefore not possible. The cystic areas in both CCRCC and MCNLMP can have prominent CK7 staining.[59]

Clear cell papillary renal cell tumour

CCPRCT (previously referred to as clear cell papillary RCC) accounts for 2–4% of all renal tumours. These tumours occur both sporadically and in end-stage renal disease settings, and patients may present with multiple tumours.[60–62] They are indolent tumours, with no reported cases of metastasis. However, given their occurrence in end-stage kidney disease and as multiple tumours, their management can sometimes be challenging.

FIGURE 2 Microscopic features of morphologically defined RCCs.

A. Clear cell RCC (CCRCC) with prototypic architecture of nests of tumour cells with clear cytoplasm surrounded by interconnecting vascular network (100x magnification).
B. Immunohistochemical (IHC) staining for CAIX with diffuse membranous positivity in a case of CCRCC (200x magnification).
C. Clear cell papillary renal cell tumour (CCPRCT) with cystic and papillary architecture. The cells are small with a clear cytoplasm. Nuclei are of low grade and are characteristically aligned away from the basement membrane (40x magnification).
D. CAIX shows diffuse cup-shaped distribution of positivity in CCPRCT (arrow). There is absence of staining along the luminal border of the tumour cells, in contrast to the pattern seen in CCRCC (200x magnification).
E. IHC staining for CK7 typically shows diffuse strong positivity in CCPRCT. This is in contrast to CCRCC, which is mostly negative for CK7 (200x magnification).
F. Papillary RCC showing papillary fronds with fibrovascular cores that are lined by columnar cells with scant clear-to-amphophilic cytoplasm (typical of type 1). The fibrovascular cores focally have numerous foamy macrophages (arrow), which are especially common in low-grade tumours (100x magnification).



Morphologically CCPRCT has a tubulopapillary and cystic architecture. CCPRCTs are composed of cells with clear cytoplasm and low-grade nuclei oriented away from the basement membrane in a linear pattern (**Figure 2C**). Like CCRCC, they have diffuse CAIX expression, but characteristically in a "cup-like" distribution without staining of the luminal surface (**Figure 2D**).

The differential diagnosis includes CCRCC, PRCC, ELOC-mutated RCC, and tuberous sclerosis complex (TSC)-associated (tubulopapillary) RCC (**Table 2A**). CCPRCTs can be differentiated from CCRCCs and PRCCs by their diffuse CK7 expression (**Figure 2E**) and lack of AMACR and CD10 expression. They can be distinguished molecularly by the absence of the characteristic mutations and copy number changes seen in CCRCC and PRCC. Instead, CCPRCTs have been shown to exhibit severe mitochondrial DNA depletion.[61,62] Tumours with CCPRCT histology have been reported in patients with VHL syndrome and are more closely genomically related to CCRCC. Both ELOC-mutated RCC and TSC-associated (tubulopapillary) RCC can have prominent fibromyomatous stroma that may also be observed in CCPRCT. Exclusion of RCCs with mutations in *TSC1/TSC2/MTOR* and *ELOC* may sometimes be necessary in this setting to establish the diagnosis.[63]

Papillary renal cell carcinoma

PRCC represents about 15% of all renal cell tumours and is the second most common renal carcinoma after CCRCC. The proximal nephron has been proposed to be the cell of origin of PRCC.[33] Tumours are typically well circumscribed, with or without a fibrous capsule. While multifocal or bilateral tumours are not infrequent, even in sporadic settings (such as in patients with chronic renal disease), the presence of numerous papillary tumours and small papillary adenomas would raise the suspicion of hereditary papillary renal cell carcinoma syndrome.

PRCCs have been traditionally subdivided into two histologic types. “Type 1” has fibrovascular cores covered by single-layered tumour cells typically with amphophilic cytoplasm and low-grade nuclei (**Figure 2F**). “Type 2” is characterized by pseudostratified, often large tumour cells with higher nuclear grade and eosinophilic cytoplasm. However, tumours with “type 2” morphology show significant variability in their features and clinical behaviour. Importantly, many tumours with prominent papillary architecture that may have been considered “type 2” PRCC, are now being recognized as distinct molecular or histologic types, such as FH-deficient RCC, MiT family translocation RCC, ALK-rearranged RCC, and acquired cystic disease–associated RCC (ACD-RCC).[64,65] Results from recent analyses of large PRCC cohorts argue against the clinical significance of “type 1 and 2” subtyping, while supporting the prognostic value of WHO/ International Society of Urologic Pathology (ISUP) grade.[66,67] Based on this conceptual change, in the 5th edition of WHO, the former “type 1” PRCC is regarded as the classic PRCC, and subtyping into type 1 or 2 is no longer recommended. Other parameters with prognostic value in PRCC typically include pathologic stage and lymphovascular invasion.

The morphologic spectrum of PRCC can be broad, and few recognizable patterns have been described as morphologic variants, such as solid, biphasic (alveolar/squamoid), Warthin-like PRCC (tumour mimicking Warthin tumour of the salivary gland), and papillary neoplasms with reverse polarity.[5] While most PRCCs show diffuse positivity for CK7 and AMACR, these markers lack specificity, and CK7 can show variable to minimal staining, especially in eosinophilic tumours.

The differential diagnosis is broad. For the low-grade spectrum (for classic PRCC), this includes papillary adenoma (size cutoff, 1.5 cm), metanephric adenoma, mucinous tubular and spindle cell carcinoma (MTS RCC), and CCPRCT. For the high-grade cases, it is important to exclude tumour types with prominent papillary

architecture, such as FH-deficient RCC, MiT family (TFE3/TFEB) translocation RCC, ALK-rearranged RCC, ACD-RCC, CCRCC with papillary architecture, tubulocystic RCC (TC RCC), SMARCB1-deficient RMC, and CDC. Identifying focal areas with classic PRCC morphology in otherwise high-grade cases can be helpful. The definitive diagnosis may also require specific ancillary studies (e.g., FH/2-succinocysteine [2SC] IHC, TFE3/TFEB IHC) or molecular analysis (e.g., TFE3/TFEB FISH, copy number alterations, mutations) (**Table 2B**).

Molecularly, the large majority of sporadic PRCCs are characterized by gains or trisomy of chromosomes 7 and 17 and less frequent gain of chromosomes 2, 3, 12, 16, and 20.[64] Mutations of the *MET* gene (7q31), which are paradigmatic of hereditary PRCC, are also found in 10–13% of sporadic cases.[64,68] In PRCC with mixed "type 1 and 2" features, "type 2" may represent a morphologic variant and the product of subclonal evolution.[67] Mutations of *TP53* and *PBRM1*, as well as alterations of *CDKN2A*, are associated with poor survival in PRCC.[69]

Chromophobe renal cell carcinoma

Chromophobe renal cell carcinoma (ChRCC) is the third most common subtype, accounting for approximately 5% of RCCs.[34,70–72] These tumours are thought to originate from the intercalated cells of the distal tubules.[73,74] Most occur as sporadic tumours in adults, and rarely in a hereditary setting (such as, Birt-Hogg-Dubé (BHD) syndrome and Cowden syndrome).[75,76]

Macroscopically, ChRCCs are frequently large, with a mean size of nearly 7 cm, but most remain confined to the kidney. The tumours are typically well circumscribed and with tan to light brown cut surface. Microscopically, two morphologic subtypes have been described—classic and eosinophilic. ChRCC is composed of sheets of cells separated by thin septae. Infrequent architectures include trabeculae, small cysts, nests, and variably sized tubules. The cells have a classic "plant cell–like" appearance, with distinct cell membranes and alternating clear and eosinophilic cytoplasm. Nuclei vary in size and shape, and many have marked nuclear irregularities (raisinoid or koilocytotic appearance) and perinuclear halos (**Figure 2G**). The eosinophilic variant of ChRCC is composed of cells with exclusively eosinophilic cytoplasm but maintains the nuclear features of ChRCC (**Figure 2H**). In 2–8% of cases, sarcomatoid differentiation can occur, often including pleomorphic cells.[77,78] Localized ChRCCs have a favourable outcome. However, large size, coagulative necrosis, vascular invasion, and sarcomatoid change have been associated with metastasis and adverse prognosis.

FIGURE 2 Microscopic features of morphologically defined RCCs. *(Cont'd)*

G. Chromophobe RCC, classic type with sheets of neoplastic cells that have abundant clear and eosinophilic cytoplasm admixed together. The cells are separated by incomplete vascular septation and lack the encircling vascular network seen in CCRCC. The cells have prominent cell borders and hyperchromatic wrinkled nuclei (100x magnification).

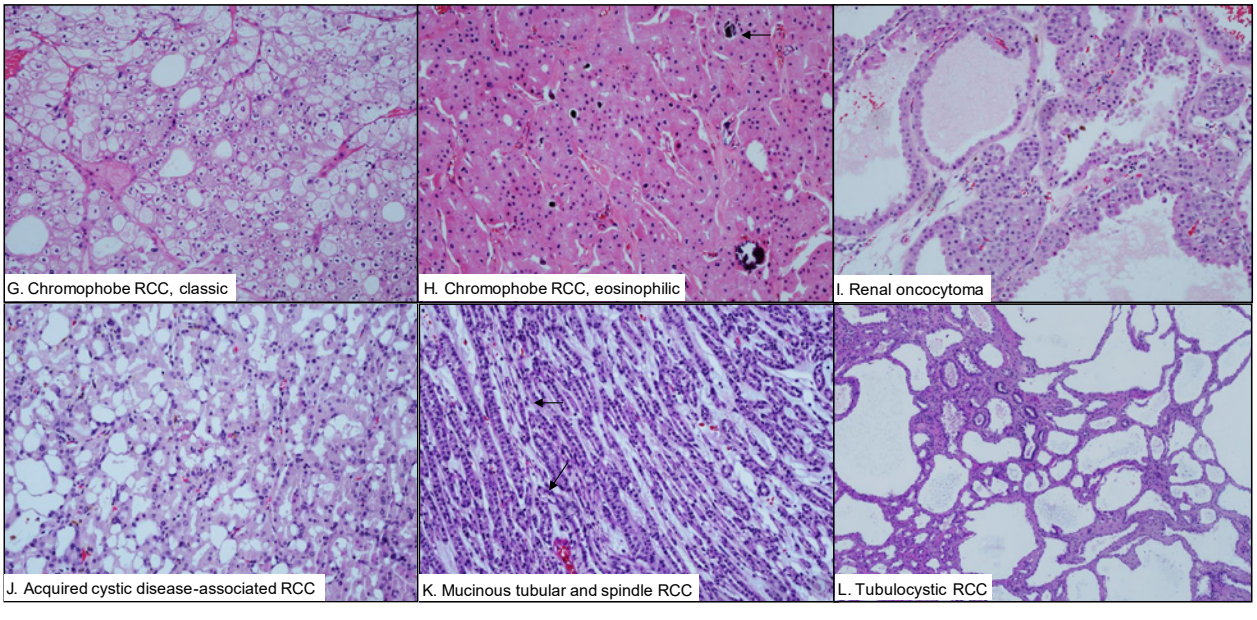
H. Chromophobe RCC, eosinophilic type is composed exclusively of cells with eosinophilic cytoplasm. Nuclear features including nuclear membrane irregularities and perinuclear cytoplasmic clearing (halos) are present. Microcalcifications (arrow) are not uncommon in both subtypes (100x magnification).

I. Renal oncocytoma with nests and microcysts of oncocytic cells that have an eosinophilic granular cytoplasm and round uniform nuclei surrounded by loose edematous hypocellular stroma (100x magnification).

J. Acquired cystic disease–associated RCC showing the characteristic cribriform or sieve-like appearance. The cells are large and have eosinophilic cytoplasm. This tumour arose from the wall of a cyst in a kidney with end-stage disease (100x magnification).

K. Mucinous tubular and spindle cell carcinoma exhibiting long tubules that have narrow slit-like lumina, bland spindle cells (arrow) that are intimately admixed with the tubular component and prominent myxoid stroma (100x magnification).

L. Tubulocystic carcinoma composed exclusively of cysts and tubules that are lined by a single layer of cuboidal cells with eosinophilic cytoplasm and grade 2–3 nuclei (40x magnification).



Immunohistochemically, ChRCCs show diffuse CD117 (KIT) membranous staining, membranous e-cadherin, cytoplasmic CK7 (may be patchy in eosinophilic ChRCC), and nuclear PAX8. Tumours are negative for CAIX and vimentin, but may express CD10 in a minority.[44] ChRCC shares a similar immunophenotype with oncocytoma, except that the latter typically shows only rare scattered cells with CK7 expression. Genomically, classic ChRCC shows chromosomal losses of 1, 2, 6, 10, 13, 17, and 21, and mutations in the *TP53, PTEN,* and *TERT* promoter. In contrast, the eosinophilic variant is less complex, with few or no alterations.[79–82]

The diagnosis of ChRCC with predominantly clear cells is usually straightforward, but in limited cases, may need to be differentiated from CCRCC (**Table 2A**). The differential for eosinophilic tumours is broad and includes oncocytoma, LOT, EVT, and PRCC with prominent eosinophilia. IHC may be helpful in this setting (**Table 2C**).

Renal oncocytoma and other oncocytic renal neoplasms

Renal oncocytomas (ROs) are benign renal tumours that are characterized grossly by a mahogany brown colour and frequently have with a central stellate scar that stems from a hypocellular hyalinized and loose stroma. Microscopically, they have a solid, nested, or cystic architecture. The neoplastic cells are round to polygonal, with granular eosinophilic cytoplasm and round uniform nuclei (**Figure 2I**). Multiple ROs, including microscopic ones, can also occur ("oncocytosis").[83] Interestingly, fat and vascular invasion can be seen in RO but do not influence its "benign" course.[84] ROs are uniformly CD117 positive. Vimentin is consistently negative, except in areas of scar or fibrosis, and CK7 stains only scattered tumour cells or clusters of cells.

Molecularly, RO frequently has a normal karyotype.[81] Using exome and transcriptome sequencing two main subtypes of RO have been identified. Type 1 is diploid with *CCND1* rearrangement, and Type 2 is hypodiploid with losses of chromosome 1, X/Y, and/or 14 and 21.[85] However, these molecular "types" have no recognizable phenotypic differences and have the same indolent clinical behaviour.

The differential diagnosis of oncocytic renal tumors includes RO, a benign entity; hybrid oncocytic chromophobe tumour (HOCT), typically occurring as multiple/bilateral tumours associated with BHD syndrome;[71,84,86,87] and a group of renal oncocytic neoplasms that show morphologic and IHC overlap with oncocytoma-eosinophilic ChRCC. This heterogeneous group of sporadic tumours requires further characterization but typically has an indolent clinical behaviour.[5] For such sporadic oncocytic tumours, the term "oncocytic renal neoplasm of low malignant potential, not further classified" was recommended by GUPS.[5]

Acquired cystic disease–associated renal cell carcinoma

ACD-RCC occurs exclusively in patients with acquired cystic disease on long-term dialysis. Its increased occurrence with duration of hemodialysis and male gender have been reported.[62,88,89] Though the vast majority of ACD-RCCs do not have an aggressive clinical course, rare cases have been associated with metastatic disease.[89,90]

ACD-RCC is frequently multifocal and bilateral. Grossly, most form an intracystic mass; however, tumours without any anatomic relation to a renal cyst may occur. On cut section, the tumours are brown to yellow-tan, with areas of hemorrhage or necrosis.[62,88–90] ACD-RCCs are characterized by cribriform "sieve-like" architecture with multiple glandular lumina. However, papillary, solid, microcystic, and tubulopapillary patterns are frequently encountered. Tumour cells have an eosinophilic cytoplasm with intracytoplasmic vacuoles and prominent nuclei (**Figure 2J**). The tumours may have cysts lined by identical neoplastic cells.[62,89,90] Calcium oxalate crystals are typical. However, these can be rare or even absent in some cases.

The immunohistochemical profile is variable; however, ACD-RCCs are usually positive for PAX8, CD10, and AMACR and negative for GATA3, CK7, and CD117 (KIT).[62,89,90] Though molecular genetic data are sparse, recurrent mutations in *KMT2C* and *TSC2* have been documented.[91]

Mucinous tubular and spindle cell carcinoma

MTS RCC represents <1% of RCCs in adults and occurs in a broad age range including pediatric patients. They are more frequent in women and rarely metastasize.[92–94]

The tumours are usually well demarcated, without a capsule, and gray to tan on cut section.[92] The characteristic architecture is a combination of spindle cells arranged in whorls and streams, and cuboidal cells arranged in tubules. Tubules are filled by bluish mucin or solid structures amid a myxoid stroma (**Figure 2K**). The stromal component can be inconspicuous. Both epithelial and spindled cells are cytologically bland and of low nuclear grade. Rare MTS RCC with high-grade nuclei have also been reported.[95,96] Tumours with overlapping morphology between PRCC and MTS RCC are frequent, and a papillary architecture favours PRCC.[94,97,98] Sarcomatoid differentiation is rare.[99]

MTS RCCs are positive for PAX8, CK7, AMACR, and vimentin.[5,100] They are characterized by multiple chromosomal losses (1, 4, 6, 8, 9, 13, 14, 15, and 22). In contrast to PRCC, polysomies (particularly of chromosome 7 and 17) are uncommon.[84,101] Recently, V-set and transmembrane domain containing 2A (*VSTM2A*) RNA expression by in situ hybridization was reported as a diagnostic marker for MTS RCC.[102]

Tubulocystic renal cell carcinoma

TC RCCs are rare (<1%) and have male predominance. Most patients are over 50 years (range, 30–74 years).[103–105] Most tumours are diagnosed incidentally, and metastatic disease is rare.[106]

TC RCC is well circumscribed, solitary, with a brown-to-tan, spongy, or honeycomb cut surface. Histologically, TC RCCs are composed exclusively of variably sized cysts, lined by cuboidal-to-columnar cells, rarely with hobnailing (**Figure 2L**). The cytoplasm is usually pale to eosinophilic. The nuclei are round to oval and have prominent nucleoli (equivalent to WHO/ISUP grade 3).[103–107] Tumours with tubulocystic growth and papillary patterns, or other architectural patterns, as well as high-grade features, should raise the possibility of other diagnoses,

particularly FH-deficient RCC and PRCC. A low threshold for performing FH and/or 2SC is recommended, and FH must be retained to make the diagnosis of TC RCC.[107] TC RCC is positive for CK7, CD10, vimentin, and AMACR.

Collecting duct carcinoma

CDC is typically a noncapsulated, poorly defined, infiltrating tumour, often located in the renal medulla. CDC has a grey-white and firm cut surface.[108–111] Histologically, CDC has a predominantly tubular architecture and high-grade nuclei, and the epithelial component is set in a desmoplastic stroma, frequently admixed with inflammatory cells. Histologic variability is common, and the tumors can have solid, nested, sheet-like, or trabecular patterns. The tumour cells often infiltrate around glomeruli, and sometimes follow the tubular system of the kidney (thigmotactic growth pattern). The neoplastic cells are typically high grade, with eosinophilic cytoplasm, but they can also be clear. Hobnail-shaped cells are particularly common. Mitotic activity is brisk. Sarcomatoid differentiation and rhabdoid cells are frequently present.[111] Angioinvasion and/or lymph node metastases are common at the time of diagnosis.[108–111]

Prior to making the diagnosis of CDC, metastases from another epithelial tumour, urothelial carcinoma, SMARCB1-deficient RMC, FH-deficient RCC, and high-grade RCC of any type should be excluded.[108,109] CDC is not associated with either hemoglobinopathy or *SMARCB1* abnormality, in contrast to RMC.[5,109,110]

CDC is positive for CK7, CK19, CK903 (34βE12), and PAX8. SMARCB1 and FH should be retained (normal expression).[44,111]

Renal cell carcinoma, not further specified

RCC, NOS (referred to also in the literature as RCC unclassified) is a diverse group of renal tumours that does not fit any currently recognized diagnostic category. These tumours account for less than 5% of all RCCs.[112] As such, these tumours are heterogeneous, and the morphology and IHC profiles are highly variable.[113–116] It is important to rule out an extrarenal or urothelial origin. Some use this diagnosis only for high-grade RCC; however, both low-grade and high-grade renal tumours may be unclassified with a comment on whether they are likely to be low grade (indolent behavior) or high grade. With the increased number of new and emerging entities, this category has significantly been reduced. It is likely that molecular studies will allow us to classify these tumours more precisely in the future.

Molecularly defined entities

MiT family translocation RCC

The microphthalmia transcription (MiT) family translocation RCCs are driven by activating gene fusions involving predominantly transcription factor E3 (TFE3), located at Xp11.2; transcription factor EB (TFEB), located at 6p21[117] and rarely micropthalmia transcription factor (MITF), located at 3p13.[81,118] TFE3 and TFEB frequently

heterodimerize and bind to same target genes and functionally overlap. Collectively, MiT family members regulate pathways such as autophagy, lysosome biogenesis, and cell metabolism, which are indispensable for cellular homeostasis.[119]

They represent up to 40% of pediatric and 5% of adult RCCs,[81,120–122] and commonly occur at a younger age, with female predominance and advanced stage. No cases with hereditary predisposition have been reported. Prior exposure to cytotoxic chemotherapy is a risk factor.

The morphologies of both TFE3-rearranged RCC and TFEB-altered RCC often overlap, may mimic other common renal tumours, and are likely significantly underestimated.[122–124] A useful clue to the diagnosis is low expression of epithelial markers and occasional focal expression of melanocytic markers, such as Melan-A and HMB45. TFE3-rearranged RCC with PRCC::*TFE3* fusion and TFEB-altered RCCs also strongly express cathepsin K.[125] TFE3 and TFEB IHC assays are technically challenging, can be upregulated in other RCCs, with mTORC1 constitutive activation and *TSC1/2* loss,[126] and many laboratories use fluorescence in situ hybridization (FISH) with break apart probes. However, some variants cannot be picked up by FISH assays and are identified by more sensitive tools such as RNA sequencing or fusion arrays and reverse transcription polymerase chain reaction.[127–129]

MiT family translocation RCCs have been reported to have similar survival as CCRCCs. Recent studies suggest that these tumours have a permissive immune microenvironment; however, significant benefit from immune checkpoint inhibitor–based regimens has not been observed.[120,124]

TFE3-rearranged renal cell carcinoma

TFE3-rearrangement RCCs (also known as Xp11 translocation RCC) are characterized by in-frame gene fusions that preserve TFE3 DNA binding and other functional domains. They involve *TFE3* (Xp11) and one of numerous fusion partners enriched in chromosomes 1, 17, and X, most commonly *ASPSCR1* (ASPL), *PRCC*, and *SFPQ*.

The most distinct morphological features include a papillary architecture with neoplastic cells with abundant clear cytoplasm, discrete cell borders, and round nuclei with prominent nucleoli. Psammoma bodies are abundant (**Figure 3A**). Different fusion partners have been associated with differing morphologic features.[130,131] Though IHC assays remain problematic to standardize, strong and diffuse nuclear immunoreactivity using an antibody to the C-terminal portion of TFE3 may correctly identify these tumours (**Figure 3B**).[132] This is particularly helpful for the diagnosis of tumours with paracentric inversions of Xp11 (*RBM10*, *GRIPAP1*, *RBMX*, *NONO*), resulting in false-negative FISH results.[133] RNA sequencing/fusion arrays are particularly helpful in these scenarios. More recently, high expression of glycoprotein nonmetastatic B (GPNMB) has been proposed[134,135] as a specific marker. PAX8 expression can help differentiate these tumours from perivascular epithelioid cell tumours (PEComas), which may also exhibit TFE3-rearrangement.

TFEB-altered renal cell carcinoma

TFEB-altered RCC includes TFEB-rearranged RCC and TFEB-amplified RCC. TFEB-rearranged RCC typically involves a t(6;11)(p21;q12) translocation resulting in a *MALAT1::TFEB* (formerly Alpha) gene fusion. Less-frequent partners have been reported recently.[136]

Morphologically, the characteristic biphasic pattern, with large and small epithelioid cells and nodules of basement membrane material, is relatively infrequent (**Figure 3C**).[137] More frequently, they share overlapping features with *TFE3*-associated and other RCCs and can have frequent oncocytic and papillary features.

TFEB-amplification RCC was recently described as harbouring amplification of the 6p21 region, with resultant TFEB overexpression and possibly overexpression of other nearby genes, such as *VEGFA*.[81,138,139] Unlike TFEB-rearranged RCC, these occur in older patients and have a worse outcome. Though often eosinophilic, the morphology is not distinct and may appear as poorly differentiated. Expression of melanoma markers, and less often cathepsin K, can be helpful though observed in only 50% of the cases.

ELOC (TCEB1)-mutated renal cell carcinoma

ELOC-mutated RCC is currently a molecularly defined entity with distinctive genetic and consistent morphologic features. The tumours harbour recurrent hotspot mutations of the *ELOC* (*TCEB1*) gene (8q21), encoding elongin C, a component of the VHL E3 ligase complex. The concurrent *ELOC* mutation and chromosome 8 loss of heterozygosity (LOH) provides another mechanism for disrupting the VHL complex and activating the HIF pathway.[140,141]

ELOC-mutated RCC is characterized by thick fibromuscular bands traversing the tumour parenchyma, imparting a multinodular appearance at low power. Tumour cells have clear and voluminous cytoplasm and prominent cell borders, and they assemble into solid acinar and papillary architectures (**Figure 3D**). The tumour cells are positive for CAIX (diffuse box-like membranous staining similar to CCRCC), CK7 (often diffuse, but can also be patchy), and CD10 by IHC. The differential diagnosis includes primarily CCRCC and CCPRCT, both of which can also contain prominent fibromuscular stroma. Additionally, a subset of tumours in TSC patients as well as some sporadic RCC driven by TSC/mTOR complex 1 pathway mutations (referred to as RCC FMS) can display very similar morphology.[142] A morphologic assessment combined with an IHC panel, including CK7, CAIX, CD10, and 34βE12, can be helpful to distinguish this entity from CCPRCT. However, it has limited value for a definitive distinction from CCRCC or RCC associated with mTOR pathway mutations. The *ELOC* hotspot mutation and concurrent 8/8q loss can establish the diagnosis in such scenario.

The reported cases predominantly occur in male patients.[141,143,144] While the vast majority of tumours exhibit indolent behaviour, some cases have shown aggressive behaviour and developed metastasis.[145]

FIGURE 3 Microscopic features of molecularly defined RCCs.

A. TFE3-rearranged RCC showing tubulopapillary architecture. Cells have an abundant clear-to-eosinophilic cytoplasm and grade 3 round nuclei. Microcalcifications (arrow) and psammoma bodies are frequent (200x magnification).

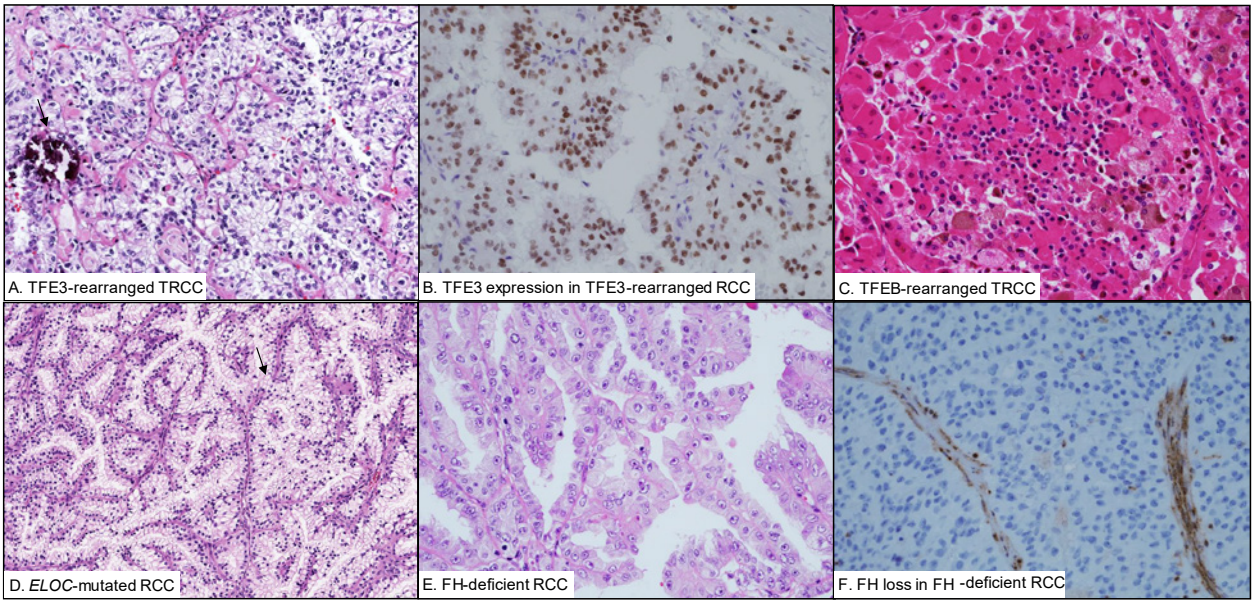
B. TFE3 IHC staining in a TFE3-rearranged RCC showing diffuse strong nuclear staining irrespective of the fusion gene partner (200x magnification).

C. TFEB-altered RCC with prototypic biphasic morphology. Among the large tumour cells with abundant eosinophilic cytoplasm are dispersed clusters of smaller cells forming pseudorosettes and focally clustering around basement membrane material. This pattern though classic is infrequent, and most tumours show overlapping morphologies with other RCC subtypes (200x magnification).

D. ELOC (TCEB1)-mutated RCC with branching tubulopapillary architecture. Neoplastic cells have an abundant clear cytoplasm with distinct cell borders that stain consistently with CK7 (not shown) (100x magnification).

E. Fumarate hydratase–deficient RCC demonstrating a papillary architecture. Cells have an abundant eosinophilic cytoplasm and large nuclei with macronucleoli that focally have perinucleolar clearing (200x magnification).

F. IHC staining for fumarate hydratase in a case of FH-deficient RCC showing loss of the cytoplasmic staining in tumour cells. The expression is retained in the normal stromal, endothelial, and inflammatory cells (200x magnification).



Fumarate hydratase–deficient renal cell carcinoma

Hereditary leiomyomatosis renal cell cancer (HLRCC) syndrome is an autosomal dominant disorder, characterized by uterine and cutaneous leiomyomas and increased predisposition to an aggressive form of RCC.[146] Patients harbour germline mutations of the fumarate hydratase (*FH*) gene and have an estimated lifetime RCC risk of 15%.[147] Initially named "HLRCC-associated RCC" in the WHO (4th edition) classification, the term "FH-deficient RCC" is favoured and will be adopted by the 5th edition of WHO. This is owing to the discovery of a significant number of cases in the sporadic setting with biallelic somatic *FH* alterations.[64] These individuals lack a personal or family history of HLRCC and do not have germline mutations.

FH-deficient RCC exhibits a wide morphologic spectrum. The tumours typically show mixed architectural patterns, and include papillary, tubular, tubulocystic, solid, and cystic elements. They may also include areas closely mimicking collecting duct carcinoma or tubulocystic carcinoma.[107,110,148,149] Cytologically, the most characteristic feature is the presence of a "cherry-red" viral inclusion-like nucleolus, often surrounded by a perinucleolar halo (**Figure 3E**).[148] However, this feature can be focal and often lacks specificity for FH-deficient RCC when considering other high-grade RCCs. Rare examples of low-grade FH-deficient renal tumours have also been reported.[115,150] Loss of FH by IHC is highly specific for the diagnosis (**Figure 3F**), but is less sensitive, as a retained defective FH protein can be detected in some cases.[151] IHC for S-(2-succino)-cysteine (2SC) is a highly sensitive marker for the aberrant protein succination that occurs in FH-deficient tumours. However, distinguishing the typical 2SC pattern (i.e., diffuse nuclear and cytoplasmic staining) from nonspecific staining patterns (e.g., focal/patchy or cytoplasmic-only) can be challenging.[149] A combination of these two markers can achieve high sensitivity and specificity.[152] Given the expanding clinical and pathologic spectrum of FH-deficient RCC, the correct diagnosis requires vigilance when encountering cases with unusual clinical or pathologic features.

Molecularly, biallelic *FH* alterations are found in both germline and somatic cases.[152,153] Both somatic and germline FH-deficient RCCs appear to have similar molecular characteristics, often with a low tumour mutational burden and a high fraction of the genome altered. The majority of FH-deficient RCCs show a CpG island methylator phenotype (CIMP), with concerted hypermethylation at numerous CpG sites. This likely contributes to the oncogenic pathways in these tumours.[64,153] The accumulation of the Krebs cycle intermediate fumarate, which functions as an oncometabolite, can also activate complex oncogenic cascades and lead to metabolic dysregulation.[154]

Succinate dehydrogenase–deficient renal cell carcinoma

Germline mutations in genes encoding the protein subunits of succinate dehydrogenase (*SDHA*, *SDHB*, *SDHC*, and *SDHD*) or the regulatory factor *SDHAF2* have been identified as the causal aberrations in patients with familial paraganglioma-pheochromocytoma (PGL/PHEO) syndromes. Such mutations have also been found in other types of tumours, such as gastrointestinal stromal tumours (GIST), pituitary adenomas, and RCCs. SDH-deficient RCC is currently defined by a loss of SDHB protein expression, a marker reflective of a dysfunctional mitochondrial complex II. There is a strong hereditary association, most commonly involving the *SDHB* gene.[155,156]

SDH-deficient RCCs are often solitary, unilateral, and well circumscribed. Bilateral tumours have been reported in 8–26% of cases.[155,157] The tumours characteristically consist of monomorphic cells in solid, nested, and tubular patterns, with flocculated eosinophilic cytoplasm and frequent intracytoplasmic vacuolations and inclusions (**Figure 3G**). The tumour cells have round to oval low-grade nuclei. High-grade nuclear features occur in a subset of tumour cells and are typically associated with aggressive behaviour. Other adverse features include coagulative necrosis and sarcomatoid change. Loss of SDHB staining is a sensitive and specific marker for these tumours and should prompt genetic assessment (**Figure 3H**).[155] Molecularly, aside from germline SDHB mutations, these tumours are characterized by LOH on chromosome 1p and typically show a low tumour mutation burden.[158]

SMARCB1 (INI1)-deficient renal medullary carcinoma

RMC is a rare and distinctive entity occurring almost exclusively in young patients with sickle cell trait and rarely in patients with other hemoglobinopathies.[159,160] The loss of nuclear expression of SMARCB1(INI1/BAF47) protein is a consistent finding in RMC.[161–163] The tumours are usually large and poorly circumscribed. A renal medulla-centered location can be appreciated in smaller tumours. Microscopically, architectural patterns often include reticular, cribriform, solid, tubulopapillary, and infiltrating tubules and cords. Tumour cells exhibit marked nuclear pleomorphism, often with rhabdoid features and high mitotic activity (**Figure 3I-J**). Necrosis and neutrophil-rich inflammatory infiltrate is common. Drepanocytes (sickle-shaped erythrocytes) in small vessels within the tumour and in the adjacent renal stroma are typically present. Molecularly, the mechanisms of SMARCB1 deficiency include hemizygous deletion and concurrent translocation or homozygous deletion.[164]

Loss of SMARCB1 protein has been described in rare cases of RCC that display morphology indistinguishable from RMC, but occurs in patients without hemoglobinopathies (previously called RCC, unclassified, medullary phenotype).[109,165,166] Those tumours can be regarded as a subtype of SMARCB1-deficient RMC, as recommended in the 5th edition of WHO. For nonmedullary RCCs with SMARCB1 loss, which is likely due to a secondary event, it is recommended that these tumours are classified according to their primary tumour types.

The differential diagnosis of SMARCB1-deficient RMC includes high-grade urothelial carcinoma of the renal pelvis, CDC, FH-deficient RCC, ALK-rearranged RCC, and metastatic poorly differentiated carcinoma involving the kidney.

Anaplastic lymphoma kinase–rearranged renal cell carcinoma

Anaplastic lymphoma kinase–rearranged renal cell carcinoma (ALK-RCC) was first described in 2011[167,168] and is characterized by *ALK* gene fusions with various partner genes, leading to aberrant *ALK* activation. Fusion partners include *VCL, HOOK1, STRN, TPM3, EML4*, *PLEKHA7*, *CLIP1, KIF5B,* and *KIAA1217.* [6,169] ALK-RCC is a clinically important diagnosis, as targeted therapies with ALK inhibitors are available.[170,171] ALK-RCC has been reported in patients of a wide age range, including pediatric and adolescent patients. In younger patients, sickle cell trait is common. Patients have a diverse racial background, including African American, Caucasian, and Asian.[169] ALK-RCCs are indolent tumours in the majority of cases, although some may show an aggressive clinical course and may metastasize.

FIGURE 3 Microscopic features of molecularly defined RCCs. *(Cont'd)*

G. Succinate dehydrogenase–deficient RCC with compact nests of tumour cells that lack distinct cell borders and an eosinophilic cytoplasm with focal, pale flocculent material (arrow). Nuclei are of low grade (200x magnification).

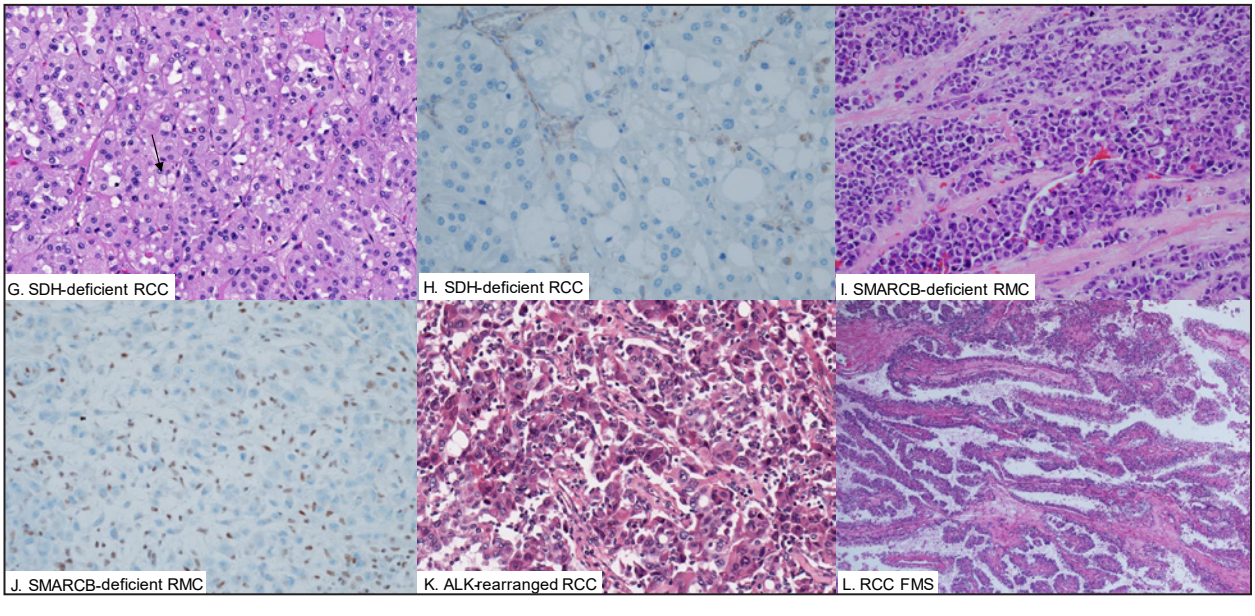
H. IHC staining for succinate dehydrogenase B in a case of SDH-deficient RCC showing loss of the cytoplasmic staining in tumour cells. The expression is retained in the normal stromal, endothelial, and inflammatory cells (200x magnification).

I. SMARCB1-deficient renal medullary carcinoma showing infiltrative growth pattern composed of cords, sheets, and single cells with prominent desmoplastic stroma. The cells show marked nuclear pleomorphism, prominent nucleoli, and eosinophilic cytoplasm rendering a rhabdoid appearance (200x magnification).

J. IHC staining for BAF47 (INI1) in a case of SMARCB1-deficient RMC showing loss of the nuclear staining in tumour cells. The expression is retained in the normal stromal, endothelial, and inflammatory cells (200x magnification).

K. Anaplastic lymphoma kinase–rearranged RCC with cells forming irregular glands and desmoplastic and inflamed stroma. The neoplastic cells demonstrate abundant eosinophilic cytoplasm with focal vacuolization and high-grade pleomorphic nuclei (200x magnification). ALK expression is uniformly positive (not shown).

L. RCC with fibromyomatous stroma composed exclusively of branching tubules and a papillary architecture and admixed fibromuscular stroma. The epithelial cells have a clear cytoplasm (100x magnification).



ALK-RCC usually presents as a solitary and circumscribed tumour. It may be solid or solid-cystic, with a tan-grey or variegated cut surface. ALK-RCC typically demonstrates variable and diverse morphology, with no characteristic or specific morphologic features. Features include papillary, solid, tubular, trabecular cystic, cribriform, signet-ring, single cells, "mucinous tubular and spindle cell RCC-like," and "metanephric adenoma-like" (**Figure 3K**).[6,169] However, a mucinous or myxoid component (intracellular or interstitial) has been commonly found in ALK-RCC. Psammoma bodies and tumour necrosis are commonly found. Thus, screening for ALK should be considered in all difficult-to-classify renal tumours with variable and admixed patterns and unusual morphologies, or in those containing a mucinous component.

ALK protein expression by IHC, typically diffuse cytoplasmic and membranous, is a defining feature of ALK-RCC. ALK rearrangements can also be documented by FISH or by sequencing methods. The remaining immunoprofile is nonspecific and includes reactivity for PAX8, CK7, vimentin, INI1 (retained), 34βE12, and AMACR.[6,169] TFE3 reactivity by IHC was reported in some cases, but without evidence of TFE3 rearrangement by FISH.[172]

New and emerging entities

Eosinophilic solid and cystic renal cell carcinoma

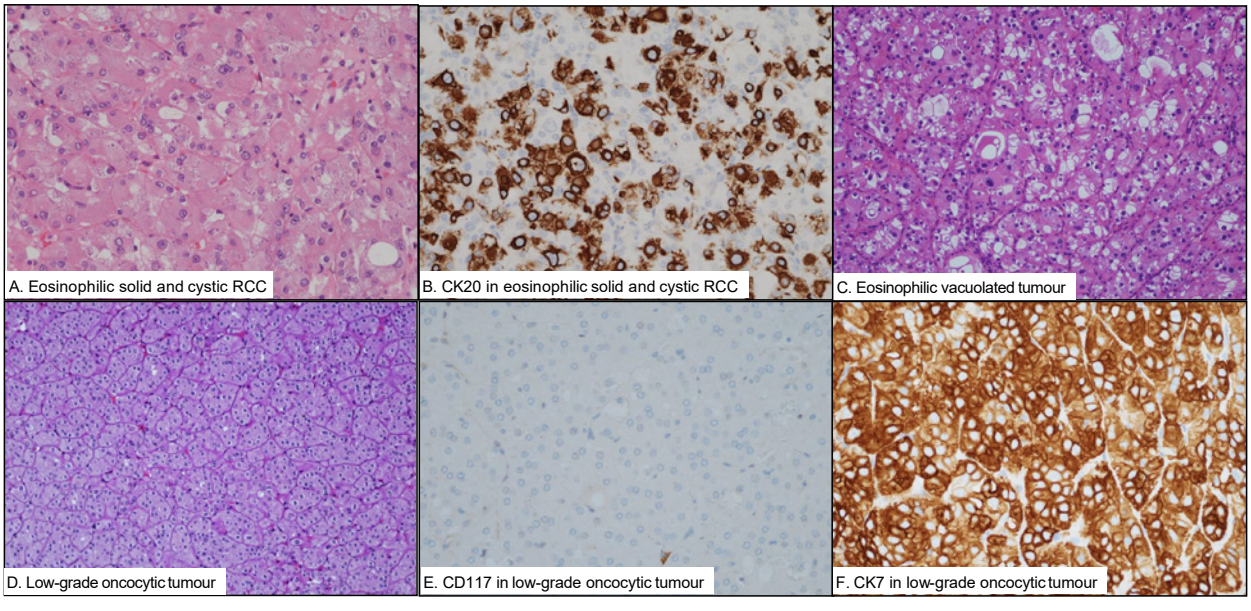
ESC RCC is a recently characterized RCC found as a sporadic and solitary tumour in patients of broad age range and predominantly in women.[115,173,174] It is observed also in patients with tuberous sclerosis complex.[175,176] Although the great majority of ESC RCCs exhibit indolent behaviour, rare tumours with metastatic disease have been reported, warranting the designation of RCC.[177–179]

ESC RCC typically has grossly identifiable solid and cystic components. The cysts range in size from few millimeters to few centimeters. Rare cases have predominantly solid growth, with only rare microcysts. Reported size varies broadly, but most tumours are less than 5 cm.[173,174] The solid parts are composed of eosinophilic cells exhibiting diffuse, compact acinar, or nested growth (**Figure 4A**).[173,174] A characteristic feature is the presence of coarse, basophilic-to-purple, cytoplasmic granules (stippling). Scattered foamy histiocytes and lymphocytes are also common, as are psammoma bodies.

ESC RCC shows either diffuse or focal CK20 expression (**Figure 4B**), but rare cases may be negative for CK20.[173,174] CK7 is typically negative or very focally positive. In the majority of cases, at least focal cathepsin K expression has been documented. Melan-A has recently been reported to be frequently positive.[180] Other positive stains include PAX8, AE1/AE3, CK8/18, and vimentin. Most ESC RCCs have biallelic loss in *TSC1* or *TSC2,* resulting in activation of the mTOR complex 1 signaling.[177,181,182]

FIGURE 4 Microscopic features of new and emerging entities.

A. Eosinophilic solid and cystic RCC with solid and cystic components. The cells have a voluminous eosinophilic cytoplasm and characteristic coarse purple cytoplasmic granules (stippling) (200x magnification).
B. ESC RCCs are typically CK20 positive (can be either focal or rarely diffuse) (200x magnification).
C. Eosinophilic vacuolated tumour (EVT) with a diffuse solid growth pattern. The tumour cells have an abundant eosinophilic cytoplasm and typical prominent intracytoplasmic vacuoles. The nuclei are large and round, with prominent nucleoli (100x magnification). EVT are typically cathepsin K positive (not shown).
D. Low-grade oncocytic tumour (LOT) with a diffuse, solid, compact nest, growth pattern. The neoplastic cells have an eosinophilic cytoplasm with round nuclei, without prominent nucleoli, that lack significant irregularities and may show focal perinuclear clearings (100x magnification).
E. LOT showing characteristically negative reactivity for CD117 (200x magnification).
F. LOT showing characteristic diffuse strong positive staining for CK7 (200x magnification).



Eosinophilic vacuolated tumour

EVT is a recently described entity that emerged from the eosinophilic/oncocytic tumours with shared features between renal oncocytoma and chromophobe RCC.[86,87,183] He *et al.* described the tumour as a "high-grade oncocytic tumour", abbreviated as "HOT",[184] and Chen *et al.* as "sporadic RCC with eosinophilic and vacuolated cytoplasm."[185] The recent GUPS 2021 consensus proposed the name "eosinophilic vacuolated tumor" (EVT) for this entity.[6] EVT was also identified in some patients with tuberous sclerosis complex.[186–189] EVT is found in patients of broad age range and occurs more frequently in women.[6,184,185,190] About 40 EVT cases have been reported to date and all cases had benign behaviour, without evidence of recurrence or metastases.[6,190,191]

EVT is frequently solitary and sporadic, typically of small size, with a solid, grey, or tan-to-brown cut surface.[6,184,185,188,190] EVT has a solid growth, often with nested and tubulocystic foci. Thick-walled vessels are virtually always present at the periphery, but a well-formed capsule is lacking. The cells have an eosinophilic cytoplasm and prominent intracytoplasmic vacuoles (**Figure 4C**). The nuclei are round to oval, with prominent nucleoli that focally can be quite large and resemble viral inclusions.[184,185]

EVT is positive for CD117 (KIT), CD10, antimitochondrial antigen antibody, and cathepsin K, in some cases focally. CK7 is typically expressed only in rare, scattered cells.[184,190] The immunoprofile "CD117+ and CK7+ only in rare cells" resembles that of an oncocytoma. p-S6 and p-4EBP1, markers of MTOR pathway activation, are induced in EVT.[185] On electron microscopy, EVT demonstrated numerous intracytoplasmic mitochondria, as well as dilated cisterns of rough endoplasmic reticulum.[188,191] Complete losses or gains of multiple chromosomes, as in chromophobe RCC, have not been found. However, isolated losses of chromosomes 1 and 19p were reported in EVT, along with LOH at 16p11 and 7q31.[184] Importantly, *TSC/MTOR* mutations appear to be a consistent finding in EVT.[185,188] A recent study demonstrated nonoverlapping mutations in *MTOR*, *TSC2*, and *TSC1* in all evaluated cases, associated with low mutational rates.[190] Thus, it appears that EVT is associated with either germline or somatic mutations leading to mTORC1 activation.[188]

Low-grade oncocytic tumour

LOT is another recently described renal tumor that emerged from the spectrum of eosinophilic/oncocytic tumors with shared features between renal oncocytoma and ChRCC.[192,193] LOT is typically a single, sporadic tumour, but multiple LOTs have also been documented, either in patients with end-stage kidney disease,[194] or in patients with tuberous sclerosis complex.[195] LOT is observed in patients of a broad age range, but usually older. All reported LOTs to date have behaved in a benign fashion.[192,194–198]

LOT is usually a smaller tumour that appears solid and compact without necrosis or cysts.[192,194,196] The surface is tan-yellow to mahogany-brown, similar to oncocytoma.[192] LOT has a diffuse and solid growth pattern, with focal tubular, tubuloreticular, or trabecular growth. LOT lacks a well-formed capsule, and entrapped tubules may be seen at the periphery.[6,192] The neoplastic cells are eosinophilic, with round-to-oval "low-grade" nuclei that lack significant irregularities and may show focal perinuclear clearing (halos) (**Figure 4D**). Sharply delineated, edematous stromal areas with scattered individual cells or irregular "tissue culture" cell arrangements are frequent.[6,192] These areas often contain fresh hemorrhage. Adverse features, such as coagulative necrosis, nuclear pleomorphism, multinucleation, and mitotic activity are uniformly absent.

LOT is diffusely positive for CK7 and is negative, or in rare cases, focally and weakly positive for CD117 (**Figure 4E-F**). LOT is also positive for PAX8, e-cadherin, BerEP4, and MOC31.[192] LOT is consistently positive for GATA3, and exhibits, at least focally, expression of p-S6 and p-4EBP1, markers of mTOR pathway activation.[195,197] FOXI1, which is typically expressed in both oncocytoma and ChRCC, is typically negative in LOT.[74,199] In the normal kidney, FOXI1 is positive in the intercalated cells.[74] Using electron microscopy, LOT exhibits abundant, closely

packed cytoplasmic mitochondria, similar to oncocytoma.[191] Complete chromosomal gains or losses, as well as *CCND1* rearrangements are not found in LOT.[194] Recent studies demonstrated common involvement of the MTOR pathway genes in LOT.[197,195]

Renal cell carcinoma with fibromyomatous stroma (RCC FMS)

RCC FMS was first described by Canzonieri *et al.* in 1993 as a "mixed renal tumour with carcinomatous and fibroleiomyomatous components."[200] Subsequently, various names have been used for this entity including: "RCC with prominent smooth muscle stroma," "mixed renal tumour with carcinomatous and fibroleiomyomatous components," "RCC associated with prominent angioleiomyoma-like proliferation," "clear cell RCC with smooth muscle stroma," and "RCC with clear cells, smooth muscle stroma and negativity for 3p deletion."[193,201] The name "renal cell carcinoma with fibromyomatous stroma" (RCC FMS) was officially endorsed by the GUPS in 2021, based on a broad consensus.[6]

RCC FMS is usually a sporadic tumour, but rare cases are associated with tuberous sclerosis complex.[202] The prognosis is generally favourable, and the majority of cases have an indolent clinical course.[6,142,203] One case with lymph node metastases was reported in a patient with tuberous sclerosis and multifocal tumours.[204]

RCC FMS tumours are generally small and solid. The cut surface is tan-brown, often with lobulated appearance due to fibromyomatous septae.[143,193,205] At low power, RCC FMS is viewed to be composed of nodules of epithelial cells separated by and admixed with a fibromuscular stroma. The epithelial component consists of cells with a voluminous clear cytoplasm, arranged in solid sheets, nests, branching tubules, and focal papillary structures (**Figure 3L**). The nuclei are WHO/ISUP grade 2 or 3 (equivalent). The fibromyomatous stroma can be variable and is often more prominent at the periphery.[6,193,205]

The characteristic IHC profile includes diffuse positivity for CK7, as well as CAIX and CD10.[6,142,206] CAIX staining is usually diffuse membranous, but it can be "cup-shaped" focally. Other positive stains include vimentin and high-molecular weight cytokeratin. AMACR is typically negative. The differential diagnosis includes ELOC-mutated RCC, which can be excluded by the absence of *ELOC* mutations and monosomy 8,[141] and a subset of CCRCC that is associated with fibromyomatous stroma. RCC FMS tumours are associated with mutations involving the TSC/mTOR pathway.[6,142,189] Unlike CCRCC, these tumours are not associated with LOH of chromosome 3 or *VHL* mutations.[6,207] The stroma has been shown to be polyclonal and non-neoplastic.[207]

Thyroid-like follicular renal cell carcinoma

TLF RCC is a rare tumour, with fewer than 50 cases documented in the literature, mostly individual case reports.[6] The clinical behaviour is usually indolent, but lymph node and distant metastases have been documented in about 10% of patients.[208–211] The reported age range is broad.[212–214]

TLF RCC is a solitary, solid, well-circumscribed, and non-encapsulated tumour. The reported size range is wide.[6,212–214] TLF RCC resembles thyroid gland morphology by architecture and cytology (**Figure 4G**). The tumours have a follicular pattern, but focal branching and papillary structures are also reported. The size of the follicles is variable, and the follicles are typically lined up by a single layer of cuboidal or low columnar epithelial cells. The reported grade was 2 or 3 (WHO/ISUP equivalent).[6,193,208,212–218]

TLF RCC has a nonspecific immunoprofile and is usually positive for CK7, vimentin, and PAX8, and less frequently for RCC, AMACR, CD10, and CK20. An important finding is the negative staining for TTF1 and thyroglobulin. This is in contrast with true metastatic carcinomas of the thyroid, which should always be ruled out when considering this entity.[6,219] An association with *EWSR1* has been reported,[219] including an *EWSR1-PATZ1* fusion in three cases. There are no consistent chromosome copy number changes or other recurrent gene alterations.[211,212,215,220–222]

Papillary neoplasm with reverse polarity

These tumours (also referred to as oncocytic PRCC) have a distinctly recognizable morphology and IHC profile and an indolent behaviour. They present as incidentally discovered masses, typically small and often with a cystic component. The tumour have a tubulopapillary architecture, and the tumour cells have an oncocytic cytoplasm, and low-grade luminally arranged nuclei (**Figure 4H**).[223] IHC is characterized by diffuse GATA3 (**Figure 4I**) and CK7 expression and weak vimentin and AMACR staining.[224] Molecularly, the majority of these tumours (80–90%) have *KRAS* mutations.[223,225] Given the overlapping features with PRCC, such as gains in chromosomes 7 and 17, there is an ongoing debate whether these tumours should be considered a separate entity or a subtype of PRCC. Given the unique morphology, IHC profile and characteristic *KRAS* mutations, we herein report this entity separately.

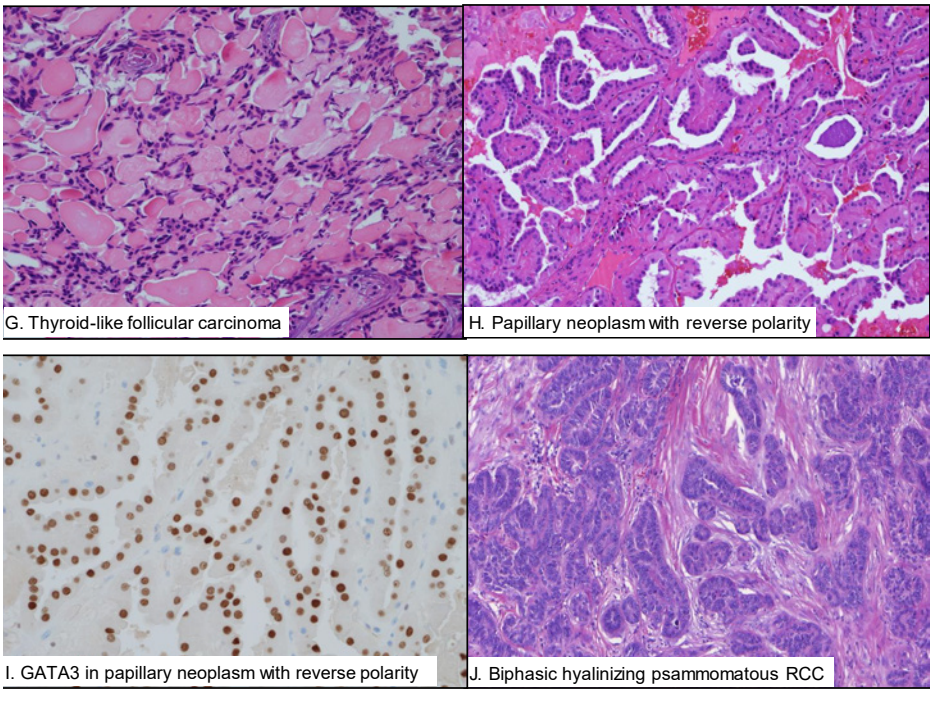
FIGURE 4 Microscopic features of new and emerging entities. *(Cont'd)*

G. Thyroid-like follicular carcinoma shows morphology resembling thyroid gland and is composed of back-to-back arranged, variable-size follicles, with "colloid-like" luminal content. The cells are arranged in a single layer with scant cytoplasm and grade 2–3 nuclei (100x magnification).

H. Papillary neoplasm with reverse polarity with cystic and papillary architecture. There are papillary within cysts. The cells are small with a clear cytoplasm. Nuclei are of low grade and are characteristically aligned away from the basement membrane (100x magnification).

I. IHC staining for GATA3 showing diffuse strong nuclear staining for papillary neoplasm with reverse polarity (200x magnification).

J. Biphasic hyalinizing psammomatous RCC showing biphasic pattern of small cells clustered around hyalinized material and surrounding large cells (100x magnification).



Biphasic hyalinizing psammomatous renal cell carcinoma

BHP RCC is a recently proposed renal tumour, with fewer than 15 cases reported.[226,227] Approximately half of the cases had metastatic disease.[228,229] BHP RCCs have variable architecture, typically biphasic with larger cells with pale cytoplasm and smaller cells. Tumour cells cluster around basement membrane material resembling TFEB-altered RCC, though no *TFE3* and *TFEB* rearrangements have been identified. The stroma is typically sclerotic (**Figure 4J**) and scattered psammoma bodies are observed.[226,227,229,230] All analyzable cases had mutations of the

NF2 gene.[226,227,229] However, additional mutations in prothymosin alpha pseudogene 1 (*PBMRT1), BAP1, ARID1A, DNMT3A, TERT*, and *SMARCB1* were found in some cases. Thus, further study is necessary to validate whether BHP RCC represents a distinct renal entity sharing *NF2* gene abnormalities.[6,113,229] At present, without genetic testing, the diagnosis of BHP RCC remains challenging.

Immunohistochemical Approach to Renal Tumours

The diagnosis of most RCCs can be made by careful morphologic interpretation and limited ancillary testing. IHC represents an economical and quick assay to support a specific diagnosis formulated on light microscopic analysis of hematoxylin and eosin-stained sections. IHC may be used more frequently when making a diagnosis on limited biopsy material. Though quite helpful, classic immunophenotypic patterns are more often observed in low-grade tumours, while poorly differentiated tumours may lose characteristic marker(s) or may express aberrant and unexpected antigens. Useful immunohistochemical panels are summarized in **Tables 2A–D**.

PAX8 (and PAX2) are members of the paired box family of transcription factors and are important in kidney development (and also thyroid, female genital tract, eye, and nervous system).[231] Diffuse nuclear expression is observed in the vast majority of primary and metastatic RCCs. These markers are of great utility for determining renal origin.[44,232]

Carbonic anhydrase IX, a protein induced by HIF, is expressed diffusely in a membranous pattern in CCRCC.[233] It remains positive in metastatic CCRCC and often even after sarcomatoid dedifferentiation. Diffuse cup-like staining can help make the diagnosis of CCPRCT.[61] However, focal staining can be seen in hypoxic areas of most RCCs and normal tissue and needs to be interpreted with caution in biopsy material, especially in areas with extensive necrosis. A caveat is that diffuse membranous CAIX is also seen in urothelial carcinoma and mesothelioma.[234] Cytoplasmic staining is seen in RCCs with eosinophilic cytoplasm and is nonspecific.

CD117 is a tyrosine kinase receptor that binds to stem factor or c-Kit ligand. Diffuse CD117 staining with peripheral accentuation is found in ChRCC and renal oncocytoma (generally cytoplasmic staining) and helps distinguish these tumours from other renal tumours, such as eosinophilic CCRCC or PRCC.

In addition, specific diagnostic stains such as those for FH, 2SC, SDHB, TFE3, TFEB, ALK, INI1, and GATA3 can be helpful in making the diagnosis of specific RCC subtypes (**Tables 2A–D**).

RCC with a predominantly sarcomatoid component needs to be differentiated from sarcomas and epithelioid angiomyolipomas. Generous sampling and IHCs (especially PAX8 and melanoma markers) can assist in making the right diagnosis. Similarly, appropriate sampling of cystic lesions (including capsule and solid morule) can help establish the correct diagnosis (**Figure 5A**). Carcinomas from other organs can, albeit rarely, metastasize to

primary CCRCC tumours and mimic intratumoural heterogeneity (ITH) (**Figure 5B**). Awareness of the clinical history and an IHC workup can help establish the correct diagnosis.

Intratumoural Heterogeneity

CCRCC is the paradigmatic model of ITH.[235] Multiregional sequencing shows that different areas accumulate different mutations and concurrent, expanding somatic copy number alterations (SCNA. Based on inferred mutation timing and rule-based clustering, the majority of CCRCC can be divided into seven evolutionary groups that explain to some extent the observed clinical and metastatic behaviour.[236,237] These groups include a "VHL monodriver" characterized by low-grade, low-stage, indolent RCCs with minimum ITH. Three aggressive subtypes: "BAP1 driven," "VHL wild-type," and "multiple clonal drivers" of high grade progress rapidly to metastases. The "BAP1 driven" subtype exhibits *VHL* and *BAP1* mutations early during evolution. No *VHL* alteration has been identified in the "VHL wild-type". Alterations in at least two of four genes (*BAP1*, *PBRM1*, *SETD2*, or *PTEN*) are present in "multiple clonal drivers". Tumours with *PBRM1* loss can progress with subsequent loss of *SETD2*, activation of PI3K/ AKT/ mTOR, or specific SCNAs. These tumours have intermediate aggressive features and maximum ITH. Spatial positioning suggests that more aggressive subclones with metastatic competency arise in the tumour centre.[238]

Prior data has shed light on the path to diversification. The signature event in sporadic CCRCC is *VHL* loss and large deletion of chromosome 3p (that removes one allele of *PBRM1, BAP1* and *SETD2*).[47,49,239,240] However, *Vhl* loss alone is insufficient, and other mutations appear necessary including the remaining copy of either *Pbrm1* or *Bap1*.[32] Notably, mutations in *PBRM1* (~50–55% of CCRCC*)* and *BAP1* (~15% of CCRCC) are largely mutually exclusive, and the tumours are phenotypically different.[47,49,241, 239] Thus, mutations in *PBRM1* and *BAP1* may split the evolutionary journey.[49,242] *PBRM1* and *SETD2* often co-occur and *SETD2* loss likely follows *PBRM1* loss, with these mutations cooperating.[49,241,243] Data from genetically engineered mice shows that BAP1 and PBRM1 are not only markers of tumour grade but also drivers of tumour grade.[32,244] Pbrm1-deficient tumours in mice tend to be of low grade, with iconic clear cells (rich in lipids and glycogen) and a prominent vascular network. mTORC1 activation in these tumours (though *Tsc1* disruption) increases tumour grade.[245,32] Unlike PBRM1-deficient tumours, BAP1-deficient tumours are of high grade and associated with worse outcomes.[47,49,48,49,241,243,246,247] Similarly, *Bap1* loss in mice induces proliferative higher-grade tumours.[32,244] In both humans and mice, these tumours are inflamed.[248] These tumours could evolve into sarcomatoid tumours, which show high *BAP1* mutation frequency (40%).[124]

Morphologic intratumoural heterogeneity has been recognized for decades (**Figure 5C**). Recent morphologic analyses have provided a framework for an ontological and evolutionary model of CCRCC.[38,249] This model builds upon the observation that CCRCC typically exhibits two or three different architectures and is built upon the following assumptions: (i) architectures have a common source and evolve from one another, which is consistent with a founder event and clonality; and (ii) architectures likely evolve from a lower to higher grade. By developing a co-occurring matrix of the different architectural subtypes, an evolutionary model was generated based on the

observation that some architectures frequently co-occurred, whereas others were hardly ever together. Based on the assumption that tumours evolve from a low to high grade, a directional vector could be superimposed.[37,245] These observations suggest that vascularity is maximum in low-grade indolent architectures and is spaced out in high-grade aggressive architectures, and the reverse was observed for tumour-associated neutrophils and lymphocytes. These findings have recently been validated by multiple groups.[37,38,245,250–254]

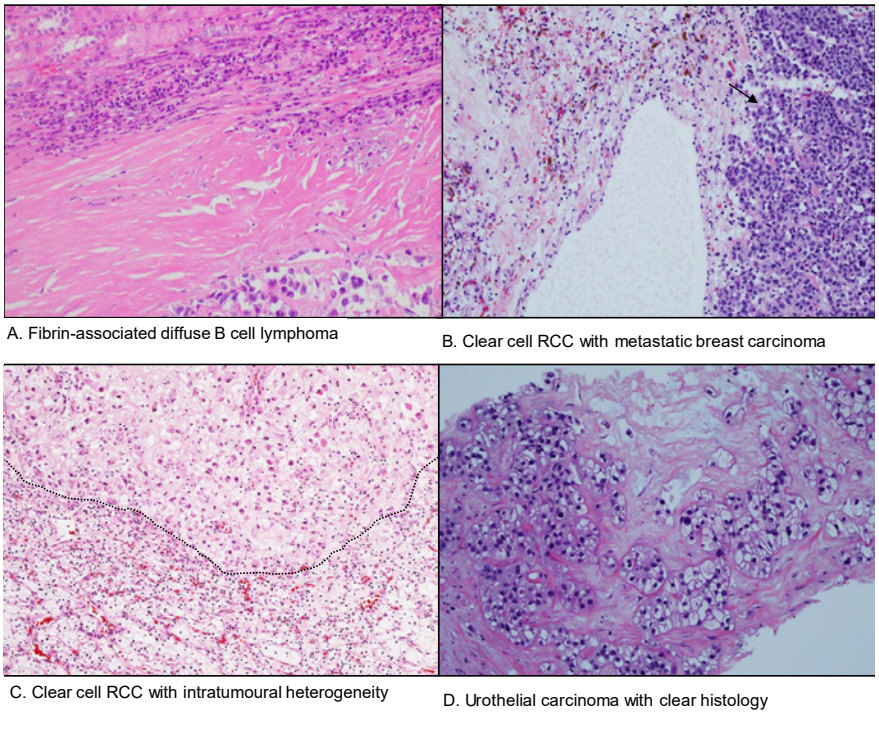
FIGURE 5 Other tumours involving the kidney.

A. Fibrin-associated diffuse, large, B-cell lymphoma presenting as a cystic lesion composed of predominantly fibrin and cellular debris with rare focal areas of large lymphoid B-cells that are positive for Epstein-Barr virus (EBV; not shown).

B. Clear cell RCC with intratumour metastatic breast carcinoma mimicking a high-grade component. The patient had prior history of breast adenocarcinoma, and this small tumour nodule stained with breast-specific markers (100x magnification).

C. Clear cell RCC with morphologic intratumoural heterogeneity. The low–nuclear grade (grade 1) area is located at the bottom half of the image and shows prototypic nests of tumour cells with a clear cytoplasm surrounded by an interconnecting vascular network. The high–nuclear grade (grade 4) area at the top shows cells with a combination of eosinophilic and clear cytoplasm and with rhabdoid cytology (100x magnification).

D. Urothelial carcinoma with clear cell histology. The nonspecific terminologies such as “clear cell histology” often used in a clinical trial can lead to confusion and inclusion of patients with biologically heterogeneous tumours (200x magnification).



Prognosis and Predictive Histopathologic Parameters

RCC is largely lethal when metastatic. 15% of patients present with metastasis, and metastasis occurs in another 25% of patients that present with apparently localized RCC.[255] Though RCC can metastasize to all organs, it most commonly involves lung, bone, liver, and lymph nodes.[256]

For localized RCC, histologic prognostic features include AJCC TNM stage at presentation, histologic subtype, nucleolar grade, rhabdoid and sarcomatoid differentiation, presence of coagulative tumour necrosis, and lymphovascular invasion (LVI).[34,257–261] Histologic and molecular RCC subtypes are associated with different prognosis and survival. FH-deficient RCC, SMARCB1-deficient RMC, TFE3-rearranged RCC, and TFEB-altered RCC are associated with significantly worse cancer-specific outcome than others.[262]

Tumour grade is a measure of tumour differentiation. The Furhman grading system uses nuclear size, shape, and nucleolar prominence and has been used widely.[263,264] More recent RCC subtype–specific analyses have shown that focal nucleolar grade (high power field of highest grade area in the case) alone retains prognostic significance in multivariate analysis of CCRCC and PRCC, but not in ChRCC.[265–267] Therefore, grading based on nucleolar prominence alone has been proposed for CCRCC and PRCC (**Table 3**). In addition, many RCC subtypes dedifferentiate to sarcomatoid morphology.[77] Universally poor outcomes have been associated with sarcomatoid/rhabdoid morphologies as well as anaplastic giant cells, which are defining features of grade 4.[39,77,257,268] This grading system has been shown to correlate with cancer-specific survival in multivariate analyses[269] and was endorsed by both the WHO and ISUP. Though grading systems have been proposed for ChRCC, there is currently no consensus, and it is not recommended to grade ChRCC.[270,271] The grading in RCCs that are not CCRCC or PRCC has been addressed in a recent review.[272]

TABLE 3 The World Health Organization/International Society of Urological Pathology (ISUP) Grading System for Clear Cell Renal Cell Carcinoma (CCRCC) and Papillary Renal Cell Carcinoma (PRCC)

Grade 1	Tumour cell nucleoli are absent or inconspicuous and basophilic at 400x magnification
Grade 2	Tumour cell nucleoli are conspicuous and eosinophilic at 400× magnification and visible but not prominent at 100x magnification
Grade 3	Tumour cell nucleoli are conspicuous and eosinophilic at 100x magnification
Grade 4	Tumours showing extreme nuclear pleomorphism, tumour giant cells, and/or the presence of any proportion of tumour showing sarcomatoid and/or rhabdoid dedifferentiation

Histologic coagulative tumour necrosis has also been shown to be an independent predictor of outcome in both CCRCC and ChRCC.[261,273] In a CCRCC study, integrating necrosis with nucleolar grading outperformed nucleolar-only grading when stratified according to TNM stage.[261] However, interobserver variability remains problematic.

LVI does not alter the stage; however, its presence in organ-confined disease has been reported to denote similar disease-free survival as locally advanced disease.[274] IHC using markers such as D2-40 can help with diagnosing LVI in challenging cases.[17] Of note, vascular invasion within the renal sinus fat is considered pT3a.

Beyond prognosis, RCCs with sarcomatoid and rhabdoid morphologies, which account for 10–15% of RCCs, preferentially respond to immune checkpoint inhibitors over angiogenesis inhibitors.[124,275–277] Retrospective molecular profiling of RCCs in patients enrolled in clinical trials such as IMmotion151, COMPARZ, JAVELIN Renal 101, and CheckMate214 have identified gene expression signatures and mutation profiles that provide insights into the determinants of response to current frontline therapies. These data suggest that tumours responsive to vascular endothelial growth factor/receptor (VEGF/R) inhibitors exhibit an angiogenic gene expression signature.[278–283]

Given that angiogenesis and inflammation, as well as presence of stroma proliferating cells, can be assessed on histologic slides, morphology may hold clues for response prediction and metastatic tropism.[242] Analyses focused on patients with metastatic CCRCC, who received VEGF/R inhibitors as frontline therapy, revealed that tumours composed predominantly of architectures with reduced vascularity had shorter time to progression.[37] In contrast, CCRCCs with pancreatic metastases were associated with vascularity-rich small nest architectures, long overall survival, and favourable response to VEGF/R inhibitors.[245,253]

ITH remains a limitation for both prognostic and predictive biomarkers. Multi-sample sequencing studies recommend an average of 7 biopsies per tumour to detect >75% of all driver variants, making the clinical applicability problematic.[236] Nevertheless, next-generation prognostic and predictive models will likely need to address ITH to accurately predict tumour behaviour for individual patients. Studies investigating morphologic ITH show trends similar to those of genetic ITH with multiregional sequencing.[236] Thus, histomorphology could tackle the complexity of ITH and may be better poised to advance the biomarker field. Advances in computational analysis of digitalized slides will likely lead to both objectivized and more generalizable new associations.

Considerations for Management

It is remarkable that morphologic assessment of a relatively small proportion of tumour tissue provides critical information supporting decisions about patient management. However, as the process involves interpretation, it is subject to sampling bias, interobserver variability, and the expertise of pathologists. The wide range of morphologic patterns within each histologic subtype, overlapping histologies, and lack of specific diagnostic markers, especially in tumours lacking classic morphology, adds to the challenge.

Accurate diagnosis begins with macroscopic evaluation, a task increasingly performed by pathologist assistants, which can confound matters. For example, tumour size is critical for risk stratification, especially of small renal masses. Most prognostic tools are based on size of surgically resected specimens; however, measurements may vary based on when and how the specimens are taken. For example, it has been shown that maximum tumour size is 12% larger when assessed by imaging than by measurement of freshly bisected specimens. In turn, these measurements are typically 4.6% larger than those taken using formalin-fixed specimens.[284]

Another critical assessment is tumour extension. Invasion into the renal sinus may not be apparent on imaging and requires diligent grossing and knowledge of the patterns of spread. The AJCC 8th edition considers both renal sinus and perinephric infiltration as pT3a. However, some evidence suggests that there may be differences in prognosis between the two.[285,286] Regardless, perinephric invasion without sinus involvement is infrequent. Furthermore, it is uncertain whether sinus invasion is an independent prognostic factor.[287] Currently, stage pT3 is substaged based on tumour cell invasion into the renal vein (pT3a) and the IVC (pT3b). Invasion of the supradiaphragmatic IVC and into the IVC wall is categorized as pT3c. Some suggest that pT3a may be subcategorized, with early invasion involving the segmental veins and advanced invasion the main renal vein.[288] Though early sinus extension is better identified by pathologic assessment, radiologic and intraoperative findings are helpful for assessing the degree of IVC extension. Vein wall tissue is infrequently submitted for histopathologic assessment, and it is typically difficult to separate invasion from attachment. It is therefore largely a "clinical impression" that is used for the final rendering of pT3c substage.

Accurate subtyping of RCC beyond "CCRCC versus non-CCRCC" is important for management. This is relevant for: (1) small renal masses considered for active surveillance, (2) RCC with metastatic disease for deciding subtype-specific therapies, and (3) locally advanced RCC when considering adjuvant therapy. For example, whereas oncocytomas are suitably followed by active surveillance, FH-deficient RCC should probably be intervened upon. In addition, while most systemic therapies for advanced RCC are deployed for different histological types, they have been largely developed for CCRCC and not all histologies respond equally. For example, chromophobe tumours tend to be poorly responsive to immunotherapy. In contrast, tumours with sarcomatoid differentiation should be treated with an immune checkpoint–containing regimen. Finally, adjuvant therapy is specifically approved by the FDA for CCRCC and not other histological types.

Appropriate histological typing is of essence also for clinical trials. Unfortunately, many trials, including phase 3 registration trials, have focused on tumours with "clear histology/features." This is often based on limited biopsy material and can be misleading. For example, biomarker studies of the IMmotion151 phase 3 trial revealed a substantial number of TRCC among the intended CCRCCs.[124] In addition, other tumours, including non-RCCs, such as urothelial carcinomas and adrenal cortical carcinomas, can often involve the kidney and mimic high-grade RCC with "clear histology/features" (**Figure 5D**). Centralized confirmatory ancillary testing and pathology review for clinical trials would therefore be highly recommended.

Finally, our predictive and prognostic molecular and IHC studies are based largely on single samples, usually from the primary tumour. It remains to be determined whether multiple samples including from metastatic tissue improve diagnostic and prognostic models and which areas within a tumour are representative or most informative. Integrating radiological features, gross morphology findings, and genomics may refine working models. Finally, artificial intelligence holds tremendous promise in pathology.

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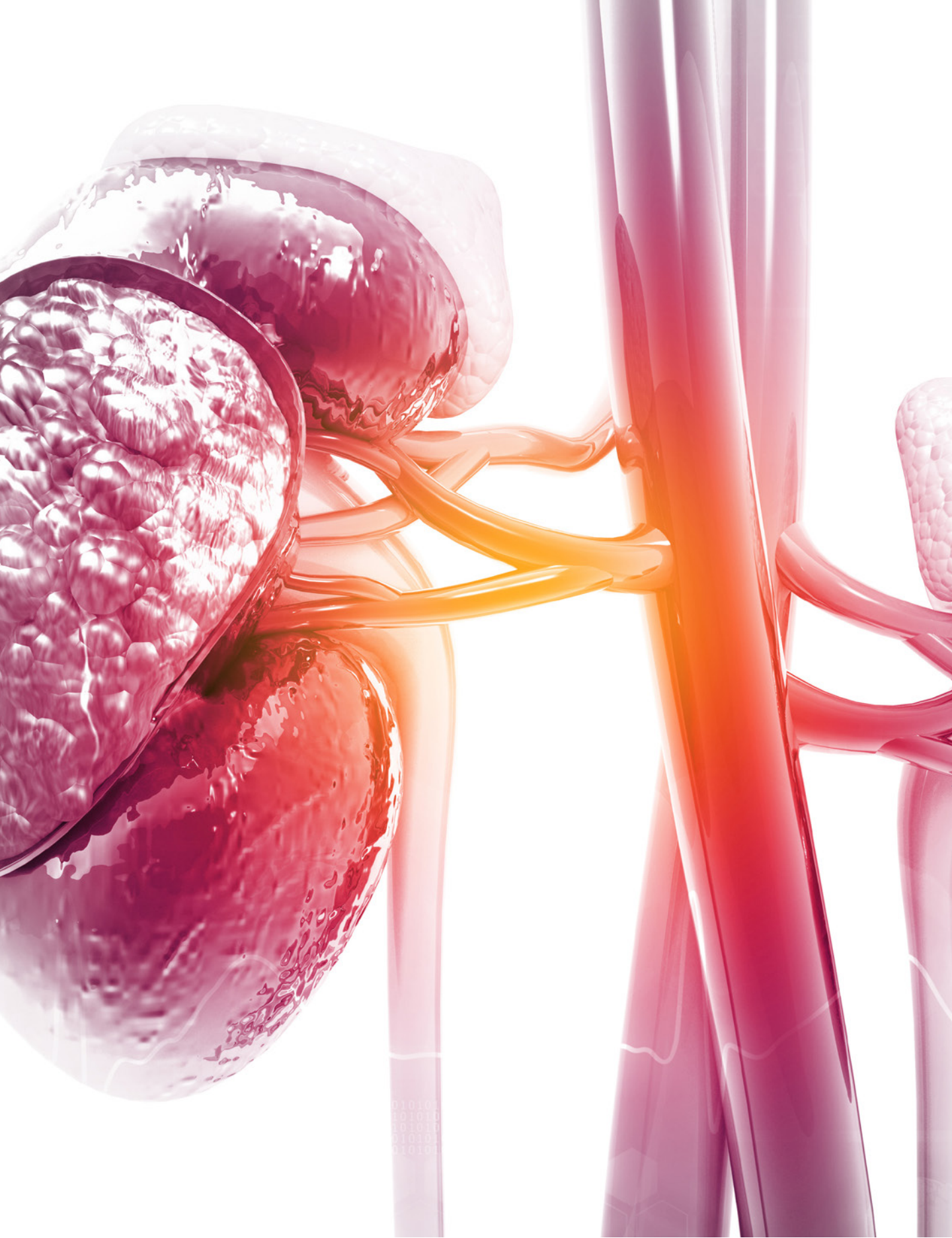

COMMITTEE 4

Genetics of Renal Cell Carcinoma

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Table of Contents

Introduction

Renal cell carcinoma is a diverse group of diseases for which the genetic underpinnings are becoming more clearly defined. In this comprehensive review, we highlight the progress in our understanding of the genetic and microenvironmental hallmarks of kidney cancer. In the first section, we review the steps in clear cell renal cell (ccRCC) initiation and progression. This includes the critical role of 3p locus and its family of tumour suppressors. We review the critical steps in tumour progression as the evolutionary trajectory and impact of intra- and intertumoural heterogeneity. In the section devoted to non-clear cell RCC, we review the genetic determinants of the dominant entities including papillary and chromophobe subtypes and highlight the diversity of a genetics event comprising the high-grade unclassified subtype. Next, we discuss recent understanding of the ccRCC microenvironment. Both single-cell and bulk RNA sequencing have identified the dominant immune populations in ccRCC, including the role of T-cell signature and angiogenic signature on predicting response to systemic therapies in RCC. Finally, we describe how genetically engineered mouse models have improved our ability to model RCC development in immunocompetent settings, which will undoubtedly lead to further mechanistic discoveries.

Genetics of Clear Cell RCC

Clear cell renal cell carcinoma has a well-defined genomic landscape. The first event toward malignant transformation is the loss of the short arm of chromosome 3 (3p loss), which is the most commonly detected copy number variant (~90% of cases).[1,2] The original description of 3p loss, more than three decades ago,[3] concluded that ccRCC must arise by deletion of a "recessive cancer gene." In reality, 3p encompasses four tumour suppressor genes that constitute the most common targets of point mutations or somatic copy number alterations (SCNAs) in RCC: *VHL* on 3p.25, and *PBRM1, BAP1*, and *SETD2* on 3p.21.[2,4] Of these genes, *VHL* is the mostly commonly altered in both hereditary and sporadic RCC, through point mutations and methylation occur in 70–80% and 5–10% of patients, respectively.[1,4] Inactivation of the *VHL* protein results in loss of regulation and thus constitutive activation of the hypoxia-inducible factor (HIF) protein and its cascade of downstream targets, including vascular endothelial growth factor (VEGF), promoting tumour cell proliferation, neoangiogenesis, and metastases.[5,6] *PBRM1* is the second most commonly mutated gene (40% of cases[2,4]), and encodes BAF180,[5,7] a component of the switching defective/sucrose nonfermenting (SWI/SNF) family of chromatin-remodelling complexes, which determine DNA accessibility to transcription factors and polymerases.[7–9] Similarly, *BAP1* (mutated in 10–15% of ccRCC patients) encodes a nuclear deubiqutinase protein that interacts with host cell factor-1 (HCF-1), which is involved in chromatin remodelling.[10,11] Interestingly, *BAP1* and *PBRM1* mutations are generally mutually exclusive.[1,4] Lastly, while the mechanism by which *SETD2* (mutated in 10–15% of ccRCC) effects tumourigenesis remains unclear, it is suspected to be involved in DNA double-stranded break repair, DNA methylation, and RNA splicing.[2,12]

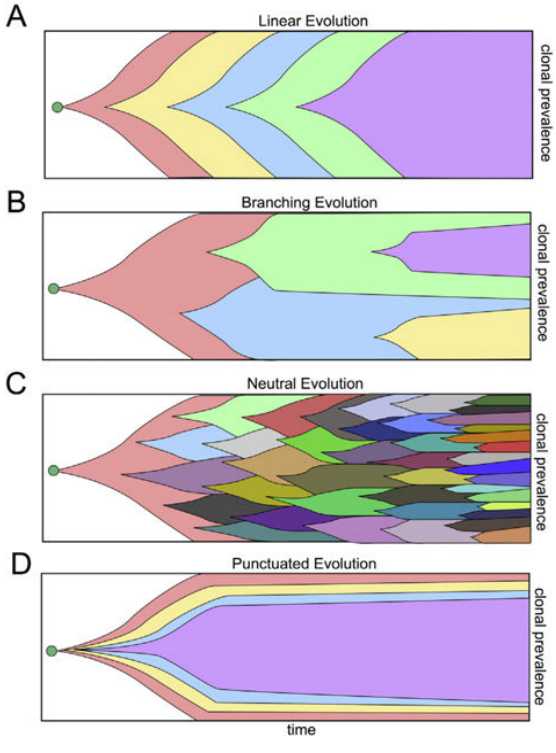
Interestingly, the mechanism of 3p loss that results in loss of heterogeneity (LOH) for the above genes is frequently underpinned by chromothripsis, a catastrophic mutational event in which one or few chromosomes undergo multiple breaks simultaneously, followed by joining of chromosomal fragments at a random order, resulting in hundreds of genomic rearrangements.[13] In ccRCC, the chromosomal loss of 3p during chromothripsis most frequently cooccurs with the gain of chromosome 5q.[1] It is inferred that this initial 3p loss constitutes the "first hit" in the malignant transformation to ccRCC, occurring somatically in the proximal tubule of the nephron (the cell of origin of ccRCC) decades before the presentation of ccRCC, and as early as adolescence. While single chromosome aneuploidy is ordinarily not tolerated in normal cells,[14] it has been postulated that a small number of cells with 3p loss survive,[1] after which a "second hit" results in their malignant transformation—usually mutation or methylation of *VHL* that results in biallelic inactivation of *VHL* and upregulation of the hypoxia response in the presence of normoxia. This is usually followed by mutations involving the neighboring *PBRM1*, *SETD2*, and *BAP1* genes, and less frequently, alterations of *TP53*, *mTOR*, *TSC1*, *TSC2, PIK3CA*, *PTEN*, *KDM5C*, and *SMARCA4*.[15] Critically, ccRCC does not harbour frequent alterations in oncogenes like other cancer types, with obvious implications for therapeutic targeting. Recurrent SCNAs are also evident in ccRCC, consistent with their selection during tumourigenesis and progression. None of these are focal events that encompass a single gene or even a limited number of genes. Instead, they are usually chromosomal arm or whole chromosome gains and losses. The most common SCNAs are losses on chromosomes 1p, 3p, 4q, 6q, 8p, 9p, and 14q, and gains on chromosomes 1q, 2q, 5q, 7q, 8q, 12p, and 20q.[16]

Although the repertoire of driver genes and SCNA in ccRCC is relatively narrow, molecular diversity is achieved through clonal evolution, i.e., selection of subpopulations of cells (clones) characterized by different driver mutations, resulting in intratumoural heterogeneity (ITH).[5] Consequently, molecular profiling, which relies on one sample of the tumour from a single spatial location, does not accurately portray all the molecular events in that tumour. Therefore, a single biopsy will capture clonal events, which are propagated in all the cancer cells of a given tumour but can easily miss events in subclones. While such issues fall under the umbrella of sampling bias, which is problematic across all solid cancers and is frequently associated with the failure to externally validate translational biomarkers, they are particularly pertinent in ccRCC due to the cancer's high levels of ITH.[17,18] This makes the reported frequencies at which different genes are altered dependent on the likelihood of their mutations being missed in single sample studies. For example, the frequency of mutations in *SETD2* is twice as high in a multiregion molecular profiling setting compared with a single tumour profile.[19]

Therefore, multiregion sampling is critical to capturing the clonal evolution of ccRCC, which is the framework applied in the TRAcking Non-small Cell Lung Cancer Evolution Through Therapy (Rx) (TRACERx) Renal program.[18] In the interim analysis of the first 100 patients recruited into the study, which involved molecular profiling of >1,200 primary tumour regions, the degree of ITH increased with tumour size and tumour stage and was associated with the clinical outcome both in the TRACERx Renal and The Cancer Genome Atlas (TCGA) cohorts.[19] This supports the notion that ITH provides substrates for selection and fuels ongoing tumour evolution, with clear evidence supporting the presence of highly conserved patterns of mutational ordering, cooccurrence, and mutual exclusivity in ccRCC which combined with the evolutionary tempo determines the evolutionary paths. Broadly, two modes of evolution are observed: linear, where only a single clonal population

is evident, with consequently low ITH; and branched, which involves multiple subclonal populations with high ITH. Two additional models have been proposed to describe the evolution of clonal or subclonal populations: neutral evolution, wherein the population(s) progress through sequential and gradual acquisition of and genomic alterations in a process of selection akin to a Darwinian process; or punctuated evolution, which is noted by short bursts of large number of genomic alterations occurring in a relatively brief period early in the tumour's evolution, most likely due to SCNA and structural chromosomal alterations (**Figure 1**).[20]

FIGURE 1 A schematic representation of potential models of tumour evolution described above. (A) Linear Evolution (B) Branching Evolution (C) Neutral Evolution (D) Punctuated Evolution. Colours indicate clones with different genotypes.



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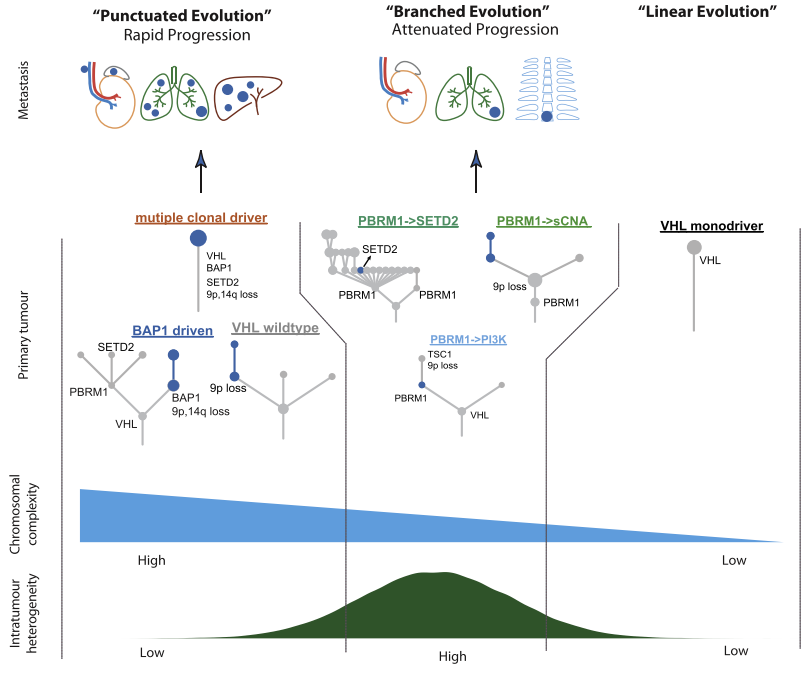
Following from these models, some ccRCC tumours are characterized by a linear evolution pattern and harbour only 3p loss and *VHL* mutation/methylation with low ITH, and are thus termed "VHL mono drivers."[19] As inactivation of *VHL* alone offers a limited fitness advantage,[21] these tumours are enriched for small renal masses (SRMs, < 4 cm in maximal dimension), which are associated with limited progression and metastatic risk. While this is reassuring, the likelihood of such tumours evolving further is unknown, a critical requirement for clinical decision-making.[22]

ccRCC tumours characterized by branched evolution harbour distinct subclones, each associated with a driver event suggesting that the branching reflects selection. These tumours exhibit high levels of ITH and parallel evolution,[19] i.e., repeat selection of distinct mutations in the same gene or pathway. The order of genomic events in these tumours is highly conserved. *PBRM1* is mutated on the background of mutant *VHL*, after which the evolutionary path proceeds down three possible routes: (1) alterations of the PI3k pathway; (2) SCNA; or (3) *SETD2* mutations, usually multiple subclones with distinct *SETD2* variants (**Figure 2**).[19] *BAP1* mutations are mutually exclusive with *PBRM1* and *SETD2* in the context of branched evolution at the clone level, although they may cooccur at the patient level if they were to harbour separate distinct clones.[19] Intriguingly, primary tumours exhibiting these evolutionary paths grow to a large size, and are highly vascular. This is in keeping with the preclinical model showing that *PBRM1* loss amplifies HIF1 upregulation caused by *VHL* deficiency.[23] Although metastatic, these tumours are associated with an intermediate metastatic efficiency resulting in solitary or oligometastases.[19] Accordingly, the patients whose primary tumours were characterized by a branched evolutionary path appeared to benefit from cytoreductive nephrectomy (CN) and metastasectomy, providing a potentially helpful biomarker in identifying patients who are likely to benefit from CN in light of recent studies emphasizing the critical role of patient selection for this procedure.[24]

FIGURE 2 Illustration of proposed evolutionary trajectories in the TRACERx cohort and their corresponding chromosomal complexity and intratumoural heterogeneity.



Source: Reproduced from Turajlic S, Xu H, Litchfield K, et al.*; TRACERx Renal Consortium. Deterministic evolutionary trajectories influence primary tumor growth: TRACERx Renal.* Cell. *2018;173(3):595–610.e11. doi:10.1016/j.cell.2018.03.043.*[19]

While ccRCC tumours characterized by punctuated evolution have low ITH and are dominated by a single clone, these tumours have additional molecular alterations in the dominant clone that distinguish them from the similarly monoclonal *VHL* mono drivers. Additional molecular alterations in the punctuated-evolution clones include *BAP1* (*BAP1*-driven subtype), and two or more of *PBRM1*, *BAP1*, *STED2*, or *PTEN* (multiple clonal driver). Finally, an evolutionary path on the absence of *VHL* mutation is also associated with punctuated evolution (*VHL* wild type). Whatever the route, all these tumours harbour high levels of clonal chromosomal complexity, consistent with the notion that early fixation of large-scale alterations leads to punctuated evolution. These tumours grow rapidly to a large size and are linked to widespread and rapid metastases, with no benefit from CN or metastasectomy.[19]

Focusing on metastatic competence, there has been no consistent association between mutations in any gene (in the primary tumour) and the risk for metastases. However, several reports have linked the presence of 9p loss and recurrence following surgery.[25] In the context of the TRACERx Renal program, it was possible to systematically compare the cancer populations in the primary tumour that are metastases founders versus those that fail to lead to metastases.[18] There was no difference relative to the number or identity of the driver genes in metastasizing and nonmetastasizing clones. However, metastasizing clones had a higher proliferation index, higher levels of aneuploidy, and more SCNAs. Furthermore, they were enriched for loss of 9p and loss of 14q,[18] two loci harbouring tumour suppressor genes: *CDKN2A* and *HIF1-α*, respectively. However, in the absence of mutation or methylation of the other allele, it is unclear whether these are the targets of the copy number alterations. Furthermore, the metastasizing clones are enriched in the centre of the primary tumour, suggesting that the environmental conditions at the tumour core select for these clones, and clones harbouring SCNAs lead to the largest clonal expansions in ccRCC, indicating a large fitness advantage.[26]

Genetics of Non-Clear Cell Renal Cell Carcinoma

While ccRCC is the most common RCC histologic subtype, approximately 25% of tumours present with a variety of other histologies. Papillary RCC (pRCC) is second most common presentation, representing approximately 15–20% of cases, which has been classically subcategorized into type 1 and type 2 pRCC. A further 5–10% of cases are chromophobe RCC (chRCC), followed by rarer kidney tumours, such as renal medullary carcinoma (RMC), each accounting for ~1% or less of the remaining cases. Included within these rarer forms of renal cancer are those associated with specific germline or somatic genetic alterations, such as fumarate hydratase (FH)-deficient RCC, succinate dehydrogenase (SDH)-deficient RCC, and translocation RCC.

While some of these genetically defined tumours are associated with specific histologies, others demonstrate considerable variation in presentation. A broad range of genetic and genomic analyses have been performed on these kidney subtypes that has highlighted the unique alterations present in them and their distinct differences in comparison to ccRCC. In this section, we summarize the genomic features of the most common subtypes of non-ccRCC.

Papillary renal cell carcinoma: types 1 and 2

Papillary renal cell carcinoma is both defined and subdivided into two main subtypes by histology and genetic features. Histologic features of papillary RCC are discussed in detail in **Chapter 3**. Briefly, type 1 pRCC is characterized by papillae and tubular structures covered with small cells containing small, uniform, oval nuclei and basophilic cytoplasm, while type 2 pRCC generally demonstrates papillae covered by large cells with large spherical nuclei with prominent nucleoli and eosinophilic cytoplasm and large spherical nuclei with prominent nucleoli.

Specific genetic and genomic alterations also distinguish between type 1 and type 2 pRCC.[27] Type 1 pRCC is associated with frequent gains of chromosomes 7 and 17 as well as lower frequency gains of chromosomes 2, 3, 12, 16, and 20.[28–31] The most frequent somatic mutational events in type 1 pRCC are activating mutations of the *MET* oncogene, which is encoded on chromosome 7, although this is present in 10–15% of type 1 pRCC cases.[32] Notably, germline activating mutations of the *MET* oncogene are the pathogenic cause of hereditary papillary renal cell carcinoma (HPRC) syndrome, where patients present with bilateral, multifocal type 1 pRCCs.[30,33] TCGA analysis of 75 type 1 pRCCs identified alteration in the *MET* gene in more than 80% of cases, due to a combination of gain of chromosome 7, somatic or germline mutations of *MET* (18.6%), and somatically induced alternative *MET* RNA transcripts and *MET* gene fusions, in a small number of cases. Of note, several oncogenes are also encoded on chromosome 7, including *EGFR* and *BRAF*, and somatic chromosomal gain involving chromosome 7 may influence these genes in addition to *MET*.[31]

Unlike type 1 pRCC, type 2 pRCC represents a heterogeneous group of cancer types that used to include what are now distinct RCC subtypes with their unique genetic alterations and histologic features, including translocation RCC, FH-deficient RCC, and SDH-deficient RCC. While type 2 pRCC is not associated with a specific pattern of copy number alterations, it has been previously associated with increased loss of chromosome 22, which encodes the *SMARCB1 SWI/SNF* complex chromatin modifying gene and the *NF2 HIPPO* pathway regulator gene,[32] and loss of the *CDKN2A* gene that encodes p16 in ~18% of cases. This latter event is caused by either focal loss of 9p21, promoter hypermethylation, or, in rare cases, somatic mutation, and correlated with poorer survival.[32] In contrast to ccRCC, type 2 pRCCs demonstrate a low frequency rate of mutation in chromatin-modifying genes associated with ccRCC, including *SETD2*, *BAP1*, and *PBRM1*, and in the HIPPO pathway, *NF2* and *SAV1*.[30,32] In light of the above heterogeneity within what was considered "type 2 pRCC" and the absence of characteristic genomic features for this group, pRCC type 2 tumours may be also interpreted as actually unclassified, aggressive unclassified RCC that exhibits papillary features but requires specific genomic subclassification for clinical outcome prediction.[34]

Chromophobe renal cell carcinoma

Like ccRCC and pRCC type 1 tumours, most chromophobe renal cell carcinomas (chRCCs) are characterized by a distinct pattern of chromosomal alteration. This pattern is defined by combined loss of chromosomes 1, 2, 6, 10, 13, and 17, seen in approximately 80% of chRCCs. Less frequent additional individual losses can occur

for chromosomes 3, 5, 8, 9, 11, 18, and 21q in 12–58% of cases.[35,36] The histology of chRCC can include a rarer eosinophilic variant in which the classic pattern of chromosomal losses is less common. ChRCCs have a lower mutation burden than ccRCC or pRCC; only *TP53* and *PTEN* are frequently mutated in ~30% and ~8% of cases, respectively.[32,37] Loss of *CDKN2A*, by either loss of 9p21 or hypermethylation, is the second most common alteration (19.8%).[32] Increased TERT expression has been observed in approximately 17% of chRCC, resulting from either the known *TERT* gene promoter mutations or genomic rearrangements involving the *TERT* promoter region, including intra-chromosomal rearrangements and translocations with chromosome 13.11. Although the rate of mutation in chRCC is generally low, a small fraction (~6%) of tumours demonstrates kataegis, a pattern of localized hypermutation, which is correlated with increased *TERT* gene expression in these tumours.[38] A recent comprehensive genomic analysis of localized and metastatic chRCC noted enrichment of *TP53* mutations (58%), *PTEN* mutations (24%), and imbalanced chromosome duplication (duplication of ≥ 3 chromosomes) in metastatic chRCC, which were also associated with worse survival in the TCGA chRCC cohort.[39]

Renal medullary carcinoma

Renal medullary carcinoma (RMC) is a rare and aggressive subtype of kidney cancer that comprises less than 1% of all RCCs and has a propensity for early metastases, resulting in a median overall survival of just more than a year.[40–42] RMC predominantly afflicts individuals with sickle cell trait, creating an enrichment of patients with African or Mediterranean decent, and the young, with a median age from 19 to 22 years old.[40–46] The characteristic genetic feature of RMC is the near universal loss of expression of the SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1) protein, which is known as Integrase interactor 1 (INI1), BRG1-associated factor 47 (BAF47), or Sucrose Non-Fermenting 5 (SNF5). Loss of SMARCB1/INI1 staining by immunohistochemistry is a marker of RMC. The SMARCB1 protein is encoded by the *SMARCB1* gene on chromosome 22q11.23, and in most tumours both copies of this gene are lost by a combination of mutation and chromosomal deletion.[47] SMARCB1 is a core subunit of the SWI/SNF chromatin remodelling complex and its loss results in dysregulation of the transcriptional activity within many pathways.[8,48]

FH-deficient and SDH-deficient renal cell carcinoma

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is a familial cancer syndrome characterized by the development of cutaneous and uterine leiomyomas, and a highly aggressive form of kidney cancer.[49–52] HLRCC is associated with germline mutation of the Krebs cycle enzyme gene fumarate hydratase (FH) and the associated tumours demonstrate complete loss of fumarate hydratase enzyme activity, leading them to be referred to as FH-deficient RCC.[53–55] Germline mutation of several subunits of succinate dehydrogenase enzyme, SDHB, SDHC, or SDHD, have been associated with increased risk for paraganglioma (PGL), pheochromocytoma (Pheo), gastrointestinal stromal tumour (GIST), and RCC.[56–58] SDH-deficient RCCs associated with these germline changes demonstrate loss of succinate dehydrogenase enzyme activity.

The complete loss of either fumarate hydratase or succinate dehydrogenase enzyme activity impairs the normal function of the Krebs cycle and oxidative phosphorylation within the tumour, promoting increased levels of

aerobic glycolysis, and significantly increases in the levels of intracellular fumarate and succinate, respectively.[59,60] Increased fumarate or succinate levels can inhibit the activity of 2-oxoglutarate (2OG)-dependent dioxygenase enzymes. These include the prolyl hydroxylases that degrade the HIFα transcription factor subunits, resulting in a pseudo-hypoxic state that upregulates many of the genes necessary to maintain the higher levels of glycolysis, and the ten-eleven translocation methylcytosine dioxygenases (TETs) involved in the maintenance of the epigenome and removal of aberrant CpG methylation, resulting in a CpG island methylator phenotype (CIMP).[31,61–64]

Increased intracellular fumarate levels cause the aberrant succination of numerous proteins, resulting in function alterations in some cases. In turn, succination induces inactivation of KEAP1, which results in the constitutive upregulation of the NRF2-antioxidant response element (ARE) pathway and inactivation the core factors responsible for replication and proofreading of mitochondrial DNA (mtDNA), resulting in both a significant decrease in mtDNA content and increased mtDNA mutation.[65,66]

A recent germline analysis comparing SDH- and FH-deficient tumours (SDH-RCC and FH-RCC, 17 and 25 patients, respectively) noted that while most of these tumours harboured germline alterations in their respective genes, SDH-RCCs had a lower mutation burden and CNA burden than FH-RCCs. All SDH-RCCs presented with deletion of chromosome 1p (overlapping SDHB), whereas FH-RCCs demonstrated high but not ubiquitous loss of 1q (FH locus), again suggesting that FH-RCCs exhibit more genomic diversity than SDH-RCCs. Metabolomic analysis of the same cohort noted clear separation from ccRCC tumours, with elevation of succinate in both FH-RCC and SDH-RCC. Furthermore, relative to normal kidney tissue, FH-RCC tumours had elevated levels of urea cycle metabolites (argininosuccinate, citrulline, and fumarate), whereas SDH-RCC tumours had elevation of numerous acylcarnitines, potentially presenting metabolomic signatures that can be used to differentiate these tumours when the genomic analysis is inconclusive.[67]

In addition to patients with germline mutation, a small number of sporadic tumours have also been shown to have complete somatic loss of FH, resulting in a non-hereditary form of FH-deficient RCC.[31]

Translocation renal cell carcinoma involving TFE3, TFEB, or MITF gene fusions

Translocation renal cell carcinomas are driven by somatic chromosomal translocations that fuse members of the MiT transcription factor family genes, *TFE3*, *TFEB, or MITF*, with a series of different partner genes that result in fusion proteins.[68,69] Translocation RCCs represent one of the most common forms of RCC in children and young adults, comprising 20–50% of pediatric RCC patients and 15% of RCC patients under the age of 45 years.[69,70] Translocation RCCs still represent an appreciable fraction of the adult population of RCC cases and can present with a variety of histologies, including both papillary and clear cell.[31,69] To date, fusions involving *TFE3* are the most common, followed by *TFEB*, with fusions of *MITF* being the rarest.[30,32,68,69,71] These fusions all result in an upregulation of the aforementioned MiT transcription factors—which are master regulators of adaptation to cellular stress and can influence many pathways, such as organelle biogenesis, cell proliferation, and cellular fate commitment—that may aid in tumourigenesis.[69,72,73]

In addition, some sporadic tumours have been shown to have amplification of the *TFEB* gene with no translocation and a specific germline alteration of the *MITF* gene (p.E318K), which dysregulates the SUMOylation of the resultant protein, and has been shown to be associated with an increased risk for RCC.[70,74,75] While neither of these genes represent translocation RCCs, they demonstrate the importance in RCC of other genetic alterations within this gene family.

Tumour Microenvironment of RCC

While malignant cells make up most of the tissue mass in tumours, they are also encircled by a dynamic and heterogeneous mixture of immune cells, stromal cells, cytokines, and extracellular proteins. The coexistence and interactions of these components within the tumour constitute a tumour microenvironment (TME).[76] The fundamental role of the TME in the pathogenesis of solid malignancy has been highlighted by the introduction of immune checkpoint blockade (ICB) agents, which have revolutionized management of solid malignancies, including RCC.[77] The TME is now viewed as an ecosystem in which the interactions of innate and adaptive immunity cells, specifically macrophages and T cells, and tumour cells modulate all aspects of tumour development.[76]

Profiling studies of the TME of RCC tumours have largely broken tumour phenotypes down into two categories, those driven by angiogenesis and those by immune inflammatory stimuli.[78] Genomic characteristics of tumours that have the more infiltrated/inflamed profile include an enrichment of several copy number alterations, including amplifications of 12q24.32 and deletion of 9p21.311.[79] Yet even when considering genomic features such as numerous copy number alterations in advanced ccRCC, including deletions of 9q34.3, and loss of the regions of 6p, which code for antigen-presenting machinery and human leukocyte antigen (HLA) class II molecules, respectively, these features do not appear to correlate with systemic treatment response.[80] Tumours that are found to have an angiogenic profile also appear to be associated with alterations in *PBRM1* and improved response with targeted therapy.[81,82] *PBRM1*-altered tumours may also be associated with decreased regulatory T cells (Tregs, FOX3P3+ T cells), which tend to be associated with inferior clinical outcomes.[80,83] Interestingly, alterations in *BAP1* appear to be less associated with angiogeneic tumours but more with those tumours having a higher macrophage infiltration/activity.[81] Tumours with *SETD2* alterations seem to be associated with decreased T-cell infiltration.[80,84]

However, profiling the RCC TME into such simple immune-infiltrated and angiogenic phenotypes oversimplifies its dynamic and heterogeneous nature. For example, while tumours with high numbers of tumour-infiltrating T lymphocytes (TILs) were classically associated with favourable clinical outcomes such as survival and response to immunotherapy,[85,86] RCC does not appear to have this association, with some studies suggesting that increasing TILs correlate with poor clinical outcomes.[79,87–89] This has been explained by heterogeneity within the infiltrating T-cell populations, which have been found to exist in a continuum from activated antitumour cells to dysfunctional "exhausted" T cells.[90,91] Similarly, the role played by tumour-associated macrophages (TAMs) in RCC TME varies from promoting antitumour response to facilitating tumour growth depending on the subsets or phenotypes of

TAMs enriched within a tumour.[2,87,88,92] Earlier studies of the TME in ccRCC tumours noted two broad phenotypes (polarizations) of TAMs: the pro-inflammatory/antitumour M1 phenotype, and the M2 anti-inflammatory/protumour phenotype. While these phenotypes have been associated with several important clinical outcomes in ccRCC and seen across multiple patient cohorts,[87,88,92–94] recent evidence shows TAM populations to be highly plastic, existing in more of a phenotypic spectrum between M1 and M2 phenotypes *in vivo*.[87,88,93,95]

While earlier analyses of tumour immune infiltrates were largely based on tissue-based approaches such as immunohistochemistry and flow cytometry, these approaches were limited by several logistic factors, including the number of predefined cell phenotypes/markers that can be analyzed in a single assay and the amount of tissue required for analysis.[78] This, in turn, limited our ability to decipher the subtleties within immune cell populations of ccRCC to determine whether they are reflective of generally pro- or antitumour response, and as importantly, whether they are likely to respond to certain systemic therapy regimens. In contrast, transcriptomic analyses of tumour TME using microarray- and next-generation sequencing (RNA-seq)-based analyses have provided a broader perspective in analyzing the TME, utilizing computational techniques such as single gene set enrichment analyses (ssGSEA[96]) and CIBERSORT[97] to deconvolute the TME into its cellular components and explore its response to systemic therapy agents through an array of gene expression signatures.[78,82,98,99] In addition to reproducing the established immune- infiltrated versus immune-excluded tumour subtypes, these analyses revealed specific enriched T-cell and macrophage populations in the TME and the influence of their interactions on disease survival. For example, such studies noted a generally negative correlation between enrichment of T-helper subtype 2 (Th2) cells and Treg cells and survival in ccRCC,[78] explaining the aforementioned potential negative association between T-cell infiltration and survival outcomes in ccRCC.[79,87–89] Similarly, worse overall survival and survival in tyrosine kinase inhibitor (TKI)-treated patients were associated with higher levels of macrophage infiltration, which were found to be driven by the levels of M2 macrophage infiltration in the TME.[81] This understanding of the TME led to investigations of transcriptomic signatures that may predict response to systemic therapy in advanced RCC, potentially providing a platform for much needed biomarker development in this disease, such as angiogenesis-associated signatures that can predict response to TKI monotherapy,[81,82,100] or immune-infiltration signatures that can predict response to ICB-based combination therapies.[82,100]

While bulk RNA sequencing provided further insights into the subpopulations within the TME, it remains a bulk-based analysis method, and is thus confounded by the well-known inter- and intratumoural heterogeneity of RCC. Therefore, bulk techniques (flow cytometry or bulk RNA sequencing) remain bound to undermine the heterogeneity of T-cell and TAM populations within RCC, even with the additional granularity offered by bulk RNA-sequencing deconvolution algorithms. Furthermore, bulk techniques are unable to describe dynamic changes occurring within sampled TME cell populations, or interactions between different cell populations.[101] In contrast, single cell–based analyses such as single-cell RNA sequencing (scRNA-seq) and single-cell mass cytometry (scMC) allow for massively parallel, high-dimensional analyses of specific cell populations in the TME, with the ability to predict potential interactions between different cell populations based on their expressed surface molecules, promoting a much granular understanding of the dynamics of the TME of RCC.[87,88,93,95,101]

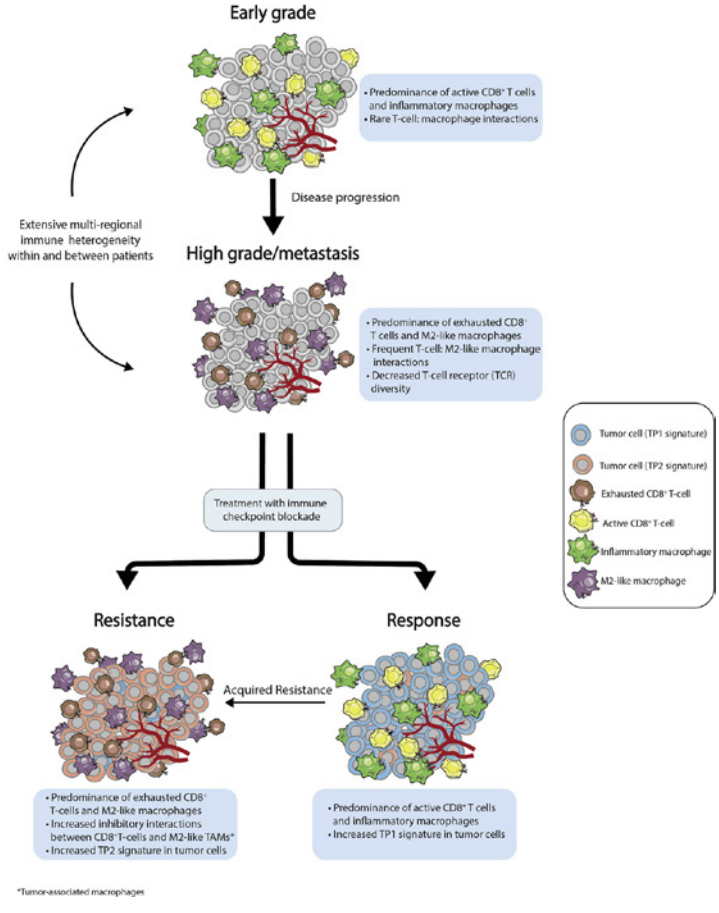
In this regard, Chevrier *et al.* (2017)[95] used scMC to analyze 73 tumour samples of untreated patients with advanced RCC and 5 healthy matched kidney samples. Using computational phenotype clustering, they demonstrated the

significant complexity of the adaptive and innate (T cell and TAM) populations in the TME of RCC, noting 22 different T-cell phenotypes, which made up over half of the immune infiltrate, along with macrophages with 17 phenotypes, which accounted for 31% of immune cells.[95] Two populations of PD1+, exhausted T cells (including CD4+ and CD8+ T-cells) were noted: a "terminally exhausted" cluster and a corresponding "progenitor exhausted" cluster of potentially immuno-oncology (IO)-responsive T cells. In contrast, TAM populations did not exhibit any clear phenotypic differences, again arguing that the M1/M2 polarization phenotypes were an oversimplification of what is a plastic and dynamically changing cell population. However, they did note immunosuppressed T-cell compartments to be associated with high levels of regulatory CD4 cells and a protumour TAM population.[95]

Following this study, Braun *et al.* (2021)[87] performed scRNA-seq and T-cell receptor (TCR) sequencing of ccRCC tissue from 13 patients across clinical stages to define changes in the immune component of the TME with advancing disease. They again noted significant diversity within the T-cell and TAM populations, with the latter existing in a continuum of antitumour (M1) to protumour (M2) polarization. However, they noted an overall linear trend of progressive T-cell dysfunction and exhaustion with advancement in disease stage, which was associated with concurrent shift in from M1- to M2-like signatures in the TAM population. The authors also noted that the predicted T-cell and TAM interactions increased along with disease stage, suggesting they played role in progression of T cells toward exhaustion in ccRCC patients.[87]

To examine the influence of ICB on RCC TME, Krishna *et al.* (2021)[93] used scRNA-seq to examine the TME of multiregional tumour samples from 4 ICB-treated to 2 ICB-naïve advanced ccRCC patients. They noted significant intratumoural and interpatient heterogeneity, along with differences in the overall TME behaviour of ICB-treated versus -naïve patients. Focusing on tumour specimens from an ICB-treated patient who exhibited complete response, they noted enrichment of CD8A+ tissue-resident populations and low TAM infiltrations in all tumour regions. In contrast, specimens from ICB-resistant patients exhibited high TAM infiltration but low T-cell enrichment (T-cell exclusion).[93] Bi *et al.* (2021)[88] performed a similar study that also compared tumours from 5 ICB-exposed to 3 ICB-naïve patients with advanced ccRCC. They noted that ICB-exposed tumours were enriched in a population of CD8+ T cells that had low levels of the activation maker 4-1BB, a feature that had been previously associated with improved response to ICB in melanoma.[88,102] Interestingly, the authors noted that while this cell cluster expressed costimulatory molecules associated with the "progenitor exhausted" T cells described by Chevrier *et al.*,[95] they also paradoxically expressed inhibitory molecules associated with terminally exhausted T cells, suggesting that these ICB-responsive cells were potentially undergoing a shift toward terminal exhaustion as well. Similarly, antitumour TAM populations in ICB-exposed patients were noted to paradoxically express molecules that correlate with a pro-inflammatory, antitumour phenotype, but again with upregulation of immune checkpoint and anti-inflammatory signalling genes. The authors proposed that these seemingly paradoxical changes in both T-cell and TAM populations of ICB-exposed patients may explain the initial response and eventual transition to resistance to ICB agents noted in ccRCC tumours. Finally, the authors noted enrichment for two tumour programs (TPs) within tumour cells: TP1, which was associated with improved survival in the CheckMate-025 (CM-025) nivolumab trial, and TP2, which was associated with upregulation of immune checkpoint molecules, immune evasion, and worse survival in the CM-025 cohort (**Figure 3**).[88] All three scRNA-seq studies also identified novel gene signatures that may have allowed for the detection of specific T-cell, TAM, and TP populations and were validated in multiple external cohorts.[87,88,93]

FIGURE 3 The tumour microenvironment of ccRCC undergoes notable changes in both the T-cell and macrophage compartments with progression from early-grade to high-grade/metastatic disease, including progression toward exhausted T-cell and protumour M2 phenotypes, respectively. Following treatment with immune checkpoint blockage (ICB) agents, responsive tumours acquire changes in these compartments, along with changes in the tumour program (TP) that are antitumour proliferation, while unresponsive tumours maintain their predominantly protumour, exhausted T-cell, TP2 phenotypes. However, ICB-responsive tumours also exhibit changes suggestive of a potential transition to eventual ICB resistance.



Source: Reproduced from Koh MY, Sayegh N and Agarwal N. Seeing the forest for the trees—single-cell atlases link CD8+ T cells and macrophages to disease progression and treatment response in kidney cancer. Cancer Cell. *2021;39(5):594–596. doi:10.1016/j.ccell.2021.03.008,* [101] *© 2022 with permission from Elsevier.*

While single cell–based technologies have revolutionized our understanding of the complexity and heterogeneity of the TME in RCC, it is important to note that even these technologies are not without their limitations—current scRNA-seq platforms are costly and allow for analysis of relatively limited cell numbers, limiting their ability to

examine large patient populations and to capture cellular complexity,[101] and scMC relies on limited, prespecified sets of isotope-labelled antibodies for detection of prespecified cell "types" by mass spectrometry.[95] Furthermore, both technologies require cell separation prior to analysis, resulting in loss of spatial orientation in the TME that they attempt to reproduce using complex computational methods,[87,88,93] which may be abrogated with newer spatial transcriptomic technologies that allow for parallel sequencing of TME cells *in situ*.[103] However, future work remains needed for the incorporation of these technologies and their derived TME signatures into clinical practice to guide management of RCC patients and identify potential new therapeutic targets within the TME of RCC.

Mouse RCC Models

Mouse models of human cancers represent valuable experimental systems that allow the study of the detailed mechanisms that underlie tumour pathology and are essential for preclinical therapeutic studies. Transplantation of human ccRCC cancer cell lines, or of fragments of human ccRCC tumours, into immunodeficient mice as xenografts or patient-derived xenografts (PDXs), respectively, represents valuable human ccRCC model systems. Excellent reviews of the available cell line xenograft models[104,105] as well as a description of an extensive resource of human PDX models[106] are described elsewhere. In this section, we focus on recent progress that has been made in generating genetically engineered mouse models (GEMMs) of ccRCC. The underlying goal of generating GEMMs is to be able to accurately mimic the genetic events that underlie the initiation, evolution, and progression of human ccRCCs in the physiologically relevant context of the mouse kidney. In contrast to xenograft and PDX models, ccRCC tumours in GEMMs arise directly from the relevant cell of origin in the context of the normal complex structures of the renal nephron and normal surrounding cells. Perhaps most importantly given the enormous recent progress that has been made in developing immune checkpoint–based therapies for ccRCC, GEMMs are immune-competent and therefore reproduce ccRCC immune microenvironments, providing opportunities to study and manipulate the interactions of tumour cells and immune cells that modulate the animal's antitumour immune response over the course of the evolution of the tumour.

For many years, the development of ccRCC GEMMs lagged behind the rapid progress that was made in modelling other common types of human tumours, in part due to lack of knowledge of the unique and complex spectrum of genetic drivers of human ccRCC tumours. However, insights from several kidney cancer exome sequencing projects fueled recent successful efforts to generate accurate mouse ccRCC models that reflect different combinations of genetic driver mutations. These models and the biological and therapeutic insights that are beginning to be derived from their study are summarized below. More detailed information about ccRCC and non-ccRCC mouse GEMMs are described in other publications.[105,107]

Initial attempts to model ccRCC revealed that genetic deletion of *Vhl* (also known as *Vhlh*), the mouse homologue of *VHL*, in renal epithelial cells in mice is not sufficient to induce tumour formation.[108–112] These findings are consistent with the conclusions of studies of the evolution of human ccRCC, which revealed that *VHL* deletion alone is insufficient to induce tumour onset,[21] but rather that tumour evolution results from the combined biallelic

inactivation of *VHL* as the truncal genetic event, followed by additional mutations or copy number alterations in one or more of a series of other genes that control cellular epigenetics, PI3K-pathway signalling, or cell cycle regulation.[1,2,4,18,19] Combinations of these mutations act as secondary and tertiary genetic events to drive tumour formation. Mouse genetic studies have confirmed this concept of ccRCC evolution by showing that mutations in a number of different genes can cooperate with *Vhl* mutation to induce the evolution of ccRCC precursor lesions or tumours from mouse renal epithelial cells *in vivo*. Studies of mice with the combined mutation of *Vhl*/*Pten*,[110] *Vhl*/*Kif3a*,[113] (*Kif3a* is a gene that is essential for the formation of the primary cilium), and *Vhl*/*Trp53*/*Kif3a*[114] implicated loss of the primary cilium in the formation of premalignant cysts that in at least some cases represent precursor lesions of ccRCC. The development of cystic as well as premalignant solid ccRCC precursor lesions was also induced by the combined mutation of *Vhl*/*Trp53*.[115] Importantly, mice with renal epithelial–specific deletion of *Vhl*/*Pbrm1*,[23,116,117] *Vhl*/*Bap1*,[117,118] *Vhl*/*Pbrm1*/*Tsc1*,[118] *Vhl*/*Trp53*/*Rb1*,[119] *Vhl* + *Myc* expression, or *Vhl*/*Cdkn2a* plus *Myc* expression[120] all develop ccRCC tumours. These tumours reproduce many of the hallmark molecular and histopathological features of human ccRCC, meaning that they represent *bona fide* GEMM models of different genetic subtypes of ccRCC that can be used to address questions about ccRCC biology and therapy. For example, genetic studies revealed that tumour development in the *Vhl*/*Trp53*/*Rb1* model requires HIF-1α but is less dependent on HIF-2α.[121] Preclinical therapeutic studies in the same model showed that different tumours exhibit variable sensitivities to the tyrosine kinase inhibitor sunitinib and the mTORC1 inhibitor everolimus, partial sensitivity to the dual HIF-1α/HIF-2α inhibitor acriflavine, complete insensitivity to the HIF-2α–specific inhibitor PT-2399, but good sensitivity to the sphingosine pathway inhibitor fingolimod.[119,121] It will be important in future studies to utilize the different models of ccRCC to investigate patterns of genotype-dependent resistance or sensitivity to particular therapies with the ultimate aim of tailoring treatment to the underlying mutations present in each patient's tumour.

Further development of ccRCC GEMMs will also be necessary, as the existing models do not include mutations in other commonly mutated ccRCC tumour suppressor genes such as *SETD2*, *MTOR*, and *KDM5C,* and do not fully reflect the complexities of human ccRCC genomes, which frequently harbour three or more combinations of genetic mutations. With the exception of the *Vhl*/*Cdkn2a* + *Myc* model,[120] the GEMM models also do not exhibit spontaneous metastasis, so they do not accurately reflect the most problematic clinical manifestation of ccRCC in patients.

The availability of existing and future ccRCC GEMMs that are driven by different combinations of genetic mutations will allow for investigation of common phenotypic traits, as well as of potential genotype-specific differences in the biology of ccRCC tumours. In this respect, the available mouse models have confirmed that proximal tubule cells represent the cell of origin of ccRCC. The *Pax8-Cre* and *Ksp1.3-Cre* lines that were used in these models induce gene deletion widely throughout different types of epithelial cells of the nephron, yet the tumours that emerge as a result of deletion of *Vhl*/*Pbrm1*, *Vhl*/*Bap1*, or *Vhl*/*Trp53*/*Rb1* always show markers and gene expression profiles of proximal tubule cells,[23,116,118,119] similarly to human ccRCC. This implies that there are as-yet-unidentified aspects of the biology of proximal tubule cells that make them highly sensitive to transformation by mutation of *Vhl* and cooperating genes. Interestingly, comparison of the effects of deletion of *Vhl*/*Pbrm1* or *Vhl*/*Bap1* using *Pax8-Cre*, which causes tumours, with *Villin-Cre* or *Sglt2-Cre*, which does not cause tumours,

suggests that the cell of origin is likely to be found in the difference between the expression patterns of these drivers.[118] *Pax8-Cre* induces gene deletion widely throughout the nephron including in parietal epithelial cells of the Bowman's capsule, while *Villin-Cre* and *Sglt2-Cre* induce deletion in subfractions of proximal tubule cells, implying that not all proximal tubule epithelial cells have the capacity to form tumours. Further lineage tracing studies using different combinations of gene mutations and different Cre drivers will be necessary to try to narrow down the precise cell or cells of origin of ccRCC.

Related to this point, another interesting biological feature of the majority of the ccRCC GEMMs that have been developed to date (with the exception of *Vhl*/*Bap1*) is that they exhibit very long latencies (typically at least 6 and up to 20 months) until tumours arise after gene deletion. It is evident that only a small fraction of the total number of cells with induced gene deletions will ultimately develop into a ccRCC tumour. This suggests that other genetic, epigenetic, or microenvironmental alterations arise in some cells during the lifetime of the animal and that these must cooperate with the induced gene deletions to cause tumour evolution. By studying the mechanisms that underlie tumour formation in the context of different sets of starting mutations, it will be interesting to investigate whether evolutionary trajectories and mutational selection pressures are in part constrained or dictated by the combinations of starting mutations that are genetically imposed in each model. While these types of studies are in their infancy, one example is that mTORC1 pathway activation is evident in tumours that arise in the *Vhl*/*Pbrm1*, *Vhl*/*Bap1*, and *Vhl*/*Trp53*/*Rb1* ccRCC GEMM models,[23,118,119] implicating activation of this pathway as a point of convergence in the process of tumour evolution in response to different sets of tumour-initiating mutations. Human ccRCCs also frequently display mTORC1 activation and about one-third of all ccRCC tumours harbour genetic mutations that lead to activation of the PI3K-mTORC1 pathway.[2,4] Another example is that exome sequencing of tumours in the *Vhl*/*Trp53*/*Rb1* model revealed recurrent mutations in primary cilia genes,[119] linking to a large body of work implicating the primary cilium in renal cyst formation and ccRCC development.[110,113,122,123] These studies also identified *Myc* gene amplifications in two of seven *Vhl*/*Trp53*/*Rb1* tumours,[119] consistent with frequent chromosomal copy number gains of the *MYC* gene in human ccRCC[2,4] and with the mouse *Vhl*/*Cdkn2a* + *Myc* model[120] in which p53 and pRb functions are abrogated by *Cdkn2a* deletion. Based on these preliminary findings of convergence in different ccRCC models on common molecular pathways, it appears likely that larger-scale studies of the genomes and epigenomes of tumours arising in different mouse ccRCC GEMMs will inform about the spectrum of molecular events that can cooperatively drive the development of human ccRCC.

Summary

As the genetic determinants of renal cell carcinoma have been more clearly defined, this has led to an increased understanding of the evolution and metastatic development, particularly in clear cell renal cell carcinoma. While increasing data supports the role of the immune microenvironment in determining therapeutic response, the molecular links to immune response remain in their infancy. Future studies of both human tissue and murine models will facilitate further progress in the quest to cure kidney cancer.

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COMMITTEE 5

Hereditary Renal Cancer Syndromes

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Table of Contents

Introduction

Some individuals are born with a gene alteration that predisposes them to develop kidney cancer—usually an inactivating mutation of a tumour suppressor gene (TSG). Though both alleles typically must be lost for cancer to occur (the classic Knudson's "two-hit" model,[1]) people with hereditary renal cell carcinoma (RCC) are born with the first "hit," making them prone to early and frequent development of tumours. Although hereditary syndromes represent only 5–8% of all RCCs,[2] it is important for urologists to recognize their features and be aware of their manifestations and management strategies. Early detection will adapt cancer management with a focus on lifelong renal preservation, direct appropriate cancer surveillance protocols, and help identify family members who may also be at risk. Family history of kidney cancer, presentation in the early decades of life, or presence of multifocal or bilateral tumours all should raise suspicion for an inherited syndrome and trigger referral for genetic counselling and screening.

von Hippel-Lindau (VHL) Disease

von Hippel-Lindau (VHL) disease is a hereditary syndrome in which affected individuals demonstrate a predisposition to develop cystic and solid tumours in multiple organs, including the kidneys.[3] von Hippel-Lindau disease is considered a rare disease by the NIH Office of Rare Diseases, with 1 case observed in 35,000 births. There is no gender or racial predisposition, and the prevalence in the United States is estimated at about 7,000–8,000.

The *VHL* gene is located on the short arm of chromosome 3 (3p25-26).[4] It is inherited in an autosomal dominant fashion, and a single mutated copy predisposes an individual to develop clinical manifestations of VHL following the classic two-hit model for a TSG. Modern technology allows for almost 100% accuracy in diagnosis of VHL mutations.[5] *De novo* germline *VHL* mutations are observed in affected patients without family history of VHL. In addition to RCC and renal cysts, patients with VHL are at risk for the development of pheochromocytomas or paragangliomas, hemangioblastomas of the brain or spine, retinal angiomas (hemangioblastomas), cysts and neuroendocrine tumours of the pancreas, endolymphatic sac tumours of the inner ear, and papillary cystadenomas of the epididymis or broad ligament. Renal cell carcinomas in VHL are characteristically early onset, bilateral, multifocal, and of clear cell or conventional histology.[6] It is estimated that patients with VHL can develop as many as 600 renal tumours and 1,100 cysts per kidney,[7] with some requiring their first RCC intervention in their 20s. Given the multi-organ nature of VHL, patients are optimally managed by a multidisciplinary team of physicians. Surveillance procedures and imaging should be coordinated to minimize patient burden and guarantee that tumours are detected and managed in a timely fashion. Renal surveillance involves annual abdominal ultrasound starting at age 8 years, with cross-sectional imaging every 2 years. Magnetic resonance imaging (MRI) is preferred over computed tomography (CT) to minimize lifelong radiation exposure. Urology surgery for VHL patients should never be performed in isolation. It is crucial to be aware of a large central nervous system (CNS) lesion or a functional pheochromocytoma before contemplating any major surgery to prevent potentially life-threatening complications.

Historically, RCC was the leading cause of death with 35–45% of patients with VHL dying from metastatic kidney cancer. Although surgical removal of both kidneys can decrease the risk for metastases, it negatively affects quality of life and long-term survival. Over 30 years, a conservative approach has been developed for the clinical management of VHL RCC that involves active surveillance of renal tumours until the largest tumour reaches 3 cm in maximal diameter, at which time nephron-sparing surgery is performed.[8–10] Because these patients have a lifelong risk for recurrent, multifocal tumours, use of parenchymal-sparing surgery helps to maintain renal function for as long as possible while reducing the risk for metastasis.[9,10] One study followed patients managed with the "3 cm rule" for more than 10 years, confirming that no VHL patient with a renal tumour ≤3 cm developed metastatic disease.[11]

Despite maximal surgical efforts, more than 80% of patients will develop a recurrent renal mass within 10 years of resection.[12] It is important to recognize, however, that these recurrences are *de novo* renal tumours rather than treatment failure, and that the "3 cm rule" can be applied again to trigger repeat nephron-sparing surgery. The success of repeat partial nephrectomy has been demonstrated in this population, with preservation of renal function in the majority[13] even with the 3rd or 4th partial nephrectomy on the same renal unit.[14] Recent advances have allowed treatment of patients with multifocal lesions using a minimally invasive approach, often without need for vascular clamping.[15] In addition to nephron-sparing surgery, percutaneous ablation using radiofrequency, cryotherapy, or microwave therapy has been reported in select patients with comparable functional and oncologic outcomes.[16,17] One limit of ablative modalities, however, is inaccessibility due to proximity to adjacent organs or vasculature, which can preclude safe and effective ablation.[18]

While surgery and ablation remain excellent options for the management of VHL RCC, a recent breakthrough in molecular therapeutics introduced the first FDA-approved HIF-2α inhibitor, belzutifan.[19] VHL patients with renal tumours less than 3 cm in diameter who received daily oral belzutifan demonstrated control of their RCC (partial response or stable disease) in 97% over 21 months of follow-up. Similarly, 91% of concurrent pancreatic neuroendocrine tumours and 30% of concurrent CNS hemangioblastomas responded to treatment. Belzutifan was generally well tolerated, with the most frequently observed side effects being anemia due to on-target inhibition of erythropoietin (an HIF-2 transcriptionally regulated gene) and fatigue.[19] Appreciation of genetics, molecular pathways, epidemiology, and decades of research in both the laboratory and clinic can now offer numerous options for VHL patients with RCC.

Birt-Hogg-Dubé (BHD) Syndrome

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominantly inherited disorder with major features of cutaneous fibrofolliculomas, pulmonary cysts, and RCC.[20–22] BHD syndrome is caused by loss of function, usually truncating, variants in the *FLCN* tumour suppressor gene.[23,24] To date no clear genotype-phenotype correlations have been described, and all individuals with pathogenic *FLCN* variants should be considered at risk of developing RCC.[23]

Clinical expression of BHD is variable. Skin involvement (fibrofolliculomas and trichodiscomas) may be overlooked, and the syndrome is widely considered to be underdiagnosed. Fibrofolliculomas (benign hair follicle tumours) generally start to appear from age 20 years and are present in at least 70% of patients by age 40 years. Fibrofolliculomas typically occur over the nose and malar regions and appear as raised whitish papules. Less frequently they occur on the neck, ears, forehead, and trunk. Fibrofolliculomas and trichodiscomas are benign and require treatment only for cosmetic reasons. Pulmonary cysts, typically localized in the lower lobes, occur in around 80% of patients. Cyst rupture can cause spontaneous pneumothorax, and the lifetime risk for pneumothorax with BHD is about 30%.[25] The lifetime risk for RCC (mean age at diagnosis ~50 years, earliest 20 years) is estimated at 25–30%.[25,26] Multifocal RCC may occur, but this is less common than in VHL disease. BHD mostly presents to dermatologists or pulmonologists, but presentation with apparently sporadic or familial RCC is well recognized.[27]

A variety of histopathologies have been described in BHD. A hybrid chromophobe oncocytic appearance is most characteristic but chromophobe, clear cell, and papillary RCC have been described (in contrast to VHL disease in which RCC is invariably clear cell).[26,28] Small microscopic nodules of oncocytic cells have been described within the renal parenchyma.[22]

Several less common features have been suggested including colorectal polyps and cancer, thyroid cancer, and melanoma, but these have not yet been confirmed to be associated. It has been suggested that an increased risk for colorectal neoplasia may be restricted to a subset of families, and therefore colonoscopy may be indicated if there is a family history of colorectal cancer.[29]

The European BHD Consortium suggested clinical diagnostic criteria for BHD to include one "major" (a pathogenic *FLCN* variant or five or more adult onset fibrofolliculomas/trichodiscomas [one histologically confirmed]) or two "minor" criteria (multiple bilateral basal lung cysts with no other apparent cause; RCC with early onset <50 years or multifocal/bilateral or mixed chromophobe/oncocytic histopathology).[30] Birt-Hogg-Dubé syndrome should be differentiated from other inherited RCC syndromes including tuberous sclerosis in which facial skin lesions (angiofibromas), lung cysts with lymphangioleimyomatosis, and renal lesions occur.[30]

Surveillance for renal tumours is offered to affected patients, asymptomatic mutation carriers, and individuals at 50% risk (affected parent) who have not undergone genetic testing. Annual MRI scans (to avoid repeated radiation) are typically offered from age 20 years, but ultrasonography can be used if MRI is unavailable or not tolerated. When a solid renal lesion is detected, it is usually monitored with sequential scans until it reaches 3 cm diameter ("3 cm rule") when nephron-sparing surgery or, in some centres, ablative interventions such as radiofrequency ablation or cryotherapy is performed.[28]

Renal cell carcinoma in BHD syndrome follows the classic Knudson's "two-hit" model of tumourigenesis. Inactivation of folliculin in mouse and cell-based models leads to activation of the mammalian target of rapamycin (mTOR) pathway, and it has therefore been suggested that metastatic RCC in BHD syndrome might be best treated with mTOR inhibitors.[31] However, clinical trial evidence for this is not available and a clinical

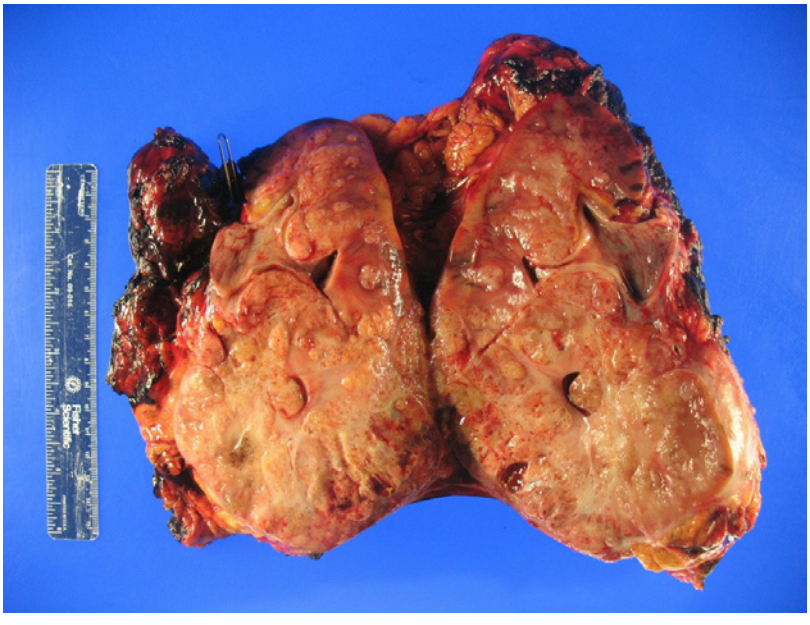
trial of topical rapamycin for fibrofolliculomas did not demonstrate a detectable therapeutic effect.[32] Recurrent pneumothoraces may be treated by a variety of surgical approaches including pleurodesis and pleural covering procedures.[33]

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)

The condition now known as HLRCC was first reported by the dermatology community as Reed syndrome nearly 50 years ago as an autosomal dominant family syndrome of cutaneous leiomyomas.[34] The recognition of linkage to uterine leiomyomas led to the condition also known as multiple cutaneous and uterine leiomyomatosis (MCUL). Finally, when RCC was accepted as part of the syndrome, Launonen and colleagues proposed the HLRCC moniker.[35] Linkage and then sequencing analyses identified *fumarate hydratase (FH)* as the causal gene in 2002.[36] Hereditary leiomyomatosis and RCC was initially thought to be a rare disease with high penetrance, but recent data suggests that HLRCC may be very common with an estimated incidence up to 1 in 1,000 individuals.[37]

The clinical manifestations of HLRCC include both non-renal and renal features, and penetrance varies greatly between family members.[38,39] Cutaneous leiomyomas are skin papules that may be painful with pressure exposure to cold and are observed in 50–80% of patients with HLRCC. Asymptomatic uterine leiomyomas are reported in 30–80%, with wide variability perhaps due to reliance on imaging for detection. They can cause heavy vaginal bleeding and early hysterectomy is frequently reported. Renal cell carcinoma is seen in 10–20% of affected individuals,[38–40] and has been reported between the ages of 11 and 90 years, with a median age of onset of 36–40 years.[21,41] Importantly, as many as 7% of RCC patients are found under the age of 20 years, highlighting the need for early screening and surveillance. When not found on screening, HLRCC kidney cancers present with symptomatic, invasive, bulky tumours (**Figure 1**) or distant metastases.[40,42] To date, most HLRCC RCCs have been unifocal, largely due to their aggressive nature and propensity for early dissemination. With screening and early treatment, however, metachronous tumours have been reported in the ipsilateral and contralateral kidney.

FIGURE 1 Gross inspection of a hereditary leiomyomatosis and renal cell carcinoma (HLRCC) radical nephrectomy specimen, demonstrating infiltrative tumour appearance.



Source: Image courtesy of Brian M. Shuch, Department of Urology, University of California, Los Angeles, Los Angeles, California, United States.

Genetic screening after appropriate counselling should test all 10 coding exons and the flanking intronic sequences. When an *FH* mutation is identified, cascade testing of all first-degree relatives should follow, with further clinical testing as needed based on the results. As the onset of kidney and uterine manifestations can occur prior to adulthood, at-risk individuals should ideally be tested prior to the age of 10 years. In the absence of family history, testing should be considered in individuals with multiple cutaneous leiomyomas, early-onset fibroids before the age of 40 years, or early-onset kidney cancer under the age of 46 years, especially those with non-clear cell histology.[43–45]

HLRCC RCCs can have variable morphology and resemble various eosinophilic subtypes of kidney cancer including type 2 papillary, collecting duct, or tubulocystic RCC.[39,42] Most exhibit two or more growth patterns including papillary, solid, cribriform, tubulocystic, or cystic. These tumours are now considered their own distinct histologic subtype: FH-deficient RCC. They typically demonstrate pleiomorphic eosinophilic nucleoli surrounded by a clear halo.[39] These nucleolar features may be focal but with careful pathologic examination can be identified in more than 90% of nephrectomy specimens.[46] Most demonstrate loss of immunohistochemistry (IHC) for FH, though some missense mutations can maintain protein expression. Staining for S-(2-succino)-cysteine (2SC) can be helpful to detect the functional consequences of excess intracellular fumarate.

The current management strategy for FH-deficient RCC is aimed at early detection with intervention as quickly as possible. Tumours may appear as complex lesions with a mixture of solid or cystic elements and are frequently infiltrative in appearance.[47] Cross-sectional imaging with MRI or CT is necessary, as renal ultrasound can easily miss complex cysts or small papillary tumours. Because lifelong surveillance is necessary, annual MRI is preferred to avoid the unnecessary cumulative radiation exposure of annual CT scans. Fluorodeoxyglucose positron emission tomography ([FDG]-PET) imaging may be useful due to the increased metabolic activity of FH-deficient RCC.[48] Once FH-deficient RCC is detected, prompt excision with clear margins is required regardless of tumour size. The "3 cm rule" does not apply to HLRCC patients. Due to the infiltrative behaviour of HLRCC, nephron-sparing surgery in the setting of HLRCC should be approached with caution and performed only if a negative margin is reasonably possible. Contrary to other hereditary RCCs, FH-deficient RCC should *never* be enucleated. For large, advanced cases of HLRCC kidney cancer, regional retroperitoneal recurrences are common, and consideration should be given to regional lymph node dissection even if the nodes are clinically negative.[47] Robotic surgery may be considered. However, if there is concern for tumour spillage, particularly with cystic lesions, open surgery is appropriate depending on the level of surgeon comfort.

Systemic therapy for disseminated HLRCC has had limited success, and tumours are frequently refractory to available agents. National Comprehensive Cancer Network (NCCN) Guidelines currently recommend a combination of bevacizumab plus erlotinib as first-line therapy based on response rates of 70%, with median progression-free survival (PFS) of 21 months.[49] Outcomes with other tyrosine kinase inhibitors have been variable. One series from France reported promising partial response rates approaching 50% for sunitinib or cabozantinib.[50] However, others report lower response rates, with most patients experiencing progression within 6 months.[51] Immunotherapy with checkpoint inhibitors has similarly shown mixed outcomes, with reports ranging from no response to complete response.[52] Due to the demonstration of homologous repair deficiencies in FH-deficient RCC, an ongoing trial (NCT03914742) is investigating whether DNA damage repair inhibitors may have therapeutic benefit.[53]

Hereditary Papillary Renal Cell Carcinoma (HPRC)

Hereditary papillary renal cell carcinoma (HPRC) is a rare autosomal dominant disease with an incidence of about 1 in 500,000. HPRC was initially described as a familial RCC syndrome in 1994 with 3 successive generations from the same family developing homogeneous papillary type 1 RCC.[54] Tumours are predominantly indolent and confined to the kidney but can be advanced. No other manifestations of HPRC have been observed. The same team subsequently linked the syndrome to germline-activating missense mutations in the tyrosine kinase domain of *MET* proto-oncogene (chromosome 7). Once activated, *MET* activates multiple signalling pathways that ultimately promote RCC proliferation and survival.[55]

Although there are no standard guidelines for genetic testing or screening for patients with HPRC, genetic screening should be considered for any individual who has a known family history of HPRC or who develops type 1 papillary RCC prior to age 45 years or multifocal papillary tumours.[56] Testing involves bidirectional DNA sequencing to isolate variants in the coding exons of *MET*. To date, all the mutations that have been described reside in 4 of the 21 exons, and currently available assays specifically test these exons with near-perfect sensitivity.[55,57–59] Unfortunately, papillary tumours are frequently isoechoic and unreliably detected by ultrasound. Routine cross-sectional imaging with CT or preferably MRI is recommended every 2 years.[60,61] Tumours are characteristically hypovascular, with enhancement of 10–30 Hounsfield units after contrast administration.

Patients with HPRC present with bilateral, multifocal, type 1 papillary RCC and renal adenomas. Rarely, clear cell RCC (ccRCC) has been seen along with papillary RCC.[55,62] The median age of onset is 41 years[2] but has been reported as young as 30 years. Penetrance approaches 100% by the age of 80 years. Most tumours are diagnosed incidentally, but an advanced tumour can present with the classic triad of flank pain, hematuria, and an abdominal mass or, rarely, lung metastasis.[63] One detailed analysis of 12 kidneys from 9 patients with HPRC estimated that a single affected kidney can contain between 1,100 and 3,400 microscopic papillary tumours.[64] Hereditary papillary renal cell carcinomas are usually International Society of Urologic Pathologists (ISUP) grade 1 or 2 and demonstrate predominantly papillary or tubulo-papillary features with type 1 papillary histology. A tumour is classified as a type 1 papillary type when at least 50% of the tumour has a tubulo-papillary growth pattern with malignant epithelial cells around a fibrovascular core.[54]

Tumours are usually small, indolent, and confined to the kidneys. In many cases, patients die of unrelated causes before they are diagnosed.[65] The current standard of care for HPRC is surveillance until the largest tumour size reaches 3 cm ("3 cm rule"), followed by nephron-sparing surgery as with VHL.[60] Because of the slow growth rate of papillary tumours, biannual cross-sectional imaging is usually sufficient. The feasibility and safety of partial nephrectomy for multifocal disease has been demonstrated with good preservation of renal function, even in patients requiring resection of more than 20 tumours from the same kidney.[66]

Though partial nephrectomy has been the mainstay of treatment for tumours over 3 cm, advances in understanding the biology of the disease have introduced novel agents with potential efficacy against HPRC. Several agents targeting the MET pathway have been studied.[55] In one phase 2 study, about 50% of patients with germline HPRC showed tumour response to oral foretinib, a multi-kinase inhibitor of MET, VEFGR2, RON, AXL, and TIE-2 receptors.[57] Other agents targeting the MET receptor pathway, including cabozantinib, are being explored in patients with HPRC,[67] potentially opening new therapeutic options for these patients.

Tuberous Sclerosis Complex (TSC)

Tuberous sclerosis complex (TSC) is a multi-organ syndrome that was described in the late 1800s. Initial work by Von Recklinghausen and Bourneville described the condition, characterized by neurologic, cutaneous, oromucosal,

pulmonary, cardiac, and renal manifestations. Inheritance is autosomal dominant. Tuberous sclerosis complex has been estimated to be present in 1 in 6,000–10,000 new births. Due to often severe neurological challenges in patients with TSC, up to 50% are *de novo* alterations.[68] Both somatic and germline mosaicism have been described and account for a subset of patients.[69]

A pathogenic alteration can be found in the genes for TSC (*TSC1*-hamartin and *TSC2*-tuberin*)* in approximately 80% of clinically affected individuals. The absence of a mutation does not change the clinical diagnosis or management in someone with established features. However, testing should be done if the TSC diagnosis is possible but cannot be clinically confirmed.[70] Additionally, patients with TSC who plan to start a family may consider prenatal genetic screening.[71]

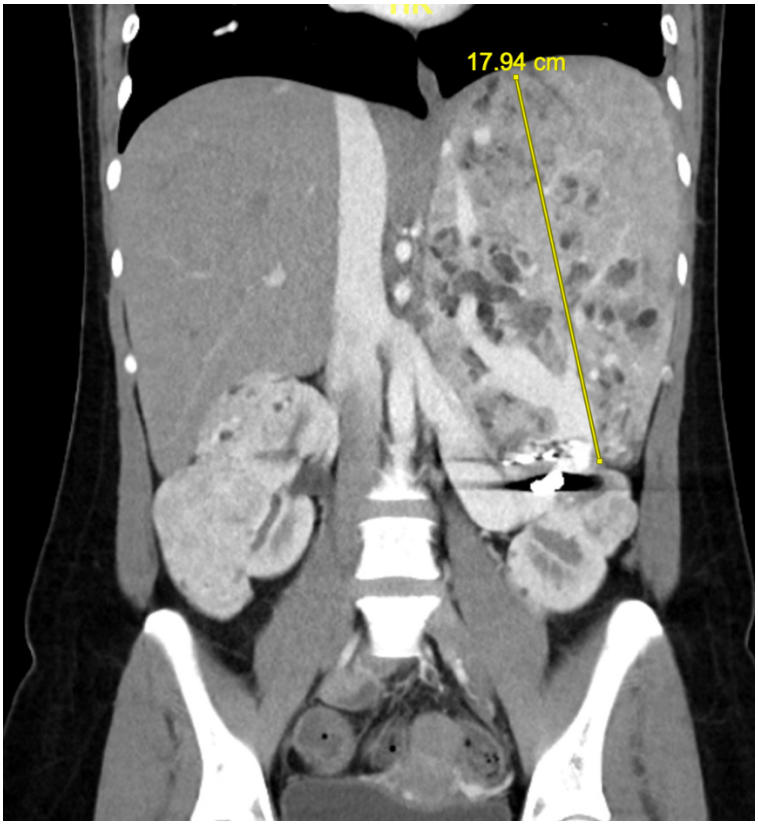
Although penetrance in TSC is over 95%, there is significant variability in the disease phenotype, including rare cases with subtle to no clinical manifestations.[72] Penetrance varies greatly by organ system, with central nervous system (CNS) and dermatologic involvement present in more than 90% of cases.[73] Central nervous system manifestations include both cognitive or behavioural impairment such as autism, and structural issues leading to the development of epilepsy or subependymal nodules of the ventricular walls. Renal angiomyolipomas (AMLs), seen in nearly 70% of affected individuals, are the most common kidney manifestation and a major source of morbidity. Renal cell carcinoma occurs in 2–4% of patients with TSC.[74] Patients may exhibit various types of retinal hamartomas.[75] There is a clear genotype-phenotype association in TSC, with greater disease burden and severity observed for *TSC2* germline defects.[76]

The age of onset for both CNS and dermatologic manifestations is early childhood.[73] Cardiac rhabdomyomas, found in up to 50% of affected infants, often regress during childhood without treatment. Renal AMLs develop in late childhood, with a median age at diagnosis of 16.9 years in one large registry study of more than 2,000 patients.[77] The rare cases of RCC that occur have a much earlier age of onset than sporadic forms of kidney cancer. In one of the largest series of TSC RCC (n=19), the median age of diagnosis was 28 years (range, 7–59).[74] As patients with TSC are frequently diagnosed in childhood, they may be screened prospectively for renal manifestation. Current recommendations include abdominal imaging at the time of diagnosis, which has led to identification of more than 80% of TSC AMLs prior to the development of symptoms.[77] For rare cases where patients may have a subtler TSC phenotype, AML may present with acute hemorrhage, flank pain, and hypotension. Perhaps due to routine surveillance imaging, most TSC RCCs are small (median size, 2.9 cm) and incidental.[74] The overwhelming majority of these cases are localized, without regional or distant disease.

Renal AMLs are typically bilateral and multifocal. Many patients have an aggressive phenotype with bulky tumours that often merge, making it difficult to distinguish clear boundaries between distinct lesions. Angiomyolipomas are part of a family of mesenchymal tumours called PEComas. The majority are benign and triphasic in nature, consisting of vascular, smooth muscle, and fatty elements. These lesions almost always stain positive for classic melanocytic markers including HMB-45 and Melan-A by IHC. A rare but important variant, epithelioid AML, is composed of epithelioid cells with minimal to no fat, with increased incidence of necrosis and hemorrhage, signalling the potential for aggressive or malignant behaviour. Epithelioid AML can

become large, and distant metastases are seen in up to one-third of cases in multiple series. Epithelioid AML should be suspected when a TSC-related tumour is treatment refractory (**Figure 2**).

FIGURE 2 Epithelioid variant angiomyolipoma (AML) in a patient with tuberous sclerosis complex (TSC) who had failed two attempts at angioembolization of large vessel (coil seen).



Source: Image courtesy of Brian M. Shuch, Department of Urology, University of California, Los Angeles, Los Angeles, California, United States.

Though TSC RCCs are rare, nearly 50% are multifocal.[74,78] Our understanding of TSC-associated RCC has evolved, as more cases have been reported. The initial morphologies reported with TSC RCC were similar to sporadic forms of RCC, including clear cell histology,[68] though molecularly distinct from VHL.[79] In recent years, common morphologic patterns have emerged including chromophobe and hybrid oncocytic/chromophobe tumours (HOCT), RCC with smooth muscle stroma (also known as renal angiomyoadenomatous tumours), and eosinophilic unclassified variants.[74,78] This final category is morphologically similar to sporadic eosinophilic solid cystic (ESC) RCCs, which have been shown to harbour somatic mTOR/TSC mutations.

Current guidelines recommend baseline abdominal imaging at the time of diagnosis, followed by lifelong assessment for the progression of AML or renal cystic disease every 1–3 years.[70] Renal AMLs are easily identified on imaging by macroscopic fat. Fat-poor lesions however may be a diagnostic challenge and often require biopsy for confirmation. Unfortunately, renal ultrasound does not adequately assess tumour size or the presence of fat in relatively "fat-poor" tumours, and enhanced cross-sectional imaging with CT or MRI is necessary. As many patients require periodic brain MRI, effort should be made to coordinate simultaneous abdominal MRI with contrast to minimize both radiation and frequency of sedation.

Standard AMLs can be safely observed until they reach 4 cm, at which time they should undergo resection or embolization. Epithelioid variants should be considered for earlier resection given their risk for aggressive behaviour. Everolimus is approved for the medical management of renal AML and has also shown efficacy in the setting of metastatic epithelioid variants.[80] There is limited data to suggest that TSC RCC should be treated differently than other forms of RCC. However, with the high propensity for renal AMLs that may require intervention, renal preservation should be prioritized, dictating use of partial nephrectomy or ablation when feasible. Identification of a small renal tumour in the setting of multifocal AML requires careful surgical planning and intra-operative ultrasound.

PTEN Hamartoma Tumour Syndrome (PHTS)

PTEN hamartoma tumour syndrome (PHTS) is a spectrum of disorders caused by heterozygous (monoallelic) mutations in the PTEN TSG. The best recognized form of PHTS is Cowden syndrome (CS), but other clinical subtypes include Bannayan-Riley-Ruvalcaba syndrome (BRRS), Proteus-like syndrome, and macrocephaly with autism and/or learning disability. Cowden syndrome is an autosomal dominantly inherited disorder with major features of mucocutaneous lesions (papillomatous papules and tricholemmomas), macrocephaly, multinodular goiter, follicular adenomas of the thyroid, and increased risks for breast (lifetime risk >80%), non-medullary thyroid (~35%), and endometrial (~30%) cancers.[81,82] Renal cell carcinoma, most commonly papillary and chromophobe subtypes, also occurs with lifetime risks varying from 15–24% and median age at diagnosis around age 50 years.[81,83,84] Renal cell carcinoma is usually unilateral and though patients with CS may present with apparently sporadic RCC, macrocephaly and mucocutaneous features of CS are usually present.[84] Colorectal polyposis is a frequent finding in CS, and there is an increased risk for colorectal cancer. Some manifestation of CS is estimated to be present in ~90% of cases by age 30 years.[85]

Clinical diagnostic criteria for Cowden syndrome comprising combinations of major and minor features (e.g., RCC) have been defined,[85] and the diagnosis of PHTS is confirmed by detecting a germline pathogenic variant in *PTEN*. Scoring systems have been developed to help identify which patients should be offered molecular testing,[86] but PTEN is now included on many germline and somatic multigene cancer testing panels. Individuals with *PTEN* variants of uncertain significance require careful assessment for features of PHTS.

Comprehensive surveillance protocols for PHTS have been described starting at age 18 years.[85,87] For women, annual mammography or breast MRI is recommended from age 30 years and consideration of endometrial cancer screening from age 35 years. In addition to surveillance, prophylactic mastectomy may be offered. All patients should be offered annual thyroid examination and ultrasound scan starting at time of diagnosis, (bi)annual dermatological assessment, and regular colonoscopy commencing at 35 years. Though surveillance for RCC by (bi)annual ultrasonography was initially recommended from age 40 years, reports of younger-onset cases have led to suggestions that biannual screening should be offered starting at age 20 years.[88] Following a diagnosis of PHTS, at-risk relatives should be evaluated and offered genetic testing. The treatment of PHTS-related cancers is generally similar to sporadic cancers and for RCC, and available data suggest that the "3 cm rule" can be applied.

BAP1 Tumour Predisposition Syndrome (BAP1-TPDS)

Germline mutations or deletions of *BAP1* are associated with a multi-organ cancer syndrome including early-onset RCC. Manifestations of BAP1-TPDS include pigmented skin lesions (BAP1-inactivated melanocytic tumours), aggressive uveal melanoma with increased risk for metastasis and poor survival, and malignant mesothelioma (MM) of the pleura and peritoneum.[89] BAP1-TPDS–related MM presents 10 years earlier than sporadic MM, with higher ratios of peritoneal to pleural involvement and female to male gender.[89] Notably, BAP1 MM also shows significantly increased 5-year survival compared with sporadic disease, possibly due to increased sensitivity to chemotherapy.[90] Less common manifestations include early-onset cutaneous melanoma, basal cell carcinoma, meningioma, cholangiocarcinoma, and breast cancer. Inheritance is autosomal dominant, and tumours demonstrate loss of both alleles consistent with a classic TSG. Penetrance is variable but high, with at least one tumour observed in nearly 90% of affected individuals.[89]

BAP1 is located on 3p21.1 near *VHL* and is frequently deleted with *VHL* in ccRCC.[91] It codes for ubiquitin carboxyl-terminal hydrolase BAP1, a nuclear deubiquitinating enzyme involved in chromatin remodelling and regulation of growth and development. The protein also functions to repair double-stranded DNA breaks.[92] Loss of BAP1 protein expression is observed in up to 15% of sporadic ccRCC and correlates with aggressive features.[93] The overall prevalence of germline BAP1-TDS remains unknown, but it is estimated to represent 1–1.5% of all ccRCCs and nearly 20% of patients who develop both RCC and uveal melanoma.[94]

Renal cell carcinoma occurs in about 10% of patients with BAP1-TPDS,[60,93] with predominantly clear cell histology though papillary and chromophobe have been reported.[60,89] Tumours demonstrate loss of heterozygosity for *BAP1*, with resulting loss of IHC staining for BAP1 protein. The median age at diagnosis is 47 years, and tumours may be bilateral and multifocal. BAP1 TPDS renal cell carcinomas tend to be high grade with poor clinical outcome. Due to this aggressive tumour biology, the "3 cm rule" may not be appropriate, and

close follow-up of affected individuals with consideration for early excision of renal masses is recommended until the syndrome is better characterized.[93]

Genetic consultation and screening should be considered in any individual with personal or family history of two or more BAP1-TPDS–associated cancers.[95] 87% of germline defects will be detected on sequence analysis, whereas the remainder on a deletion screen. Once a diagnosis is made, all at-risk family members should be offered testing. Affected individuals will require lifelong testing, including annual fundus examination starting at age 11 years and annual full body dermatology examinations starting at age 18 years. Annual abdominal imaging for RCC and/or peritoneal MM is recommended starting at age 30 years, preferably using alternating ultrasound and MRI to avoid cumulative radiation.[89] In addition, patients should be counselled to avoid known risk factors for BAP1-TPDS–associated cancers, including asbestos, arc welding, tobacco, or excessive sun exposure.

Succinate Dehydrogenase (SDH)–Deficient RCC

A rare hereditary RCC syndrome involving germline mutations of the succinate dehydrogenase complex (SDH) was added to the World Health Organization (WHO) classification in 2016.[96] In addition to early-onset RCC in the third or fourth decade, affected individuals may develop paragangliomas of the head and neck, pheochromocytoma and paraganglioma, wild-type (negative for mutations of the *KIT* and *PDGFRA* genes) gastrointestinal stromal tumour (GIST) and, less commonly, prolactin secreting pituitary adenoma.[60,93] Renal masses may be multifocal and bilateral and are morphologically distinct from other RCCs.[97] Inheritance is autosomal dominant. Germline SDH defects are present in up to 15% of all pheochromocytomas and paragangliomas and 1–1.5% of all RCCs.[60,98]

SDH is a complex enzyme composed of four subunits: SDHA, SDHB, SDHC, and SDHD (encoded by the nuclear genome (*SDHA*: 5p15.33, *SDHB*: 1p36.13, *SDHC*: 1q23.3 and *SDHD*: 11q23). It is alternatively known as the Mitochondrial Complex II and is anchored on the inner mitochondrial membrane where it participates in both the Krebs cycle and the electron transport chain.[99] SDH catalyzes the oxidation of succinate to fumarate, paired with reduction of ubiquinone to ubiqinol.[60] Loss of SDH function can result from a defect in any of the four subunits or in SDHAF2 (required for SDHA function), resulting in accumulation of intracellular succinate and a metabolic shift to aerobic glycolysis.[93] Most cases of SDH-deficient RCC involve germline mutations of *SDHB*, though mutations in all subunits have been reported.[60]

Because SDHB is rapidly degraded when it is not part of an intact SDH complex, absence of SDHB staining by IHC can identify inactivation of any SDH subunit and is used as a reliable screen for SDH-deficient RCC[96,99] with two notable caveats. First, VHL-deficient clear cell RCCs frequently show decreased SDHB staining[60] at least in part due to direct inhibition of the *SDHD* transcript by HIF-mediated upregulation of miR-210.[98] Second, fumarate hydratase (FH)-deficient tumours may demonstrate downregulation of SDHB due to accumulation of mitochondrial fumarate. Mass spectroscopy for the relative values of succinate and fumarate may be helpful in this setting.[60]

Succinate dehydrogenase–deficient RCCs are tan to brown with well circumscribed "pushing" margins.[100] Cystic features are common. Tumours have a distinctive histologic appearance of cuboidal cells with inconspicuous nucleoli arranged in nests or tubules with eosinophilic cytoplasm containing vacuoles and cytoplasmic inclusions.[60,96] Although the majority are low grade, SDH-deficient RCC can be aggressive when high grade or if sarcomatoid features or necrosis is present.[96,101] Metastasis has been observed even with small SDH-deficient RCC.[93] At-risk individuals should be screened annually for renal tumours with abdominal MRI or CT. Prompt surgical excision regardless of size is recommended using nephron-sparing surgery when possible due to the lifelong risk for RCC recurrence.

Other Hereditary RCC Syndromes

Hereditary hyperparathyroidism jaw tumour syndrome (HPT-JT) is a hereditary syndrome of parathyroid adenoma and cancer, benign ossifying fibromas of the jawbone, and renal and uterine cancers. It commonly presents as early-onset primary hyperparathyroidism, with estimated penetrance of 65% by age 50 years.[102] Inheritance is autosomal dominant and conferred by germline mutations of the *CDC73* gene, which encodes the nuclear protein parafibromin. Renal manifestations include renal cysts and tumours, with both ccRCC and Wilm's tumour reported.[103] Though there are currently no consensus guidelines, renal screening by abdominal ultrasound every 5 years has been recommended for at-risk individuals.[60]

Although a variant of micropthalmia-associated transcription factor, ***MITF*(E318K)** has been reported to predispose to RCC, and a recent meta-analysis and review of The Cancer Genome Atlas (TCGA) project data failed to demonstrate any association with RCC.[104] The MITF(E318K) variant causes a 2-fold risk for cutaneous melanoma and may be linked to uterine cancer, but no RCC screening is indicated at present.

Conclusion

Hereditary RCC syndromes are a diverse group with varying penetrance, histology, and clinical behaviour. Though hereditary RCC syndromes are uncommon, most urologists will encounter hereditary RCC, and it is important to remain vigilant, take an appropriately detailed history, make use of genetic counsellors when indicated, and select a surveillance and management strategy that addresses the tumour biology and lifelong risk for recurrence.

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COMMITTEE 6

Imaging in Renal Cell Carcinoma

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Table of Contents

Introduction

The exponential increase in the use of cross-sectional imaging, along with the increased sensitivity of imaging over the past few years, has led to an increase in the number of incidentally detected renal masses and an increase in the identification of asymptomatic renal cell carcinomas (RCCs). The characterization of an indeterminate renal mass remains challenging, but diagnostic algorithms continue to evolve and improve.[1,2] New techniques such as contrast-enhanced ultrasound have entered clinical practice and the development of new molecular imaging techniques, some of which will translate into clinical practice, have changed how renal masses have been imaged. A thorough understanding of the strengths and limitations of different imaging modalities is critical in the implementation of imaging strategies in the management of a renal mass and in particular renal cell carcinoma. A significant change in the management strategies of renal cell carcinoma with active surveillance, embolization, and ablative treatments and the development of neoadjuvant therapies including chemotherapy, antiangiogenic treatments, and immunotherapy have also had an impact on the use of imaging. This includes pretreatment evaluation as well as post-treatment follow-up and surveillance in renal cell carcinoma.

This chapter introduces the concepts of renal cell carcinoma imaging using individual imaging modalities viz, ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), molecular imaging and finally a summary of imaging strategies in staging of RCC.

Ultrasound

Detection and diagnosis

Solid masses

Ultrasound (US) is not the final imaging study performed for evaluation of a solid renal mass, as that role is typically performed by multiphase contrast-enhanced CT and MRI. However, because of the low cost and widespread availability of US, renal masses may be encountered as an incidental finding on US examinations performed for other reasons. A large study found that solid renal masses were detected incidentally in 0.4% of patients undergoing US, with roughly half of these proving to be RCC.[1] Traditionally, confirmation that a renal lesion is a solid enhancing mass is achieved with CT or MRI, but that role is increasingly being performed by contrast-enhanced ultrasound (CEUS) as well.

Another common role for US in the early workup of a renal lesion is for evaluation of an indeterminate lesion detected at single-phase CT. Typically, a lesion measuring greater than fluid attenuation at single-phase CT can

be evaluated with US to determine whether it is a simple or minimally complex cyst that can be safely ignored or instead a solid lesion that requires further workup.

Ultrasound is inferior to CT for detection of renal masses, and particularly so for smaller lesions.[3] For solid renal masses detected on imaging that measure less than 4 cm in size, about 80% will be malignant, and the rate of malignancy increases for larger masses.[4] Among malignant renal masses, RCC is the most common entity, with other etiologies including urothelial carcinoma, lymphoma, and metastases.

The appearance of RCC at conventional US is variable. The most common subtype of RCC is clear cell RCC (ccRCC), comprising 75–80% of RCCs, but even within this subtype the US appearance can vary. Most commonly, the tumour is composed of solid tissue that is heterogeneously hypoechoic or isoechoic (**Figure 1**), though it may also show hyperechoic components.[5] Fluid components may be seen within ccRCC, which may be due to cystic, necrotic, or hemorrhagic change. Doppler flow should be readily identifiable in ccRCC, owing to the hypervascular nature of ccRCC, and at CEUS this tumour shows avid, early enhancement, followed by washout (**Figure 2**).

All images are courtesy of contributing authors and have not been published elsewhere.

FIGURE 1 Clear cell RCC. Greyscale ultrasound (A) shows a heterogeneous mass (arrows) with solid and cystic components, and colour Doppler ultrasound (B) shows flow in the solid portion. Contrast CT (C) shows a heterogeneous mass with avid enhancement.

Abbreviations: CT, computed tomography; RCC, renal cell carcinoma.

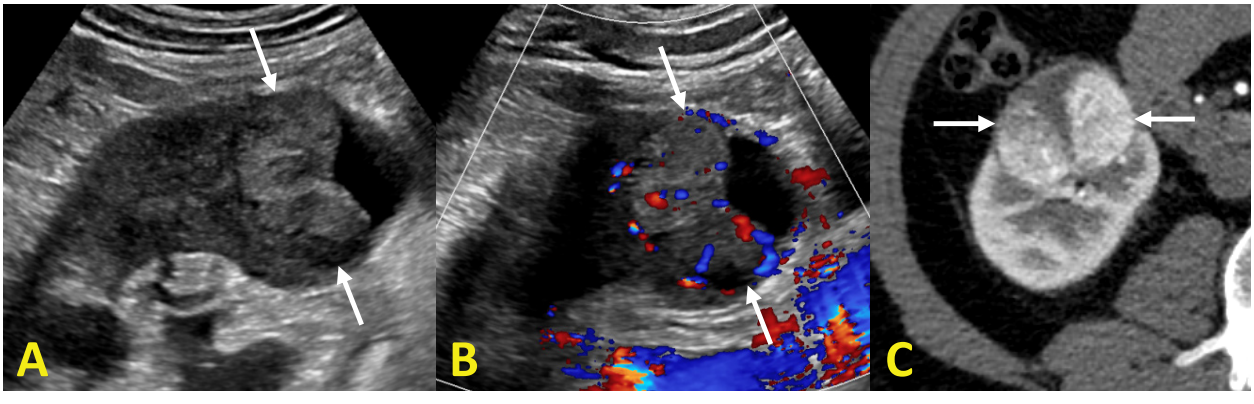
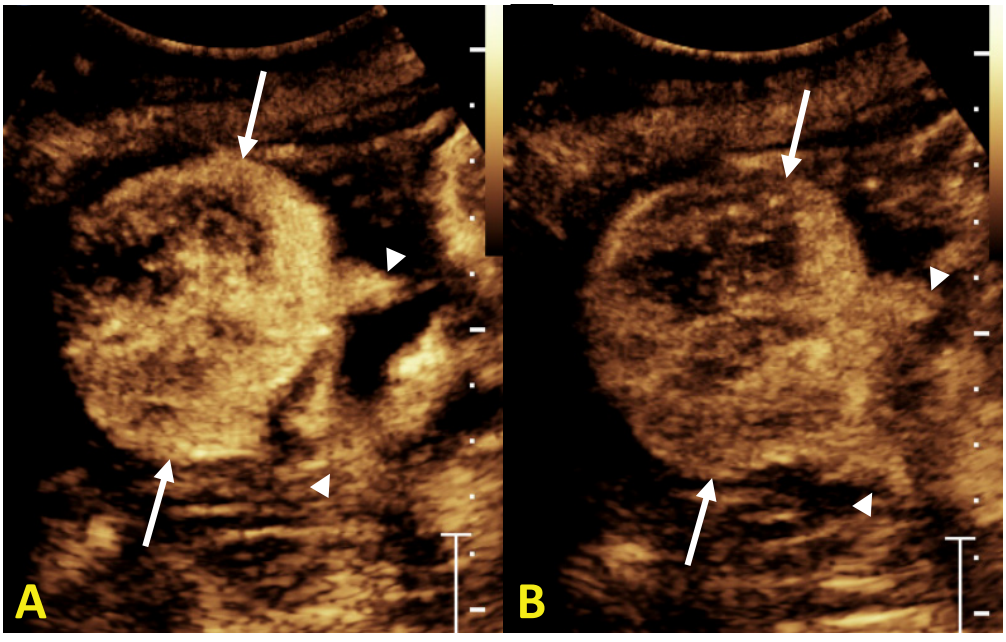


FIGURE 2 Clear cell RCC at CEUS. Corticomedullary phase (A) shows a heterogeneously hyperenhancing (relative to renal cortex) mass (arrows) exophytic from the right kidney (arrowheads). At delayed phase (B) the mass shows washout.

Abbreviations: CEUS, contrast-enhanced ultrasound; RCC, renal cell carcinoma.



Other less common subtypes of RCC include papillary RCC (pRCC) and chromophobe RCC (chRCC), making up 10–15% and 5–10% of RCCs, respectively. pRCC may be a solid, well-circumscribed mass (**Figure 3**), or sometimes may be partially solid with cystic or hemorrhagic components. At CEUS, pRCC is hypoenhancing and appears quite different from ccRCC, showing a later and lower peak of enhancement (**Figure 4**). chRCC is typically a solid, well-circumscribed mass that is more homogeneous than ccRCC. Enhancement of chRCC is commonly nearly isoenhancing to renal cortex, though this appearance can be difficult to discriminate from the more common ccRCC, especially when the lesion is small.[6]

FIGURE 3 Papillary RCC. Greyscale ultrasound (A) shows a small solid, well-circumscribed mass (arrows) that is isoechoic to mildly hyperechoic, with colour Doppler ultrasound (B) showing flow.

Abbreviations: RCC, renal cell carcinoma.

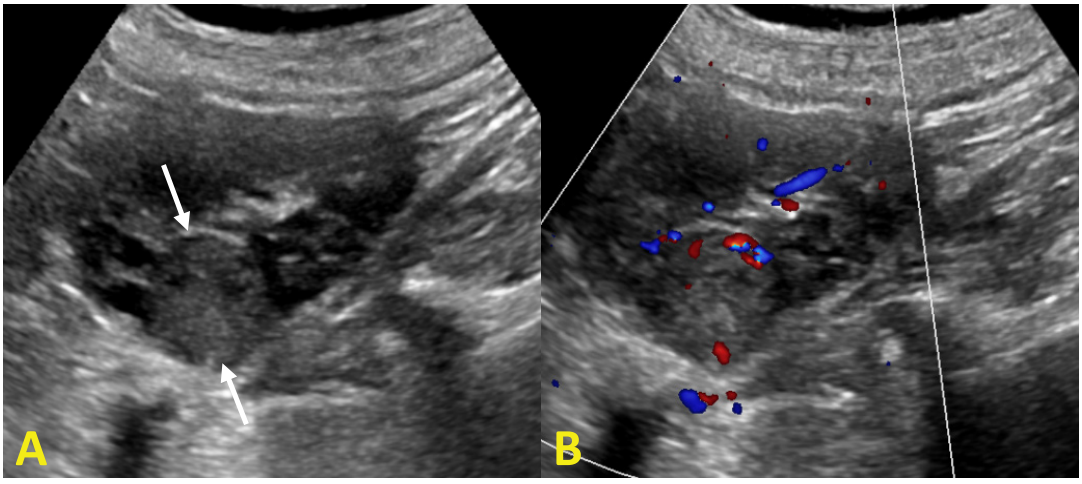
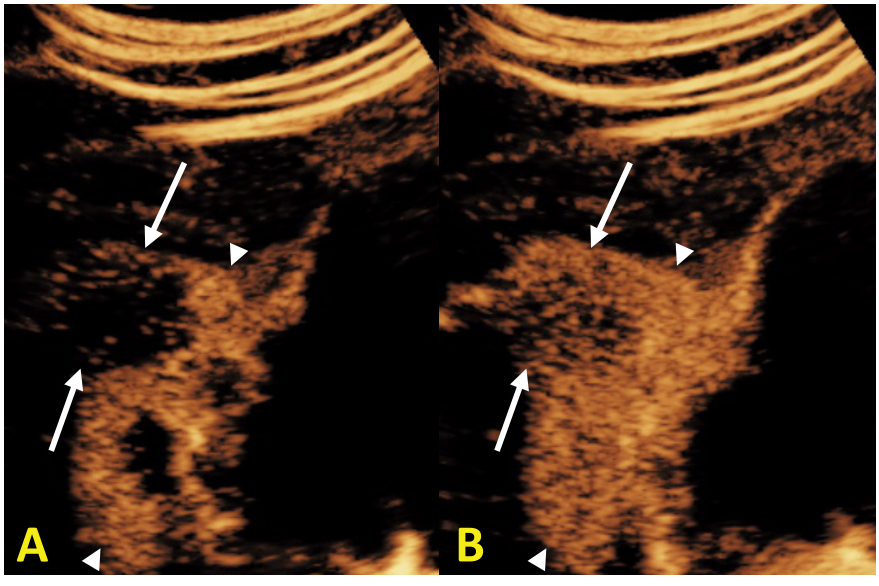


FIGURE 4 Papillary RCC at CEUS. Corticomedullary phase (A) shows only slight early enhancement of the mass (arrows), much less than adjacent cortex (arrowheads). The peak of enhancement is later, at nephrographic phase (B), but even at its peak the mass is still slightly hypoenhancing (arrows) relative to adjacent cortex (arrowheads).

Abbreviations: CEUS, contrast-enhanced ultrasound; RCC, renal cell carcinoma.



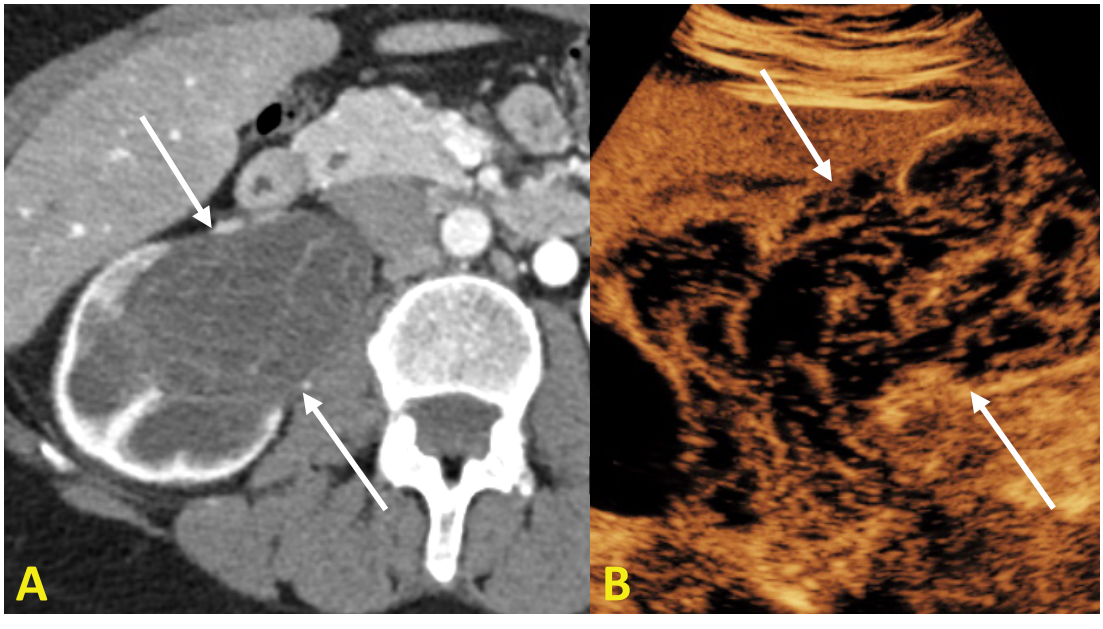
On US, the benign entities angiomyolipoma (AML) and oncocytoma can be difficult to differentiate from RCC. Angiomyolipoma is typically a homogeneous markedly hyperechoic mass, but it is not considered acceptable to definitively diagnose AML by US appearance alone, as even as many as 30% of small RCCs may be hyperechoic.[7] Confirming the presence of bulk fat in AMLs with CT or MRI is usually definitive; however, lipid-poor AMLs can present a diagnostic dilemma and may mimic RCC, regardless of modality. Oncocytoma is well known to appear similar to RCC on all imaging modalities, which can result in surgical removal; some 5–7% of masses that undergo partial nephrectomy are oncocytomas.[8,9]

Cystic masses

It is generally not considered acceptable to assign Bosniak classes to cystic renal lesions based on conventional US features, with the exception of Bosniak I simple cysts, if US depicts an anechoic lesion with well-defined smooth borders and increased posterior through-transmission.[10] Thus, US has an important role in confirming the cystic nature of a lesion that is indeterminate for solid or cystic composition at single-phase CT.

FIGURE 5 Superior ability of CEUS to demonstrate septal enhancement. Contrast CT (A) shows a large cystic lesion (arrows) centrally in the right kidney, with several internal enhancing septations. Contrast ultrasound (B) shows an even greater number of internal enhancing septations, and with superior detail. Postsurgical pathological evaluation confirmed a MEST.

Abbreviations: CEUS, contrast-enhanced ultrasound; CT, computed tomography; MEST, mixed epithelial and stromal tumor; RCC, renal cell carcinoma.



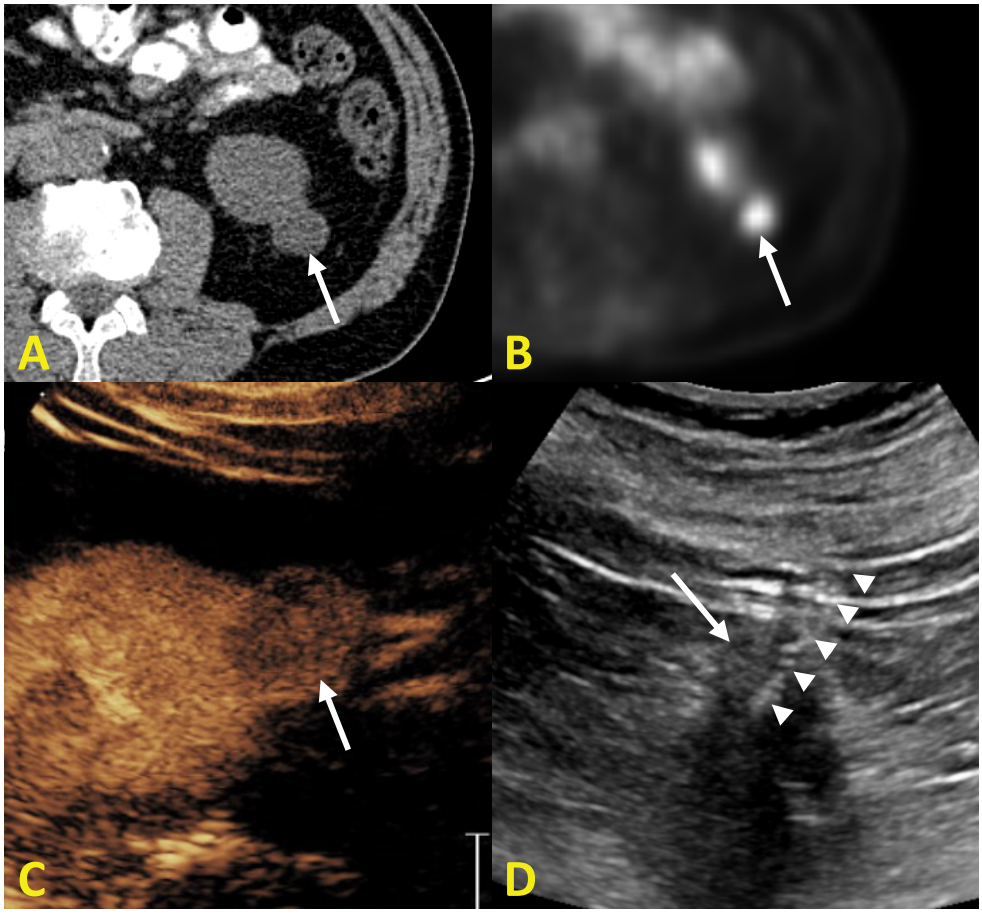
Contrast-enhanced ultrasound currently does not have a formal role in the Bosniak classification scheme, but with continued expansion in the use of and experience with CEUS, it is likely that the assignment of a Bosniak class based on CEUS features will become more acceptable in the future. Proposals for Bosniak designation based on CEUS features have been suggested.[11,12] The description of features for a CEUS Bosniak classification scheme will likely not be identical to that used for CT/MRI Bosniak classification, as CEUS is well known to surpass other modalities in demonstrating lesion septa, septa/wall thickness, and fine enhancement of small structures (**Figure 5**).[13–15]

Ultrasound-guided biopsy

Percutaneous biopsy of renal lesions has become more commonly performed in recent years. The procedure is generally considered safe, with hemorrhage requiring blood transfusion seen in 0–5% of cases, and a tumour seeding rate reported as below 0.01%.[16] Biopsy may help avoid surgery by demonstrating benign pathology, or if showing malignancy can help guide management decisions, in choosing whether to opt for resection, ablation, or active surveillance. Percutaneous renal mass biopsy may be performed by US or CT, and the choice of modality depends on multiple factors, including patient habitus, specific location of the lesion in the kidney, and operator experience. As the kidneys are in constant motion with respiration, US offers a particular advantage over CT in continuous real-time observation of the needle approach to the lesion, which is helpful with smaller lesions (**Figure 6**). Contrast-enhanced ultrasound can be performed during biopsies to verify identification of a lesion that is difficult to visualize on greyscale US alone.

FIGURE 6 Renal mass biopsy. A 74-year-old man with a history of ocular lymphoma was found on surveillance FDG PET/CT to have a 2.1-cm exophytic left renal mass that was FDG-avid (arrows on A and B). CEUS (C) showed the mass to be hypoenhancing (arrow), and biopsy of the mass (D) was performed under ultrasound, with the biopsy needle (arrowheads) seen to enter the mass (arrow). Pathology from the biopsy showed papillary RCC with eosinophilic features, and the patient underwent subsequent partial nephrectomy.

Abbreviations: CEUS, contrast-enhanced ultrasound; FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; RCC, renal cell carcinoma.



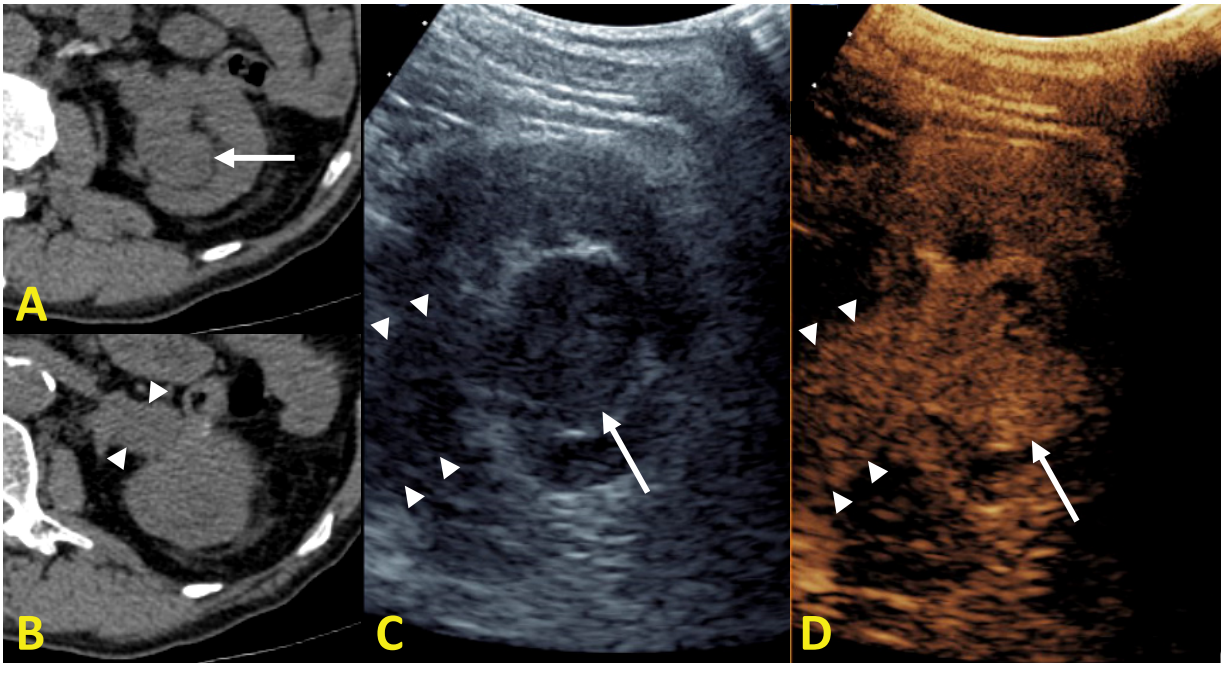
Staging, intraoperative guidance, and postsurgical follow-up

Staging

Computed tomography and/or MRI are preferred for RCC staging and preoperative planning, as these modalities are more capable of demonstrating the full complement of extrarenal findings than US. Specifically, CT and MRI are superior to US in the detection of abnormal retroperitoneal lymph nodes and other distant metastases, as well as in the assessment of the renal veins and inferior vena cava for tumour invasion. However, CEUS can be helpful in certain situations if CT/MR findings are indeterminate, or if a CT/MR cannot be performed with contrast (**Figure 7**).

FIGURE 7 Renal vein tumour invasion on CEUS. On noncontrast CT (A), a left renal lower pole mass is shown (arrow), and a more cranial image (B) demonstrates expansion of the renal vein (arrowheads), concerning for tumour invasion or bland thrombus. Greyscale US (C) shows the mass (arrow) and the renal vein (arrowheads) to have similar echogenicity. CEUS (D) shows tumour enhancement (arrow) that is contiguous with enhancing tissue in the renal vein (arrowheads), confirming venous invasion by tumour.

Abbreviations: CEUS, contrast-enhanced ultrasound; CT, computed tomography; RCC, renal cell carcinoma; US, ultrasound.



Intraoperative guidance

Images obtained with intraoperative ultrasound offer greater detail than those obtained with conventional transabdominal ultrasound, as probes with higher spatial resolution are used, and they can be placed directly on the renal capsule.[18] During partial nephrectomy, the use of intraoperative ultrasound increases confidence in selection of the site of parenchymal transection, aids in evaluation of the relationship of a mass to the renal vessels and collecting system, and can aid in detection of additional lesions. Intraoperative ultrasound is also useful in verifying extent of inferior vena cava (IVC) tumour involvement.[19] Imaging guidance during thermal ablation procedures is typically performed with CT rather than US, as obscuration by gas bubbles (created during radiofrequency ablation) or shadowing from the ice ball (created during cryoablation) makes US unsuitable for adequate visualization.

Postsurgical follow-up

In general, US is considered inferior to CT for identification of local recurrence at the operative site, and for detection of distant metastatic disease.[20] However, according to American Urological Association (AUA) guidelines, there is a role for US in postsurgical surveillance, depending on extent of surgery and patient risk.

For low-risk patients (pT1, N0 or Nx) who have undergone radical nephrectomy, AUA guidelines recommend imaging of the abdomen with US, CT, or MRI within 3–12 months after surgery.[20] If that scan is negative, additional US, CT, or MRI may be performed in the future as needed. For low-risk patients who have undergone partial nephrectomy, CT or MRI (not US) is recommended at the first imaging 3–12 months after surgery, followed by yearly US, CT, or MRI for 3 years, if the first postoperative scan is negative.

For moderate- to high-risk patients (pT2-4 N0 or Nx, or N+ with any T stage), for follow-up abdominal imaging the AUA guidelines recommend a baseline CT or MRI (not US) within 3–6 months after surgery, and then US, CT, or MRI every 6 months for a minimum of 3 years, with the interval extended to yearly until the 5th year. Continued imaging follow-up after 5 years is considered optional.

Future directions

The use of CEUS in the evaluation of renal masses is undergoing ongoing expansion, and further experience with CEUS among radiologists will likely generate additional roles for CEUS in RCC imaging. The eventual adoption of a Bosniak-like consensus statement on the CEUS evaluation of cystic renal masses would be of great benefit for reporting standardization. Additionally, advanced ultrasound techniques are being studied in renal mass evaluation, for example, the potential of elastography to differentiate benign and malignant renal masses.[21]

Key Points

- US is of great use in verifying that a renal lesion is a simple or only minimally complicated cyst in need of no further workup.
- CEUS is an emerging technique with capabilities in confirming and characterizing solid enhancing renal masses.
- Additionally, CEUS is superior to other imaging modalities in the evaluation of septal and mural enhancement of cystic renal lesions.
- US is generally considered inferior to CT/MR in staging and postsurgical surveillance for renal malignancies but does have a role in certain patients.

Cross-Sectional Imaging

Computed tomography

Multiphase contrast enhanced CT is the current imaging modality most commonly used for the evaluation of RCC.[22] Computed tomography allows the detection, characterization, staging, pretreatment planning, post-treatment evaluation, and active surveillance of RCC. Computed tomography examination is generally protocoled to include the chest, abdomen, and pelvis.

A dedicated CT protocol that allows optimal characterization of a renal mass includes non-enhanced, cortico-medullary, nephrographic, and excretory phases.[23] However, the protocol may vary between institutions.

Non-enhanced images provide a baseline attenuation of the mass to allow calculation of enhancement on subsequent contrast-enhanced phases of the study, and to determine presence of macroscopic fat and calcification. Corticomedullary, nephrographic, and excretory phases are obtained following contrast administration and allow evaluation of the dynamic enhancement characteristics of the renal mass, relationship of the mass to adjacent structures, renovascular anatomy, and regional and distant metastases.

A systematic review found that the median sensitivity and specificity of CT for the detection of RCC were 88% and 75%, respectively.[24]

Magnetic resonance imaging

Magnetic resonance imaging is frequently used to further characterize renal masses that are indeterminate on CT but can be used as the initial study for the evaluation of renal masses, especially in patients with contraindication to iodinated contrast material.[22]

Multiparametric renal MRI protocol includes multiplanar T2-weighted, dual gradient-echo T1-weighted, and T1-weighted three-dimensional fat-suppressed gradient-echo images before and after gadolinium-based contrast material.[25] Corticomedullary, nephrographic, and excretory phases following contrast administration provide qualitative and quantitative information similar to CT and help in differential diagnosis. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient values can also be obtained to further characterize a mass. Subtraction imaging can be used to evaluate for lesion enhancement in the presence of intrinsic T1 hyperintensity.

A systematic review showed that the median sensitivity and specificity of MRI for the detection of RCC were 87.5% and 89%, respectively.[24]

Imaging features of common subtypes of RCC

The three most common histologic subtypes of RCC are clear cell, papillary, and chromophobe tumours, which as a group shows a broad spectrum of imaging appearances.

Clear cell RCC is the most common subtype. It is typically exophytic and shows vivid early contrast enhancement.[26] It has low to intermediate T1 signal and high T2 signal compared to the adjacent renal parenchyma.[27] Internal tumour heterogeneity can occur owing to areas of hemorrhage, necrosis, and/or cystic degeneration, which appear as non-enhancing regions.[28,29] Clear cell RCC may show reduced signal on opposed-phase chemical shift magnetic resonance images compared to in-phase images, owing to intracellular fat.[30] A peritumoural pseudocapsule may be present, which appears as a regular low or high attenuation rim on CT,[31] and low T1 and T2 signal on magnetic resonance images.[32] Calcifications are uncommon (**Figures 8 and 9**).[33]

FIGURE 8 60-year-old male patient with typical imaging features of clear cell RCC on CT.
A: Axial unenhanced CT scan of the abdomen at the level of the kidney showing an expansile mass involving the right kidney.
B: Postcontrast axial CT scan of the abdomen of the same patient in corticomedullary phase shows heterogeneous and intense enhancement.
C: Delayed-phase image (90 seconds) shows washout. This pattern of enhancement and washout is typical in clear cell RCC.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; RCC, renal cell carcinoma.

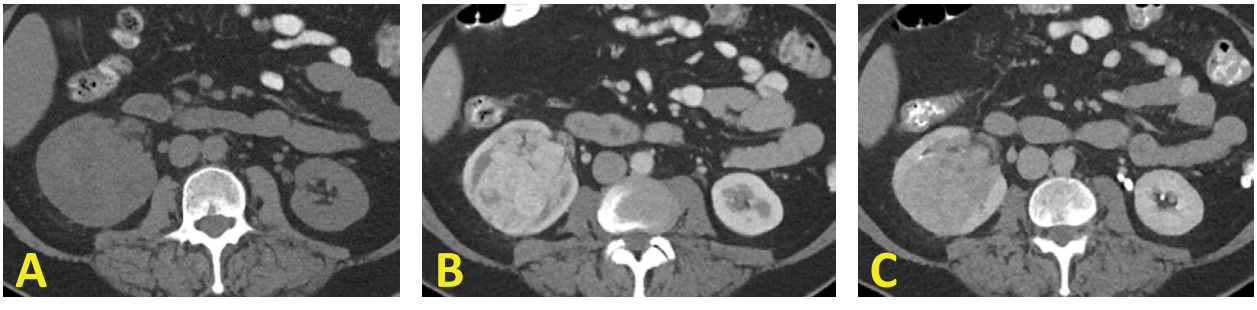
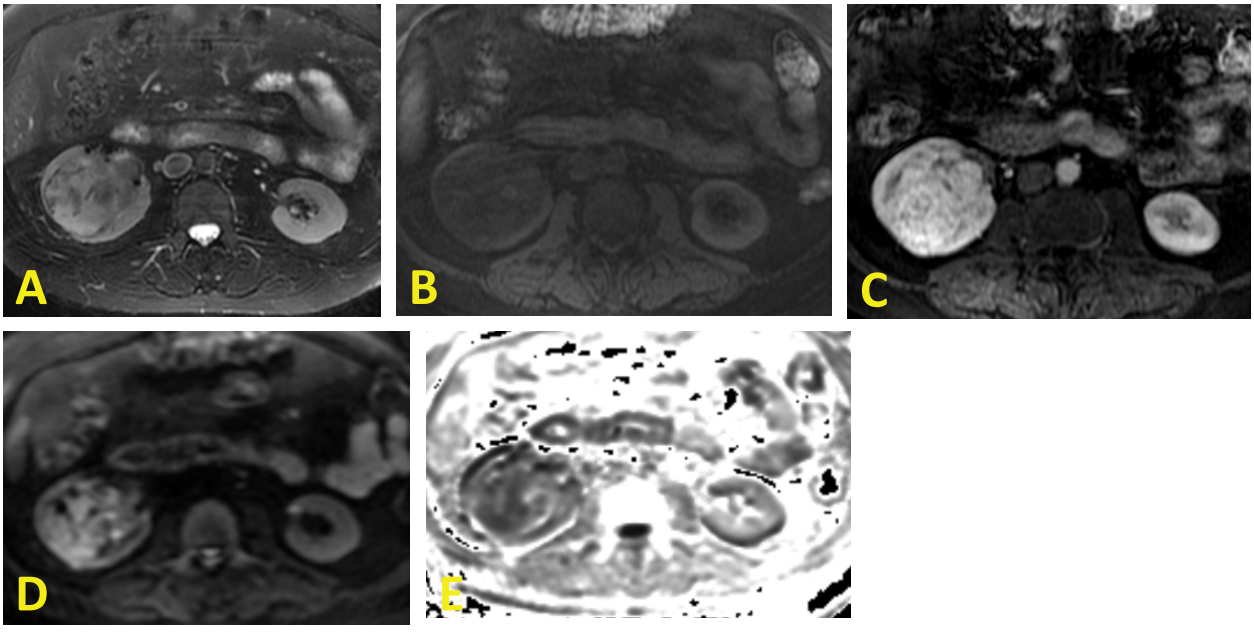


FIGURE 9 60-year-old male patient with typical imaging features of clear cell RCC on MRI.
A: Axial T2-weighted MRI image showing a right renal mass with heterogeneous high signal on T2-weighted sequences.
B: Precontrast fat-suppressed 3D T1-weighted image showing a hypointense expansile central mass in the right kidney.
C: Postcontrast 3D T1-weighted image performed in corticomedullary phase shows intense and heterogeneous enhancement.
D: Diffusion-weighted image (b=500) and corresponding ADC map (E) shows restricted diffusion.

Abbreviations: 3D, three-dimensional; MRI, magnetic resonance imaging; RCC, renal cell carcinoma.



Papillary RCC is the second most common subtype. It is generally a small peripheral homogeneous tumour that has low T2 signal compared to renal cortex, and shows weak enhancement compared to normal renal cortex that progressively increases on subsequent phases.[34] It may show loss of signal on in-phase images compared to opposed phase at chemical shift MRI owing to hemosiderin.[35] Some papillary RCC appear as hemorrhagic cystic masses with enhancing papillary projections.[36] Calcifications occur in 7% of cases in a large series of papillary RCC,[34] but they have been reported in up to 32% of cases.[33] Type 1 and 2 papillary RCC cannot be reliably differentiated on imaging but type 2 papillary RCC is more likely to be heterogeneous, show infiltrative margins, and contain calcifications (**Figures 10 and 11**).[37]

FIGURE 10 50-year-old male patient with an asymptomatic right upper pole papillary RCC.
A: Axial noncontrast CT scan, (B) corticomedullary phase scan, and (C) nephrographic phase scan showing an expansile mass in the upper pole of the right kidney with low-grade enhancement. This finding is commonly seen in type 1 papillary RCC.

Abbreviations: CT, computed tomography; RCC, renal cell carcinoma.

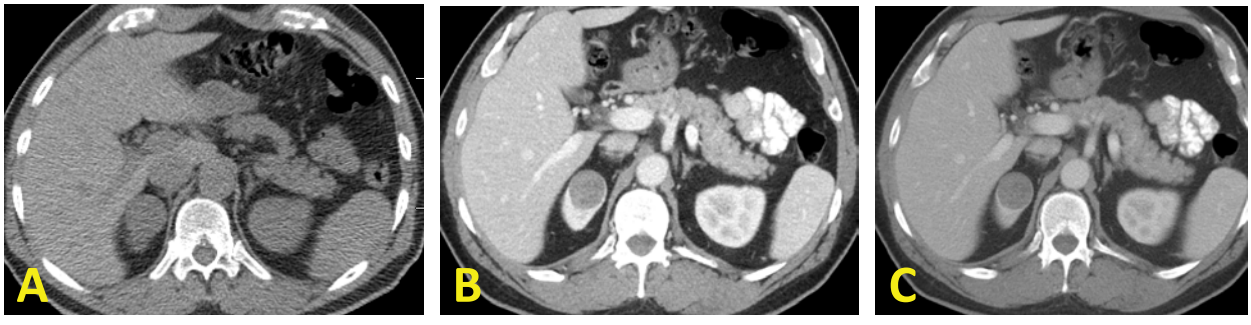
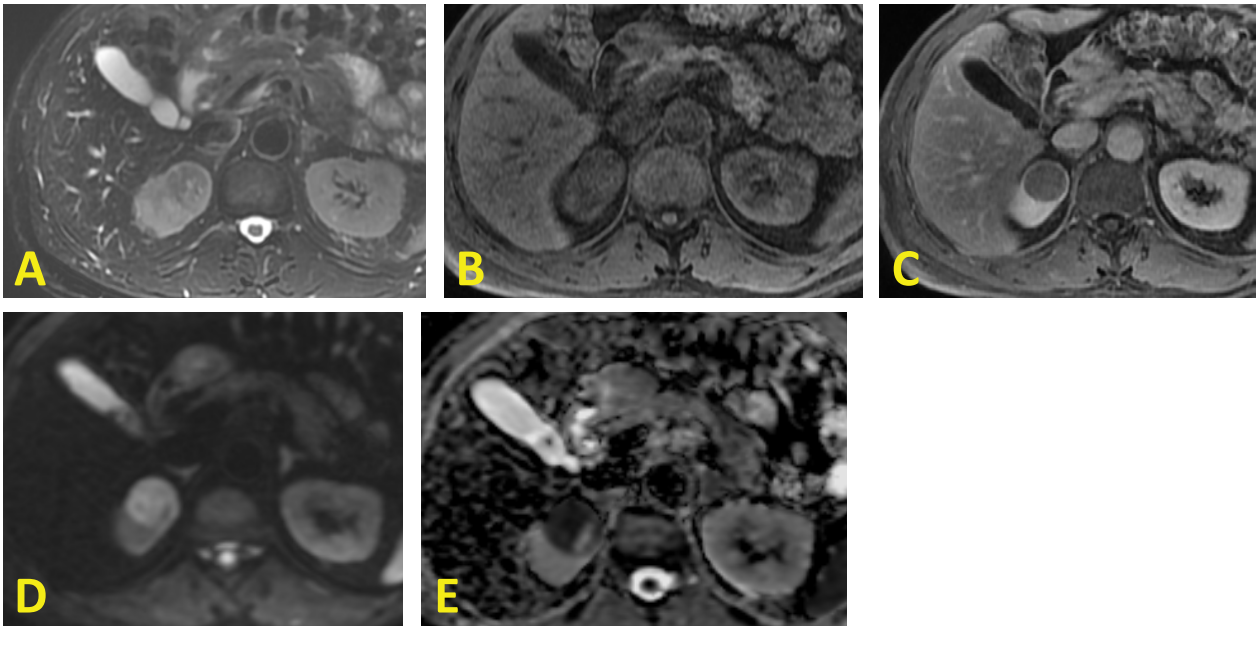


FIGURE 11 A: T2-weighted axial MRI of the abdomen at the level of the kidneys shows an expansile partially exophytic mass in the upper pole of the right kidney with relative low signal compared to the renal cortex.
B: Axial fat-suppressed precontrast T1-weighted image and (C) postcontrast T1-weighted image in the nephrographic phase showing relative hypoenhancement of the mass in the upper pole, compatible with papillary RCC.
D: Diffusion-weighted image (b=500) and corresponding ADC map (E) shows restricted diffusion in the upper pole lesion.

Abbreviations: MRI, magnetic resonance imaging; RCC, renal cell carcinoma.



Chromophobe RCC is the third most common subtype. It is usually a solid homogeneous tumour on CT, shows heterogeneous T2 signal on MRI,[38] and shows intermediate contrast enhancement in between that of clear cell RCC and papillary RCC.[26,36,39] A central scar, spoke-wheel enhancement pattern, and segmental enhancement inversion may be present, but these features overlap with oncocytoma.[38,40] Segmental enhancement inversion is whereby areas of the tumour that show early avid enhancement become reduced on more delayed images, and other areas of the tumour that showed lesser enhancement on early phases show progressive enhancement.[41] Calcifications occur in 14–38% of cases, and perinephric infiltration and venous invasion are uncommon.[33,39]

Differentiation of RCC from benign renal tumours

Computed tomography and MRI are unable to reliably and consistently discriminate between benign and malignant renal masses owing to overlapping imaging characteristics in 10–15% cases.[42] Renal cell carcinoma can be challenging to differentiate from oncocytoma and angiomyolipoma, especially the lipid poor variant. However, composite and collated imaging features can suggest a likely diagnosis.

Macroscopic fat within a non-calcified renal mass is almost diagnostic of an AML. Macroscopic fat rarely occurs in RCC.[43] Intracellular fat can be identified in clear cell RCC but this feature in isolation does not allow its differentiation from lipid-poor AML.[44] A renal mass containing fat with calcification or that shows necrosis is more likely to be an RCC than an angiomyolipoma.[36,43]

Papillary RCC shows weak progressive contrast enhancement, which allows its differentiation from a hemorrhagic cyst and lipid-poor AML. Hemorrhagic cyst shows no contrast enhancement,[45] and lipid-poor AML shows avid early contrast enhancement with subsequent contrast washout.[46]

Chromophobe RCC and oncocytoma show multiple overlapping imaging features and are most challenging to differentiate from each other.[38,47,48]

Quantitative imaging parameters, such as tumour enhancement characteristics,[49,50] diffusion-weighted MRI,[51] and texture analysis,[52] have shown some ability to differentiate between benign and malignant renal masses. A systematic review showed that the sensitivity and specificity for DWI to differentiate benign from malignant renal masses were 86% and 78%, respectively.[51]

Differentiation of subtypes of RCC

Computed tomography and MRI are yet unable to reliably differentiate between the subtypes of RCC owing to overlapping imaging characteristics. A study showed the performance of CT to predict clear cell RCC and chromophobe RCC on morphologic features alone had a positive predictive value of less than 75%, but evaluation of their contrast enhancement profile allowed differentiation of clear cell RCC from other subtypes with sensitivity, specificity, and accuracy of 64%, 87%, and 75%, respectively.[49] Application of algorithmic and scoring systems such as the clear cell likelihood score helps in achieving greater accuracy.[53,54]

Another study showed that the sensitivity and specificity of MRI in predicting clear cell RCC and papillary RCC were 92% and 83%, and 80% and 94%, respectively.[55] Dynamic contrast-enhanced MRI studies found that RCC subtypes showed contrast enhancement profiles concordant with CT findings, but considerable overlap occurs and does not allow definitive tumour histologic subtyping.[26,50,56] Clear cell RCC shows the widest differential in contrast enhancement during all contrast-enhanced phases compared to papillary RCC.[26,50] Sun *et al.* showed sensitivity, specificity, and accuracy of 93%, 96%, and 94%, respectively, in differentiating clear cell RCC from papillary RCC.[26] Type 1 and 2 papillary RCC often show overlapping imaging features that do not permit differentiation between them, though type 2 often shows more hypervascularity.[26,37]

Grading of RCC

Nuclear grade of RCC correlates with patient survival.[57] Imaging features that act as accurate surrogate markers of histologic grade of RCC would allow noninvasive prediction of prognosis and triage management.

Most studies have attempted to differentiate between low- and high-Fuhrman grade clear cell RCC. One study showed that the sensitivity and specificity of MRI to diagnose low-grade clear cell RCC and high-grade clear cell RCC were 50% and 94%, and 93% and 75%, respectively.[55] Another study showed no significant correlation between histologic grade and MRI features for papillary RCC and chromophobe RCC.[58]

Morphologic imaging features suggestive of higher-grade tumour or sarcomatoid dedifferentiation, include larger tumours with intratumoural necrosis, calcification, infiltrative margins, increased peritumoural neovascularity, larger peritumoural vessels, and renal vein thrombosis.[55,59,60,61,62] An uncommon predominantly cystic appearance of clear cell RCC has been shown to have low-grade malignant potential.[63]

Quantitative imaging parameters, such as tumour enhancement characteristics,[64] diffusion-weighted MRI,[65] and texture analysis,[66] have shown some correlation with nuclear grading. Sun *et al.* showed no significant difference in enhancement between low-grade and high-grade clear cell or papillary RCC.[26] A systematic review found that DWI showed a pooled sensitivity and specificity of 78% and 86%, respectively, to differentiate between low-grade and high-grade clear cell RCC.[65]

Emerging techniques and applications

Dual-energy spectral CT

Dual-energy CT is an emerging technique that can improve the conspicuity and characterization of renal masses.[67] The technique evaluates the material composition of a lesion by using two energy levels to simultaneously acquire images of the region of interest. Materials, such as iodine and water, have unique attenuation profiles at different energy levels. The acquired data are postprocessed using a mathematical algorithm. Datasets generated by this technique include water-based or virtual unenhanced images, and iodine-only image maps.

Iodine-only image maps or iodine quantification would allow detection of low-level contrast enhancement in tumours, which allows differentiation of clear cell RCC and papillary RCC owing to their different contrast enhancement profile. Several studies found that the sensitivity, specificity, and accuracy of this technique to differentiate between clear cell RCC and papillary RCC were 87–98.2%, 86.3–92%, and 90–95.3%, respectively.[68,69,70]

Dai *et al.* showed that iodine quantification allowed the differentiation of clear cell RCC and chromophobe RCC with a sensitivity, specificity, and accuracy of 83.9%, 90%, and 84.5%, respectively.[70]

Zarzour *et al.* found that iodine quantification showed a sensitivity, specificity, and accuracy of 100%, 96%, and 97%, respectively, in differentiating papillary RCC from complex renal cysts.[69]

Studies have shown mixed results in the ability of dual-energy CT to differentiate between papillary RCC and chromophobe RCC;[70–72] and between low-grade and high-grade clear cell RCC.[68–70,72,73]

Perfusion CT

Perfusion CT is a technique that involves multiple CT acquisitions of a fixed volume of tissue following contrast administration to generate qualitative and quantitative perfusion data. Mathematical algorithms are applied to this data to generate tumour perfusion parameters including blood flow, blood volume, and permeability.

Several authors have investigated the utility of CT perfusion to differentiate between benign and malignant renal masses,[74,75] RCC subtypes,[76] and RCC histologic grade.[77]

One study investigated the ability of perfusion CT and dual-energy CT to differentiate clear cell RCC from non-clear cell RCC using the same cohort of study subjects. It showed perfusion that CT achieved a sensitivity, specificity, and accuracy of 88%, 87%, and 87%, respectively,[78] but found no statistically significant difference in the accuracy with dual-energy CT. However, the authors found that perfusion CT involved a significantly higher radiation dose. The higher radiation dose penalty and more challenging technique of perfusion CT may limit the wider utility of the technique.

Radiomics

Radiomics is an emerging field that uses computational methods to extract quantitative metrics, such as shape, size, and texture, from any standard clinical image dataset, such as CT or MRI. Texture is the main radiomics feature used to evaluate renal tumours. It assesses tumour heterogeneity by analyzing pixel data within the image, which can provide information about the internal tumour microenvironment, such as vascularity and necrosis. The main areas under investigation in the application of radiomics in RCC research include the differentiation between benign and malignant small renal masses, nuclear grade prediction, and gene expression profile.[79]

Preliminary studies have shown that radiomics allows the differentiation of benign from malignant renal masses with CT[80–83] and MRI.[84–86]

One CT study showed a sensitivity and accuracy of 85.8% and 74.4%, respectively, in differentiating clear cell RCC from oncocytoma.[80] Another CT study of 127 RCCs showed a sensitivity, specificity, and accuracy of 89%, 92%, and 87%, respectively, for differentiating clear cell RCC from non-clear cell RCC, and 87%, 92%, and 78%, respectively, for differentiating papillary RCC from chromophobe RCC.[86] A further CT study of 62 papillary RCCs showed 84% accuracy in differentiating between type 1 and type 2 papillary RCC.[87] A MRI study found the sensitivity, specificity, and accuracy of 92%, 41%, and 70%, respectively, for distinguishing benign from malignant renal masses when using deep learning algorithms.[84]

Studies have shown the feasibility of radiomics to differentiate between low- and high-grade RCC.[88,89] One study of 53 patients showed a sensitivity, specificity, and accuracy of 91.3%, 80.6%, and 85.1%, respectively, for predicting high-grade from low-grade clear cell RCC.[90]

Radiogenomic studies have shown that mutation of BRCA1-associated protein 1 (BAP1) is associated with ill-defined tumour margins and presence of calcification, and is more commonly seen with higher-grade RCC.[91] Mutation of mucin 4 (MUC4) is found to be associated with exophytic tumour growth and reduced survival,[91] while mutation of lysine demethylase 5C (KDM5C) is found to be associated with renal vein invasion and reduced survival.[92]

A systemic review and meta-analysis of 57 studies found that translation of radiomics into clinical practice remains technically challenging owing to several factors including heterogeneous image acquisition protocols, reproducibility of radiomics signature, and big data sharing.[93]

Three-dimensional imaging technology

Three-dimensional (3D) imaging technology, such as 3D printing model, augmented reality, and mixed-reality technology, is a novel application of a CT or an MRI dataset to produce a visually concise representation of a renal tumour to improve its localization within the kidney and understand its relationship to relevant anatomical structures. 3D printing models and augmented reality have been used for preoperative surgical planning in complex cases[94] and for patient counselling.[95] One study showed the utility of a 3D-printing model for robot-assisted partial nephrectomy of tumours with a nephrometry score of ≥ 7, reducing operative time by about 20%.[96] A systematic review found improved perioperative outcomes, such as intraoperative blood loss, reduction in estimated glomerular filtration rate (eGFR), and complications, in laparoscopic partial nephrectomy for complex renal tumours using a 3D-printing model in preoperative planning compared to surgery without the model.[97]

Key Points

- Multiphase contrast-enhanced CT or MRI is critical in the characterization and staging of renal masses and RCC in particular.
- Multiplanar and volumetric reconstructions help in evaluation as well as treatment planning for renal masses.
- Semiquantitative and quantitative imaging methods are increasingly being used in the evaluation of renal masses.
- Artificial Intelligence (AI)-enabled techniques of renal mass evaluation are being explored but have not yet translated into clinical practice.

Molecular Imaging in Renal Cell Carcinoma

Molecular imaging provides additional anatomic and physiologic information through noninvasive means to assist in characterizing, diagnosing, staging, and monitoring disease. Positron emission tomography/computed tomography (PET/CT) is the dominant modality of this class, wherein the PET portion of the exam depicts biochemical and metabolic processes specific to the unique radiotracer injected into the patient and the CT portion provides anatomic context. Annihilation coincidence photons from positron emission decay are detected by the PET camera and the spatial positioning of the event is coregistered with the CT for accurate anatomic localization. Here, we will discuss the specific application of PET/CT in renal cell carcinoma.

18F-FDG and primary renal cell cancer

The most commonly used radiotracer, 18F-Fluorodeoxyglucose (18F-FDG), is a radiolabelled glucose analogue highly avid in many tumours that has been moderately studied in RCC. Unfortunately, many reports are small and from single institutions while prospective and multicentre studies are few. A significant issue is that distinguishing tumours from normal parenchyma within the kidney is challenging due to the physiologic urinary excretion of 18F-FDG. One of the first large studies to examine 18F-FDG in RCC retrospectively reviewed 66 patients. FDG PET had a sensitivity of only 60% for detecting RCC but had a high specificity of 100% for primary RCC tumours. Evaluating the contralateral kidney for concomitant malignancy in a mixed group of primary and restaging patients, 18F-FDG was only 50% sensitive (but 98.8% specific) for identifying renal masses. A major limitation of this study was that scans were not on a PET/CT scanner, and detection was based on PET alone.[98]

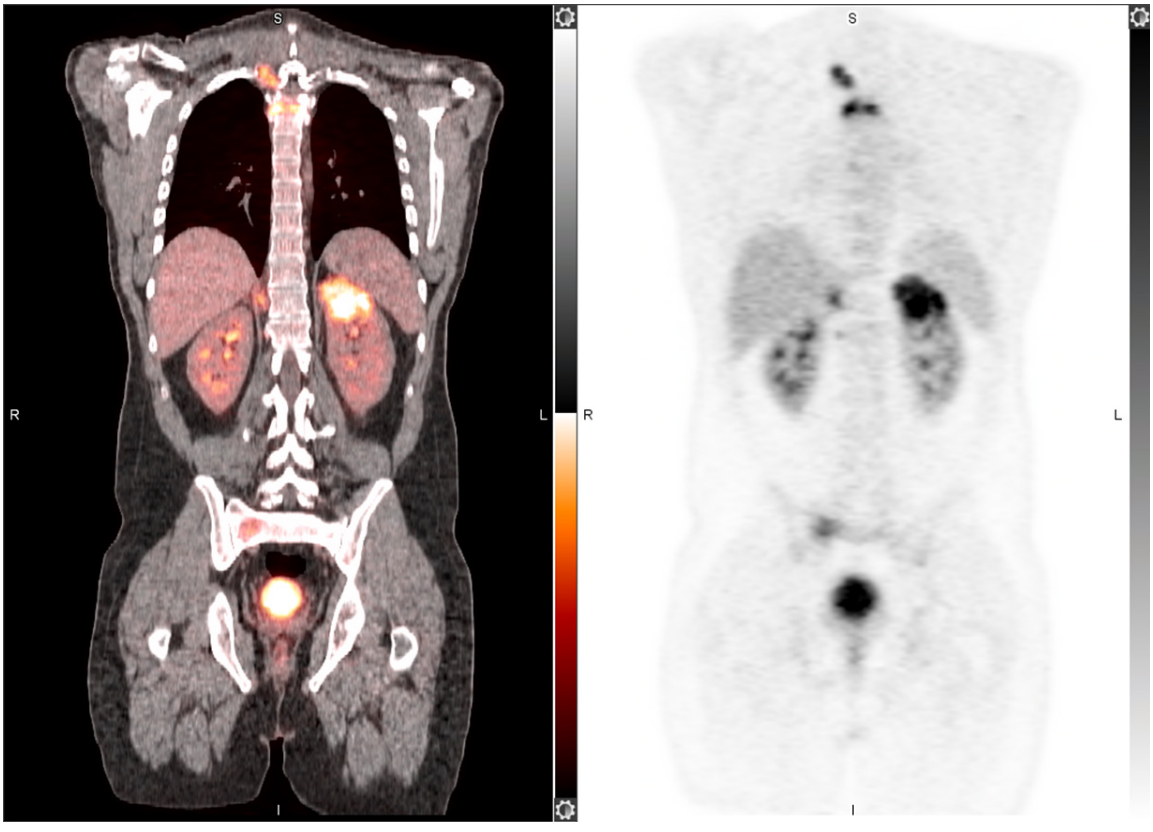
In a meta-analysis evaluating the diagnostic performance of 18F-FDG PET in RCC, sensitivities ranged widely from 40–100% in the diagnosis and staging of primary tumours with large variations in methodology.[99] A systematic review of RCC imaging found only two studies meeting specific criteria for primary tumour evaluation with 18F-FDG. The result was a relatively high median sensitivity of 88% and specificity of 87.5%.[99,100] This is in contrast to a prospective study evaluating indeterminate renal masses. Patients with suspicious lesions identified

by conventional imaging underwent 18F-FDG PET/CT and were compared to gold standard histopathology obtained from nephrectomy or resection. 18F-FDG showed an overall accuracy of 50%, sensitivity of 46.6%, and specificity of 66.6% for primary RCC in this more difficult cohort of patients.[101] Another prospective study of primary renal tumour detection with 18F-FDG PET/CT reached a sensitivity of 98% with strong correlations with tumour maximum standardized uptake value (SUV_{max}) and Furhman grading. The notable addition of contrast enhancement on CT and larger tumour sizes (mean of 5 cm) significantly contributed to the impressive detection rate in this publication.[102] A different systematic review found 18F-FDG PET/CT performed equivalent to conventional imaging in primary renal tumour detection.[103] From this work it can be concluded that 18F-FDG PET/CT has a high specificity for RCC, but its sensitivity varies according to the size and type of the renal lesion.

Renal cell carcinoma can be further categorized by pathological subtypes with separate risk profiles. Clear cell RCC is the most prevalent subtype. Papillary type 2 and some clear cell carcinomas can be extremely aggressive with high rates of recurrence and metastasis, resulting in poor patient outcomes. Recognizing critical subtypes could affect treatment strategies. Early dynamic imaging with 18F-FDG PET/CT may be more helpful than traditional static scanning in distinguishing aggressive RCC subtypes. In a prospective study of 100 patients undergoing renal resection, the SUV_{max} from dynamic scans was higher in clear cell tumours than non-clear cell variants. Because the other subtypes were low in numbers, further differentiation could not be made. With whole body static imaging, researchers observed that elevated SUV_{max} and tumour-to–normal reference tissue ratios corresponded to more aggressive RCC features with higher TNM stage, Fuhrman grade, as well as venous and lymphatic invasion, but could not be used to separate tumour subtypes.[104] The same authors later showed that chromophobe RCC demonstrated lower SUV_{max} values than clear cell and papillary tumours. There was no real distinction in SUV_{max} between papillary and clear cell variants, but high-grade tumours had higher SUV_{max} than low-grade tumours in both groups and were associated with Fuhrman grading in clear cell tumours.[105] In papillary RCC, 18F-FDG sensitivity has been reported as high as 81.5% and similarly could distinguish between high-grade and low-grade tumours but not papillary subtypes (**Figure 12**).[106] In contrast, a recent retrospective analysis found that 18F-FDG was useful in distinguishing papillary type 2 renal cell cancer from papillary type 1, clear cell, and oncocytoma. Tumour-to-liver ratios were higher in papillary type 2 tumours than the other types of RCC and also higher in patients with papillary type 2 tumours with distant metastasis compared to those without.[107] Papillary type 2 tumours, usually show high uptake because they are often associated with defects in the fumarate hydratase gene causing increased glycolysis. Other researchers have found that 18F-FDG uptake in benign oncocytoma and angiomyolipoma is difficult to distinguish from malignant RCC subtypes of clear cell, chromophobe, and papillary.[102] Reliably discriminating the varied histologies of RCC through radionuclide imaging may not ultimately be possible but could guide diagnostic workups.

FIGURE 12 18F-FDG PET/CT demonstrates focal uptake in the primary left upper pole papillary RCC and in metastatic lesions in the ribs, spine, pelvis, and retrocrural lymph nodes. Physiologic activity is within the renal collecting system and bladder. Coronal PET and CT fusion image is on the left and coronal PET is on the right.

Abbreviations: FDG, fluorodeoxyglucose; PET/CT, positron emission tomography/computed tomography; RCC, renal cell carcinoma.



Other metabolic measures in addition to SUV_{max} appear to correlate with RCC tumour grading. In a prospective study, metabolic tumour volume (MTV) and tumour-to-liver ratios could also distinguish between Fuhrman high-grade and low-grade RCC tumours. Diuretic use did not improve tumour detection.[108] Significant differences were seen between high-grade and low-grade primary clear cell tumours and tumour SUV_{max}, tumour-to-liver SUV ratio, and tumour-to-kidney SUV ratios in a retrospective trial of 125 subjects with newly diagnosed RCC.[109] Radiomics and texture analysis have also been suggested as a means of using 18F-FDG to determine RCC subtype. Fuhrman grading of clear cell RCC could be predicted using standardized uptake normalized to lean body mass (SUL) and 18F-FDG texture models.[110] Texture analysis also appears to distinguish RCC and renal lymphomas.[111] Computed tomography characteristics on 18F-FDG PET/CT as well as higher SUV_{max}, SUV_{mean}, and SUV_{peak} could likewise distinguish sarcomatoid differentiation from clear cell type in these limited studies.[112]

The combined value of 18F-FDG and novel tumour or serum markers have also been explored. TP53-inducible glycolysis and apoptosis regulator (TIGAR) is a newly discovered enzyme controlling cellular glucose degradation that is hijacked by some cancers. Expression of tumour induced molecular pathway changes and 18F-FDG metabolism were investigated in 62 patients with clear cell RCC. Identified by immunohistochemistry on renal tumour specimens, evidence of positive TIGAR in clear cell RCC correlated with high tumour SUV_{max} and shorter overall survival (OS).[113] Others have probed associations with the tumour immune microenvironment and FDG metabolism in clear cell RCC. Interestingly, high SUV_{max} correlated with increased tumour infiltrating lymphocytes and higher grade. SUV_{max} also predicted disease-free survival with patients who had elevated tumour SUV_{max} developing progressive disease earlier. No correlation was seen between SUV_{max} and programmed cell death 1 ligand 1 (PD-L1) expression.[114] Primary tumour SUV_{max} has also been linked to progression-free survival (PFS) with shorter PFS in patients with increased SUV_{max}.[106]

A major limitation of 18F-FDG in assessing primary RCC is the physiologic excretion through the kidneys, which can obscure all or parts of RCC. Therefore, recent guidelines from major societies including the National Comprehensive Cancer Network (NCCN), the European Association of Urology (EAU), and American Urology Association (AUA) do not recommend 18F-FDG use in diagnosis or evaluation of RCC.

Restaging and detection of extra-renal metastasis with 18F-FDG

18F-FDG is more successful in detecting metastatic or recurrent RCC tumours rather than primary RCC, and despite expert opinion against its use in restaging RCC, it could have prognostic benefits and influence clinical decisions. Renal cell carcinoma recurs at a rate of 20–50% even after nephrectomy.[115] Consequently, accurate detection of tumour recurrence is important in managing treated RCC. Moreover, metastatic tumour identification by postsurgical 18F-FDG PET/CT is reported to have predictive value. Overall survival rates decreased in patients with positive scans by 5 years and lower PFS was seen at 3 years. Scan results were shown to affect management decisions in 43.2 % of patients including the decision for curative or palliative treatments or surveillance without therapy.[116] Added support includes a small prospective study in patients with metastatic renal disease that found poor prognosis correlated with high tumour SUV_{max}, which is in keeping with the experience with most other types of tumours.[117]

A meta-analysis by Ma *et al*. included 14 studies with 853 patients and calculated a pooled sensitivity of 86% and pooled specificity of 88% for detecting metastatic disease.[118] This is in line with another meta-analysis evaluating 18F-FDG PET/CT detection of extrarenal lesions, which reported a pooled sensitivity of 91% and specificity of 88%, but again, the evaluation was limited by small numbers.[119] Compared to CT and MRI, 18F-FDG PET/CT was superior in staging and detecting metastasis in a small prospective study.[102] Similarly, in a retrospective review of 343 patients who underwent surveillance after surgery for RCC, 18F-FDG PET/CT was comparable to conventional imaging with diagnostic CT. Researchers also pointed out that 18F-FDG PET/CT delivered less

radiation exposure, which is an appealing consideration for its use in the recurrent setting.[120] However, 18F-FDG PET/CT was not clearly superior to conventional imaging, decreasing the impetus to employ it.

A retrospective study reviewing 18F-FDG in restaging RCC offered a detailed analysis of metastatic lesion locations. Retroperitoneal lymph node metastases and/or renal bed recurrence was identified with 75% sensitivity and 100% specificity. Lung metastases were detected with 75% sensitivity and 97.1% specificity. Mediastinal/hilar lymph nodes were detected with 69% sensitivity and 97.9% specificity. 18F-FDG was 61.5% sensitive and 100.0% specific for liver metastases. 18F-FDG PET was strongest in detecting bone lesions with a sensitivity of 77.3% and specificity of 100%. FDG demonstrated 98.4% positive predictive value (PPV) but 29.6% negative predictive value (NPV) for soft tissue metastases. Meanwhile, the PPV was 100% and NPV was 93.2% for bone metastases. Again, the use of an older PET scanner without a built-in CT for this study likely influenced the lower percentages.[98]

In papillary RCC, 18F-FDG performance in restaging was impressive, with 100% sensitivity and 72.7% specificity and analogously affected clinical management. Compared to CT and MRI, 18F-FDG found additional lesions in bone and lymph nodes.[106] Interestingly, 18F-FDG may have more difficulty in detecting clear cell metastases compared to papillary RCC, but clear cell carcinomas are far more common and thus likely represent the majority of cases in most series.[121]

Therapy response with 18F-FDG

18F-FDG PET/CT shows potential in predicting response to therapy for metastatic disease. Caldarella *et al.* published a systematic review including 7 prospective studies evaluating 18-FDG PET/CT as a marker of response to tyrosine kinase inhibitors (TKIs) in patients with advanced RCC. Despite variable findings and heterogeneity in studies, the authors concluded that 18F-FDG PET/CT was a beneficial tool in assessing prognosis.[122] The largest study in this review, which consisted of 44 patients, looked at the TKI sunitinib and 18F-FDG as a biomarker of response in patients with untreated metastatic clear cell cancer. At baseline and 16 weeks post-treatment, 18F-FDG PET/CT assessments were predictive of outcome. High number of PET-positive lesions and increased SUV_{max} at baseline were linked to shorter OS while disease progression seen on 18F-FDG at 16 weeks correlated to decreased OS and PFS.[123]

Volumetric indices of 18F-FDG have also been studied to assess response to TKIs. Changes in peak SUL and total lesion glycolysis (TLG) correlated to PFS and OS as early as 14 days after treatment in patients with metastatic RCC. Changes in SUV_{max} did not have a meaningful impact.[124] In a small prospective trial with sunitinib in metastatic RCC, 18F-FDG parameters included TLG and MTV in addition to SUV_{max} in examining relationships to PFS. Baseline and interim 18F-FDG PET/CT at 12 weeks (after 2 cycles) were evaluated. Baseline PET metrics were predictive of PFS at 12 months post-therapy and changes in these quantitative measures between baseline and interim images showed correlations with PFS, but the interim scan itself was not as effective in predicting outcome.[125] Similarly, a retrospective study of 18F-FDG prior to TKI therapy found that TLG and MTV predicted

OS and PFS. Furthermore, high MTV or TLG predicted worse OS and PFS in intermediate- and poor-risk groups as defined by the International Metastatic RCC Database Consortium (IMDC).[126]

Separately, a small prospective study evaluated 18F-FDG metabolism at baseline and after 1 month of nivolumab treatment in patients with metastatic clear cell RCC, finding that high SUV_{max} corresponded to treatment response at 4 months.[127] A larger prospective study looked at 100 patients with metastatic or recurrent RCC planning to undergo systemic therapy. On pretreatment 18F-FDG PET/CT, the highest tumour SUV_{max} per patient was predictive of poor prognosis.[128] The same authors prospectively evaluated 18F-FDG metabolism in 81 patients with advanced RCC prior to second-line systemic therapy. They also observed that high maximum SUV_{max} at baseline was associated with poor OS.[129] 18F-FDG PET/CT shows merit as a prognostic tool for metastatic therapy response and could inform clinicians on risks and benefits on an individualized level. 18F-FDG imaging could guide selection of patients poised to derive favourable treatment outcomes.

Other PET agents

PSMA radiotracers

Prostate-specific membrane antigen (PSMA) PET radiotracers have exploded into use in prostate cancer over the past several years because of their excellent targeting abilities. 68Ga-PSMA is the most used worldwide, but 18F-DCFPyL and 18F-PSMA-1007 are also in clinical practice. Research has been plentiful in exploring their efficacy in other tumours largely based on PSMA expression associated with malignant angiogenesis. A systematic review in nonprostate tumours indicated that PSMA PET/CT was useful in the diagnosis, staging, and management of RCC, but larger prospective studies are needed.[130] Another mini-review of PSMA PET/CT in RCC evaluated 13 studies and concluded that PSMA radiotracers could be useful in staging, restaging, and predicting treatment response, but not in primary tumour evaluation. Most studies were small and retrospective, highlighting the need for better studies on this topic.[131] In a retrospective analysis of 6 patients, 68Ga-PSMA PET/CT easily identified metastatic RCC lesions but again, was not as distinct in primary tumours. An early pilot study looked at 18F-DCFPyL PET/CT in 5 patients with metastatic clear cell RCC and reported more lesions seen with 18F-DCFPyL than CT or MRI.[132] However, the clinical importance of these added lesions is uncertain. Several studies have compared the performance of PSMA and 18F-FDG in RCC and found that more lesions were detected by PSMA PET/CT. Differences in time to visualize response to therapy were also noted for each agent.[133,134]

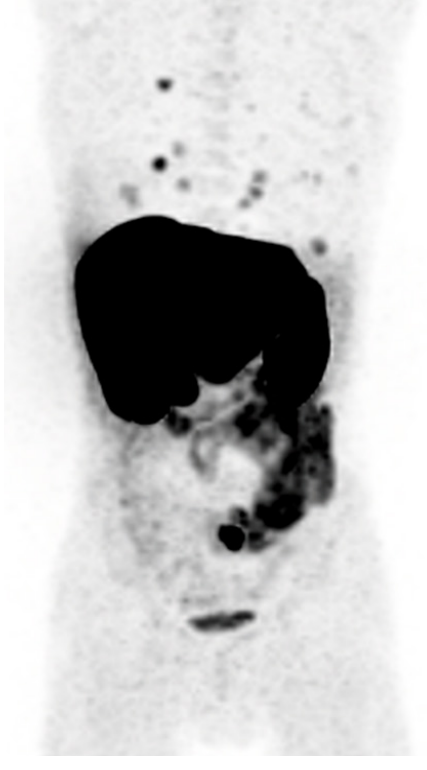
PSMA PET/CT can also be helpful in distinguishing aggressive features seen with clear cell variants. 68Ga-PSMA tumour SUV_{max} values correlated to World Health Organization/ International Society of Urological Pathology (WHO/ISUP) grades and the presence of pathological characteristics with poor prognosis (such as tumour necrosis, sarcomatoid or rhabdoid features) in a group of patients with primary clear cell tumours.[135] Surprisingly, PSMA expression in clear cell RCC on immunohistochemistry does not correlate well with 68Ga-PSMA PET uptake such as SUV_{max}, SUV_{mean}, or lesion-muscle-ratio.[136] This may reflect the heterogeneous expression of PSMA in tumours. Moreover, PSMA radiotracers may not be helpful in non-clear cell subtypes.

A recent trend has been the resection of all metastases in patients with oligometastatic RCC, which has been reported to improve OS in carefully selected patients.[137] PSMA agents may be helpful in identifying RCC oligometastases that could be curatively treated by surgery. 18F-DCFPyL PET/CT was prospectively compared to CT or MRI in 14 patients with presumed oligometastatic clear cell RCC and had a high detection rate of 88.9% versus 66.7% with conventional imaging.[138]

CAIX tracers

Another potential target for molecular imaging is the cell surface antigen carbonic anhydrase IX (CAIX), which is overexpressed in RCC and promotes tumour growth through acidosis. While more than 94% of clear cell RCC express CAIX, it is not found in other RCC subtypes or benign renal tissue (**Figure 13**).[139] Geruntuximab is an anti-CAIX monoclonal antibody that was initially labelled with 124I to explore PET/CT tumour imaging. In 195 patients with renal masses, 124I-geruntuximab demonstrated 86% sensitivity and specificity compared to contrast-enhanced CT sensitivity of 76% and a specificity of 47% for clear cell RCC; however, this was ultimately judged to not be of sufficient clinical value.[140]

FIGURE 13 Maximum intensity projection image of 18F-VM4-037, a small molecule targeting carbonic anhydrase IX, in a patient with metastatic renal cell carcinoma. Physiologic soft palate, hepatic, renal, gastrointestinal, and bladder activity is intense while metastatic lung lesions are focal.



More investigations with this antibody have shifted to the 89Zr labelled agent, which improves PET image contrast and spatial resolution over 124I owing to its longer retention in tumour, making it advantageous for research efforts. 89Zr-girentuximab is safe, with the liver, kidneys and heart wall receiving the most radiation exposure and a mean whole body effective dose of 0.57 ± 0.08 mSv/MBq, which is comparable to other 89Zr agents. The radiotracer successfully differentiates between clear cell RCC and non-clear cell RCC lesions.[141] In newly diagnosed metastatic clear cell RCC, 89Zr-girentuximab PET/CT and 18F-FDG PET/CT may provide complementary data. Studying a population of 42 patients with good and intermediate prognosis, 89Zr-girentuximab and 18F-FDG detected considerably more lesions, particularly bone and soft tissue than CT alone. 89Zr-girentuximab detected slightly more lesions than 18F-FDG in this preliminary analysis of a larger trial.[142]

An international, multicentre, phase 3 trial is underway to prospectively determine the sensitivity and specificity of 89Zr-girentuximab PET/CT for clear cell RCC in primary tumours (clinicaltrials.gov identifier NCT03849118).

Additional tracers

Other novel metabolic and cellular processes can be illustrated with molecular imaging, and scattered studies have been published to test their capabilities in RCC. These include:

a. Measuring hypoxia with 18F-fluoromisonidazole PET/CT.[143]
b. Accuracy of identifying bone metastases was similar with 18F-NaF, 18F-FDG, and 99mTc-bone scan in patients with RCC.[144,145]
c. Assessing tumour cell proliferation and cell membrane synthesis with 18F-fluorothymidine (18F-FLT).[146]
d. 11C-choline[147,148] and Acetate[149,150] have also been explored.
e. Imaging tumour angiogenesis with research tracers such as 18F-FPPRGD2, an integrin receptor targeting ligand, have been explored.[151]

Future directions

Advances in molecular imaging bring the hope of translation to targeted therapy. Radioligand treatments with beta and alpha emitters attached to compounds directed at PSMA are actively under investigation in prostate cancer and are being considered for other tumours. Although PSMA is not specific to RCC, damage to the cancer's PSMA-positive neovasculature through radioligand therapy could nevertheless be a worthwhile adjuvant treatment. Similarly, girentuximab has been "armed" with a beta emitter, and a phase 2 trial with 177Lu-girentuximab in 14 patients with metastatic clear cell RCC resulted in stabilized disease in 64%, although most patients developed reversible grade 3–4 myelotoxicity, precluding treatment beyond 1 or 2 cycles.[152] Hence, customized 177Lu regimens based on patient 89Zr-girentuximab dosimetry could improve radioimmunotherapy. Pairing functional nuclear medicine imaging with targeted therapeutic radionuclides helps map biodistribution and suggests likelihood of treatment efficacy. Developing more theragnostic options for RCC opens exciting opportunities for future progress.

Key Points

- Molecular imaging in RCC is constrained by physiologic excretion of PET agents and the role is limited in tumours smaller than 2 cm.
- Novel radiopharmaceuticals such as PSMA and CAIX radiotracers as well as tracers directed at various cellular processes have demonstrated potential in RCC, but larger prospective trials are necessary to determine clinical impact.

Imaging in Staging and Follow-Up of RCC

Imaging plays a key role in staging of the primary tumour. Computed tomography and MRI are equivalent in staging accuracy of primary renal tumours based on multiple different studies.[153,154] It should be noted that both these modalities suffer from similar weaknesses when compared to postoperative pathology, mainly due to disparities in radiographic and pathologic size or subtle perinephric or renal sinus fat invasion, which may be difficult to detect on imaging.[155,156] In most institutions, CT is the primary modality used for evaluation of renal masses. Magnetic resonance imaging is generally reserved for patients who cannot receive a contrast-enhanced CT scan due to allergy to iodinated contrast medium or a depressed renal function.

Renal cell carcinoma is a multifocal disease. An optimal CT scan and MRI protocol should be able to detect and assess small renal masses, which can be addressed at the time of surgery. Hence it is important to obtain a high-quality CT and MRI that includes a nephrographic or excretory phase to optimize detectability and characterize small lesions.

The 8th edition of American Joint Committee on Cancer (AJCC) TNM staging system depicted in **Table 1**[157] is universally used and allows for stratification of patients based on predicted prognosis. This also forms the basis for modality and frequency of evaluation on follow-up post-treatment.

TABLE 1 T Staging Categories

Tx	Primary tumour cannot be assessed
T1	T1a: ≤ 4 cm, limited to the kidney T1b: > 4 cm and ≤ 7 cm, limited to the kidney
T2	T2a: > 7 cm and ≤ 10 cm, limited to the kidney T2b: > 10 cm, limited to the kidney
T3	T3a: invades renal vein / branches, perirenal fat, renal sinus fat, or pelvicalyceal system T3b: extends into vena cava below the diaphragm T3c: extends into vena cava above the diaphragm or invades vena cava wall
T4	Invades beyond Gerota's fascia, including direct extension to adrenal gland

Source: Amin MB, Edge SB. AJCC Cancer Staging Manual, 8th Edition. Springer Nature Switzerland AG; 2017.[157]

Presurgical evaluation staging of primary tumour

Size, extent, degree of local invasion of the primary tumour (perinephric invasion, renal sinus fat invasion, renal calyceal invasion, adrenal glands, involvement of other structures in the retroperitoneum, involvement of Gerota's fascia), renal arterial anatomy, and tumour extension into the veins are to be assessed on presurgical imaging.[157] The American College of Radiology (ACR) appropriateness criteria recommend CT and MRI of the abdomen without and with contrast as the most appropriate imaging modalities to stage renal cell carcinoma. CT scan of the chest may be considered in high-risk patients such as those with very large tumours and those with locally aggressive disease to assess for lung metastases. Imaging of brain and bone scans is reserved for symptomatic patients with aggressive disease.[158]

Size and degree of local invasion determines the T stage in the AJCC TNM staging system. Tumour confined to the kidneys is staged as T1 and T2. Tumours with extension into the perinephric fat or renal sinus fat, or tumours extending into the renal vein are staged as T3a. Tumors extending into the inferior vena cava are staged as T3b and T3c depending on the most distal extension of tumour in relation to the diaphragm. Tumours involving the adrenal gland or extending beyond the Gerota's fascia are considered T4 disease.[157]

Perinephric tumour extension and invasion of the renal sinus fat are difficult to accurately detect on CT and MRI. Nonspecific perinephric stranding due to edema or fibrosis can be misinterpreted as perinephric extension of tumour on CT.[153,155] Some authors have shown that the presence of a pseudocapsule on MRI has an accuracy of 93% in distinguishing T1 / T2 tumours from T3a.[159] Direct continuous spread to the adrenal gland is considered

T4 disease. CT and MRI have high sensitivity of nearly 100% NPV of detecting adrenal involvement. However, the PPV is lower, as it may be difficult to distinguish abutment from direct invasion. Tumour thrombus in the renal vein and its extent is best delineated on contrast-enhanced images performed in nephrographic or delayed-phase studies on CT, as arterial and portal venous phase are limited by admixture of an opacified blood in the IVC. It is also important to identify the cephalad extent of tumour thrombus within the IVC, which can also determine the surgical approach and preoperative planning. Extensive mobilization of liver and/or cardiac bypass may be required in tumours that show significant careful out-extension of tumour thrombus. Occasionally, transmural invasion of caval wall may have to be treated with excision and reconstruction with a graft.[160] The significance of extent of venous thrombosis is a topic of controversy, but supradiaphragmatic extension of IVC thrombus appears to be associated with a poorer prognosis than subdiaphragmatic extension of disease. Both CT and MRI have a similar sensitivity in detecting venous involvement, particularly in the main renal vein and the IVC. Noncontrast MRI, however, has significant advantages over noncontrast CT due to higher tissue contrast. Hence, in patients with impaired or significantly impaired renal functions, MRI is the preferred modality for local staging of tumour.

In addition to arterial variants such as multiple renal arteries, it is also important to identify venous anomalies such as retro aortic and circumaortic renal vein, as these have significant implications in surgical planning.

Presurgical evaluation of nodes and distant metastasis

Cross-sectional imaging criteria for diagnosis of metastatic nodes relies on size, disruption of normal lymph node architecture, and enhancement characteristics mirroring those of the primary tumour. Significant false-negative rates are encountered when size alone is used as a cutoff criteria.[161] MRI has not shown to be superior to CT in overcoming this weakness. CT-guided aspiration of suspicious lymph nodes is an alternative and can be performed if this information is required for treatment planning.

Distant metastases are commonly seen in the lungs, bones, liver, and brain. The risk for metastasis increases with the size of the tumour and stage of the tumour. CT of the chest is justified for larger and more locally advanced primary tumours.[162] Bone metastases is considered a poor prognostic indicator in patients with metastatic RCC.[163] In symptomatic patients who have advanced primary tumours or who have abnormal laboratory findings such as elevated alkaline phosphatase, bone scan can be considered for diagnosis of bone metastases. Brain metastasis is seen in up to 17% of patients with metastatic renal cell carcinoma. Patients with neurological signs should receive contrast-enhanced MRI of the brain or CT scan. Asymptomatic occult brain metastases in patients with advanced RCC may be detected with brain MRI.[164]

Imaging in follow-up

Risk for recurrence following surgery depends on the size of the tumour, the pathological stage of the tumour, the grade, and pathological subtype. Patients undergoing surgery are classified into risk groups depending on the pathologic stage and grade of the tumour into low-risk, intermediate-risk, high-risk, and very high–risk

categories. Patients with positive surgical margin on resection are considered at least one level of risk category higher and subject to increased clinical vigilance. The frequency of follow-up visits and imaging is based on the risk category and subject to increased clinical vigilance the patient belongs to. The risk categories are depicted in **Table 2**.[157]

A follow-up schedule after surgery for renal cell carcinoma as recommended by the American Urological Association expert committee is detailed in **Table 3**.[1,2]

Chest X ray is recommended for patients belonging to the low-risk and intermediate-risk categories. Chest CT is recommended for patients belonging to the high-risk and very high–risk categories. Patients undergoing ablative procedures should undergo pre- and post-contrast cross-sectional abdominal imaging (or MRI) within 6 months and follow-up should be according to the recommendations for the intermediate-risk category group.

Hematogenous and lymphatic spread are both seen in renal cell carcinoma. Hematogenous spread commonly is seen in the lungs, occurring via the renal vein. Metastasis to the lymph nodes in the perinephric space is the initial manifestation of lymphatic spread. Occasionally, tumour cells may travel via the thoracic duct to involve nodal groups elsewhere in the body. Postsurgical recurrence of renal cell carcinoma in the surgical bed is also seen. A comprehensive review of patterns of tumour recurrence or spread found that 83% of the recurrences occurred within the first 2 years of surgery. However, late recurrences sometimes as long as 10 years after initial surgeries have also been reported. Lung and bone metastases most commonly occur within 1 to 2 years. The recurrence in the nephrectomy site, however, has occurred at varying times, between 1 to 3 years after surgery. The most frequent sites of distant metastases are, in decreasing order of frequency, the lung, bone, lymph nodes, and liver, followed by adrenal gland, contralateral kidney, retroperitoneum, and brain. Metastases to almost any organ or muscle can also occur.[165,166]

TABLE 2 Risk Categories Based on Pathology

Low Risk	pT1 and grade 1/2
Intermediate Risk	pT1 and grade 3/4, or pT2 any grade
High Risk	pT3 any grade
Very High Risk	pT4 or pN1, or sarcomatoid/rhabdoid dedifferentiation, or macroscopic positive margin

Staging system refers to the AJCC TNM staging (8th edition) and grading system corresponds to ISUP grading system (2016).[157]

Source: Reproduced from Campbell SC, Uzzo RG, Karam JA, et al. *Renal Mass and Localized Renal Cancer: Evaluation, Management, and Follow-up: AUA Guideline: Part II*. J Urol. *2021;206(2):209–218. doi:10.1097/JU.0000000000001912.*[2]

TABLE 3 Suggested Follow-Up Schedule After Surgery for RCC (in months)[1,2]

Risk	3	6	9	12	18	24	30	36	48	60	72–84	96–120
LR				x		x			x	x	x	x
IR		x		x		x		x	x	x	x	x
HR		x		x	x	x	x	x	x	x	x	x
VHR	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: HR, high risk; IR, intermediate risk; LR, low risk; VHR, very high risk.

Source: Reproduced from Campbell SC, Uzzo RG, Karam JA, et al. *Renal Mass and Localized Renal Cancer: Evaluation, Management, and Follow-up: AUA Guideline: Part II.* J Urol. *2021;206(2):209–218. doi:10.1097/JU.0000000000001912.*[2]

Key Points

- Imaging strategies in RCC follow-up are related to risk categorization of the patient's tumour.
- An understanding of the surgical and nonsurgical treatments that the patient has had influences the imaging appearances.

Conclusions

Imaging plays a central role in clinical staging and therefore in the management of patients with RCC. It is therefore imperative that dedicated imaging protocols are used as discussed in this chapter. Special situations such as patients with poor renal function may necessitate the use of multiple imaging techniques and modalities. Contemporary management RCC in the past few years has emphasized the role that imaging now plays in the multidisciplinary care of these patients. For the radiologist, it is imperative that they are cognizant of the management options for these patients. For the urologists and oncologists, it is critical that they recognize the strengths and limitations of these different imaging techniques. New imaging techniques and the expanding role of artificial intelligence, some of which may translate into clinical practice, will impact the multidisciplinary management of these patients.

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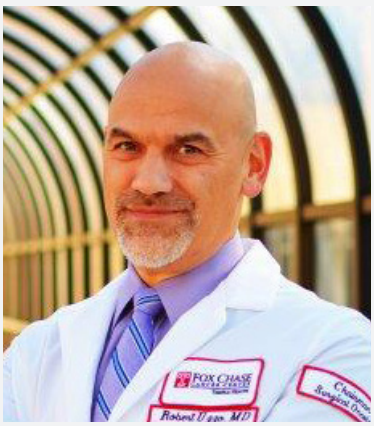
COMMITTEE 7

Renal Cell Carcinoma: Diagnosis, Staging, and Prognosis



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Introduction

The central pillar of cancer management is an accurate disease conceptualization, which then informs the most appropriate treatment strategy. The American Joint Committee on Cancer (AJCC) TNM staging system has been the foundation for cancer conceptualization since its introduction in 1977.[1] In renal cell carcinoma (RCC), TNM staging is primarily based on the tumour characteristics (tumour size, invasiveness, presence of regional adenopathy, or distant disease) on cross-sectional imaging. While TNM staging provides an excellent framework for cancer communication and standardization, it has limited ability to provide individualized risk assessment and treatment-associated feasibility/morbidity, or to predict disease prognosis beyond banded ranges.

As a result, anatomic complexity models have been introduced to better conceptualize localized renal lesions and inform the feasibility and potential morbidity of different treatment options (partial vs. radical, resection vs. ablation, treatment vs. active surveillance). Robust clinicopathological prognostic models have also been introduced to guide patient counselling, surveillance strategies, the use of adjuvant therapies, and clinical trial design. Emerging RCC-specific biomarkers (urine and serum) are poised to further optimize tumour characterization (benign vs. malignant and indolent vs. aggressive) and guide surveillance strategies and adjuvant treatments.

Renal Cell Carcinoma Presentation

The clinical presentation of RCC has changed dramatically with the wide utilization of cross-sectional imaging. Once considered the "internist tumour" due to the vast constellation of symptoms associated with RCC at presentation, nowadays, most RCCs are diagnosed as incidental findings in cross-sectional imaging obtained for seemingly unrelated reasons.

Clinical symptoms associated with RCC include hematuria (microscopic or gross), a palpable abdominal mass, varicocele, or symptoms related to advanced disease including anorexia, weight loss, anemia, or hepatic dysfunction.[2] The diagnosis of symptomatic RCC tends to be associated with higher tumour grade and stage, with a significant number of patients, deemed metastatic at diagnosis.[3,4] Paraneoplastic syndromes are relatively common in patients with RCC and are caused mainly by the increased excretion of pro-inflammatory cytokines or pseudo-endocrine hormones.[2]

While most renal cancers are believed to occur sporadically, familial clusters have led to the discovery of at least seven RCC susceptible syndromes.[5] It is estimated that approximately 4% of RCCs have a hereditary basis,[5] of these, the most common being Von Hippel-Lindau (VHL) disease, hereditary papillary renal cell carcinoma, Birt-Hogg-Dubé Syndrome, and hereditary leiomyomatosis renal cell carcinoma. In hereditary RCC syndromes, tumours tend to be bilateral and multifocal, and arise at an early age of onset.[5] A careful family history and knowledge of accompanying clinical findings on physical exam findings are crucial for the accurate diagnosis of these patients.

As a result of increased access to healthcare, there has been a significant increase in the detection of incidental asymptomatic RCCs.[6–8] The most common imaging modalities for the diagnosis of incidental RCC are abdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI).[6] The vast majority of incidentally diagnosed RCCs are of lower stage (cT1a-b), leading to a significant stage migration over the past 20 years.[9]

The resultant stage migration seen with the increased use of abdominal imaging has led some to advocate for regular screening for RCC, especially for patients at risk. Common risk factors associated with RCC include smoking, obesity, and hypertension.[10] A recent study assessing the discriminatory ability of a model that included several known risk factors (age, sex, hypertension, diabetes, smoking history) was able to discriminate well between those at risk, but given the low prevalence of the disease in the general population, the authors questioned the use of the model in clinical practice.[11] For instance, one large study in which more than 50,000 adults were screened for abdominal malignancy with ultrasound only found 192 cases of screening detected–RCC (0.4%).[12] Screening has, therefore, been proposed in target populations, including individuals with familial RCC syndromes and those on hemodialysis, who are known to be more likely to be diagnosed with RCC.

Differential Diagnosis and Clinical Evaluation of the Renal Mass

As mentioned, increased imaging is associated with increased detection of asymptomatic solid and cystic renal masses. While most incidental renal masses are simple cysts (40%),[13] some renal lesions, especially solid enhancing masses, can represent renal cell carcinomas and require further characterization.

The characterization of the renal mass starts with the determination if the mass in question is solid or cystic. A solid mass is defined as a tissue mass that disrupts the normal renal architecture and demonstrates contrast uptake, which reflects the vascular nature of the mass. Microlesions (< 1 cm) can be challenging to characterize with CT alone, and an MRI may provide a better assessment. Pseudotumours, representing vascular malformations, focal infectious processes, and congenital malformations, can also present as a renal mass and require further characterization with other imaging modalities, especially MRI and, rarely, angiography. Many may require follow-up studies to fully characterize and/or identify changes in lesions which may not be completely characterized given their size, location, or imaging features. In cases where the diagnosis remains inconclusive, a renal mass biopsy or imaging surveillance should be considered once a vascular malformation has been ruled out.

The majority of renal masses, especially those over 4 cm in size, represent a primary renal malignancy.[14] Conversely, benign lesions (angiomyolipoma and oncocytoma) of the kidney are commonly noted in smaller masses, representing up to 30% of tumours less than 3 cm in size.[14] Angiomyolipoma (AML) is diagnosed mainly by noncontrast CT, where a CT attenuation of –10 HU or less is pathognomonic for intralesional fat. That being said, the absence of fat cannot exclude the presence of an AML, as up to 5% of AMLs are of a fat-poor type.[15]

Oncocytomas tend to have imaging characteristics similar to malignant lesions, but some present with a "central stellate scar," which can help with the diagnosis.[16] The presence of a stellate fibrous core is not pathognomonic, as it cannot be readily differentiated from central necrosis commonly found in large malignant lesions.[15]

RCC represents a constellation of three distinct malignant histologies: clear cell, papillary, and chromophobe renal cell carcinoma. Clear cell RCC (ccRCC), the most common histology, is known for its intense uniform enhancement and rapid washout due to its hypervascular nature.[17] This imaging characteristic is not universal, as clear cell RCC can be quite heterogeneous due to tumour necrosis and hemorrhage.[17] Papillary RCC (pRCC) is known to be a more homogeneous tumour in terms of tissue density and signal intensity. Moreover, pRCC demonstrates more delayed contrast uptake and slower washout.[17] Imaging modalities remain limited in their ability to predict solid renal mass histology and, importantly, RCC aggressiveness (grade). This has resulted in the introduction of several predictive models to aid in the identification of masses in need of intervention. Most of the available models include tumour size as the most important determinant of renal mass histology and grade, followed by age and gender.[18–20] Lane *et al.*[18] were the first to introduce a predictive model for renal mass histology and grade. The model included tumour size, patient age, gender, smoking history, and the presence of symptoms as key variables and reported an adequate discriminatory ability for histology (c Index = 0.64) but poor ability to predict grade (c index = 0.56). Others combined the aforementioned variables with tumour location data,[19] noting improved predictive ability for both histology (0.76) and grade (0.73). The predictive ability of the tumour location as a predictor of renal mass histology has been questioned, with several groups demonstrating limited predictive ability.[20,21] A systematic review and meta-analysis,[22] which assessed all the available renal mass predictive models, concluded that the only consistent predictors of malignancy were increasing tumour size (odds ratio [OR], 1.33 per cm increase; 95% confidence interval [CI], 1.22–1.43) and male gender (OR, 2.71; 95% CI, 2.39–3.02).

Cystic lesions of the kidney present a different diagnostic challenge. The majority of cystic lesions of the kidney are simple and uniformly benign in nature. Characterization of a simple cystic lesion can be complicated by hemorrhage or infection, which can be mistaken for radiographical features noted on cystic RCC given that both of these conditions increase tissue density and heterogeneity, making the finding of pre- and postcontrast enhancement more difficult to discern. Several hereditary disorders present with renal cysts, adult polycystic kidney disease being the most common. Other cystic benign pathologies include multilocular cystic nephroma (MCN), a benign mixed mesenchymal and epithelial neoplasm of the kidney, which can be difficult to differentiate from a multilocular cystic RCC or cystic Wilms tumours.[23] Multilocular cystic nephroma has a bimodal age distribution, with male predominance in pediatric cases and a female preponderance in middle age.[23]

Cystic clear cell carcinoma represents 4–15% of renal cancers, and may present as a single or multilocular cyst (1–4%).[23] The risk for malignancy associated with renal cysts increases with increasing cyst complexity.[23] Bosniak[24] was the first to introduce a classification system to grade renal cystic complexity and its association with the risk for RCC. The original classification divided cystic renal lesions into four categories based on cyst morphology on CT-based imaging (**Table 1**). Since its introduction in 1986, several refinements have been made to the classification,[25–27] aiming to reduce the number of resected benign cystic lesions. Over time the Bosniak

IIF group was introduced, limiting Bosnaik III lesion to those with thick septations demonstrating measurable enhancement. At its last publication on 2012,[27] Bosniak reported that after several refinements over 25 years, Bosniak I and II lesions were "clearly benign" and Bosniak IV lesions "clearly malignant." Bosniak IIF lesions represent a group of "indeterminate" lesions, which were likely malignant but deserved close surveillance, while Bosniak III lesions tend to be removed. Problematic in the Bosniak classification is interobserver variability in the reading of Bosiak IIF vs III lesions. Clinically, this is a meaningful distinction, as Bosniak IIFs are typically observed, while current guidelines recommend Bosniak IIIs be resected given the data that >50% harbour malignancy.

TABLE 1 2019 Updated Bosniak Grading System of Renal Cysts

Class	CT—Cyst characteristics	MRI—Cyst characteristics	Recommendations
I	Well-defined, thin (≤ 2 mm), smooth wall Homogeneous simple fluid (-9 to 20 HU) No septa or calcifications, the wall may show enhancement	Well-defined, thin (≤ 2 mm), smooth wall Homogeneous simple fluid (signal intensity similar to CSF); no septa or calcifications, the wall may enhance	Benign simple cyst; requires no follow-up
II	Six variations, all well defined with (≤ 2 mm) smooth walls 1. Cystic mass with thin (≤ 2 mm), and few (1–3) septa, may have calcifications 2. Homogeneous hyperattenuating (≥ 70 HU) masses at noncontrasted CT 3. Homogeneous nonenhancing masses > 20 HU at renal mass protocol, may have calcifications 4. Homogeneous masses -9 to 20 HU at noncontrast CT 5. Homogeneous masses 21 to 30 HU at portal venous phase CT 6. Homogeneous low-attenuation masses that are too small to characterize	Three variations, all well defined with (≤ 2 mm) smooth walls 1. Cystic masses with thin (≤ 2 mm) and few (1–3) enhancing septa, any nonenhancing septa, may have calcifications 2. Homogeneous masses markedly hyperintense at T2-weighed imaging (similar to CSF) at noncontrast MRI 3. Homogeneous masses markedly hyperintense at T1-weighted imaging (approximately x 2.5 normal parenchymal signal) at noncontrast MRI	Likely a benign renal mass requiring no follow-up

TABLE 1 2019 Updated Bosniak Grading System of Renal Cysts *(Cont'd)*

Class	CT—Cyst characteristics	MRI—Cyst characteristics	Recommendations
IIF	Cystic masses with a smooth minimally thickened (3 mm) enhancing wall, OR smooth minimal thickening (3 mm) of one OR more, of many (≥ 4) thin (≤ 2 mm) enhancing septa	Two types: 1. Cystic masses with a smooth minimally thickened (3 mm) enhancing wall, OR smooth minimal thickening (3 mm) of one or more OR many (≥ 4) smooth thin (≤ 2 mm) enhancing septa 1. Cystic masses that have a heterogeneously hyperintense at unenhanced fat-saturated T1-weighed imaging	The majority of IIF are benign If malignant, nearly all are indolent Follow-up scheduled: Every 6 months for the 1st year Annually thereafter for 5 years
III	One or more enhancing thick (≥ 4 mm width) OR enhancing irregular (displaying ≤ 3 mm obtusely margined convex protrusion[s]) walls or septa	One or more enhancing thick (≥ 4 mm width) OR enhancing irregular (displaying ≤ 3 mm obtusely margined convex protrusion[s]) walls or septa	Intermediate probability of being malignant If malignant, the majority are indolent Recommend urology consultation
IV	One or more enhancing nodule(s) (≥ 4 mm convex protrusion with obtuse margins OR convex protrusion of any size that has acute margin)	One or more enhancing nodule(s) (≥ 4 mm convex protrusion with obtuse margins OR convex protrusion of any size that has acute margin)	The majority of the masses are malignant A significant number represent high-grade malignancies Recommend urology consultation

Abbreviations: CSF, cerebrospinal fluid; CT, computed tomography; HU, Hounsfield units; MRI, magnetic resonance imaging.

Source: *Adapted from Schieda N, Davenport MS, Krishna S,* et al. *Bosniak Classification of Cystic Renal Masses, Version 2019: A Pictorial Guide to Clinical Use.* Radiographics. *2021;41(3):814–828. doi:10.1148/rg.2021200160*[28]

Recently, an update to the Bosniak criteria was proposed, which aimed to further improve the predictive ability of the classification to accurately identify cystic RCC.[28] The new classification provides a less ambiguous definition of septal and wall thickness, increasing the likelihood of cystic RCC in Bosniak III and IV lesions. The new classification incorporates MRI-specific definitions into the classification system, given the increased use of the imaging modality and its superior capability in characterizing complex cystic lesions. Lastly, a standard reporting

template was introduced to guide non-radiology or urology clinicians in the management of these lesions, often identified incidentally on cross-sectional imaging (**Table 1**). Of particular importance when assessing cystic lesions of the kidney is to try and distinguish cystic lesions harbouring necrosis from those with serous contents. This distinction is best made by evaluating the Hounsfield units of the cystic component, which is usually lower (<10) for serous elements and higher (>15) for necrotic content.

Imaging Modalities for Evaluation of the Renal Mass

While simple cysts are well characterized by US, other lesions require further evaluation by multiphase imaging, such as contrast-enhanced CT and MRI. However, over the past few years, contrast-enhanced ultrasound (CEUS) with microbubble emerged as an interesting option able to overcome the limitations of grey-scale and Doppler US modes in the evaluation of solid renal tumours. Although not widely adopted, CEUS can demonstrate specific enhancement patterns, allowing for the differentiation of benign and malignant solid tumours as well as focal inflammatory lesions.[29]

Contrast-enhanced multislice computed tomography (MSCT) is the mainstay modality for detection, characterization, staging, and treatment planning of solid kidney tumours, as it provides optimal spatial resolution.[30] Contrast-enhanced MRI is an alternative that is mostly utilized in equivocal cases because it is more expensive and less readily available. MRI is also indicated in patients with contraindication to receiving iodine-based contrasts (allergy or significant renal insufficiency) due to its superior contrast resolution. Also, MRI is a better option in pregnant and young patients in whom radiation exposure is a concern.[31] In addition, MRI may characterize small and/or cystic masses more accurately.[32] Both MSCT and MRI should be performed first without and then with an intravenous contrast agent. Due to nephrotoxic and tissue retention concerns in recent years, most regulation agencies advocate the use of macrocyclic gadolinium-based agents. The imaging protocol varies among institutions but should include at least a precontrast phase and a postcontrast nephrographic phase (100–120"), the latter being the most sensitive for tumour detection.[33] Many institutions use a multiphase technique, which adds corticomedullary (40–60") and excretory phases for lesion characterization and collecting system evaluation, respectively (**Figure 1 a-d**).[34–37] The excretory phase is particularly useful in diagnosing urothelial lesions. Additionally, renal angiographic mapping during the arterial phase imaging may be extremely useful for surgical planning, particularly before a partial nephrectomy. Contrast-enhanced imaging is crucial to determine the solid nature of the lesion as well as to characterize the type, dynamics, and intensity of enhancement. Assessment of enhancement is usually performed qualitatively (visually) or by means of objective quantification with Hounsfield units (HU). Enhancement greater than 20 HU is considered significant and is the threshold to differentiate a proteinaceous cyst from a solid mass.[34] Also, MRI allows for objective evaluation of enhancement through a subtraction technique.[35] Dual-energy CT is a novel CT technology that can digitally subtract materials and tissues from images and enhance iodine contrast without the added image noise typical with low-energy settings. It improves image quality without increasing the overall radiation dose.[36]

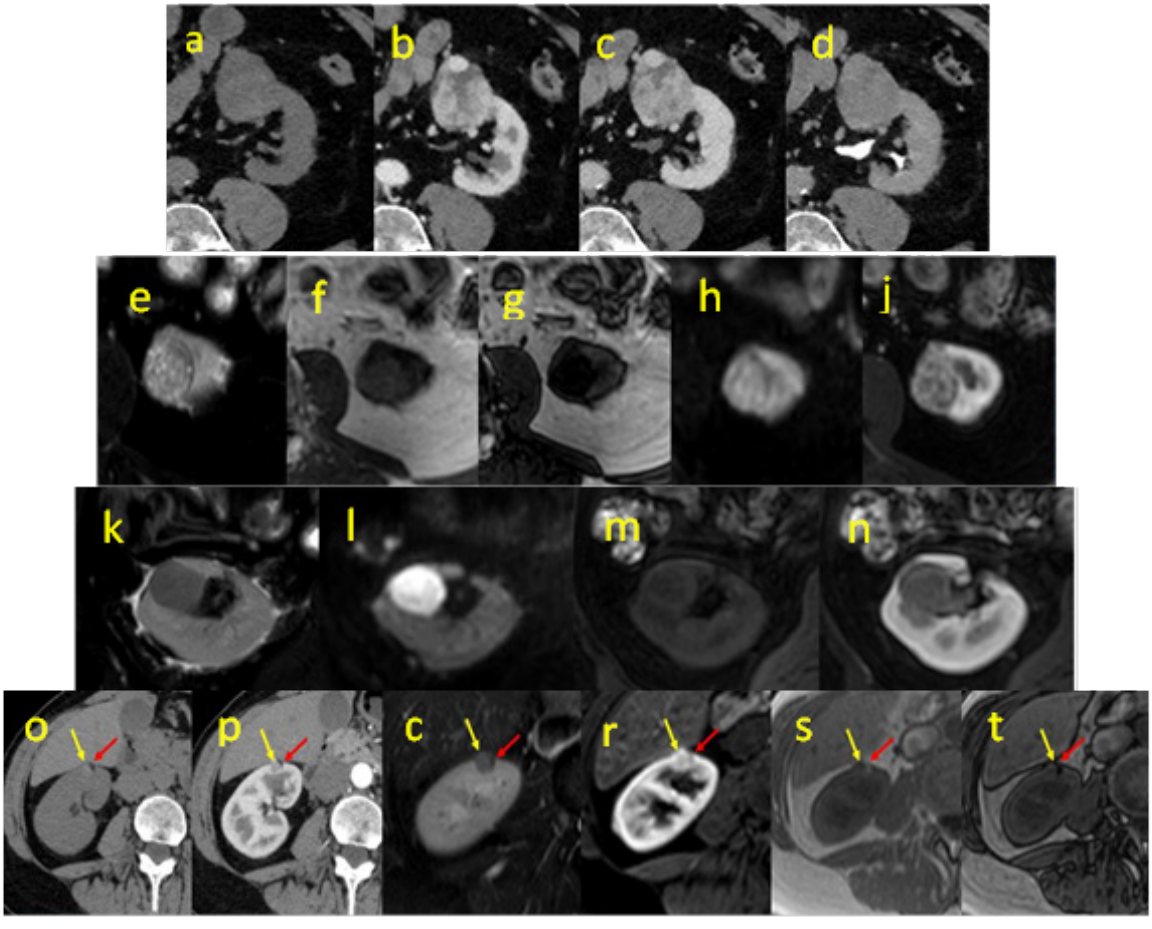


FIGURE 1 a-d. Clear cell renal cell carcinoma (ccRCC). Unenhanced **(a)**, corticomedullary **(b)**, nephrographic **(c)**, and excretory phase **(d)** contrast-enhanced multislice computed tomography (MSCT) shows ovoid-shaped partially exophytic hypervascular mass with amorphous hypodense areas in keeping with necrosis and/or cystic degeneration in 77-year-old male patient with ccRCC.

1 e-f. ccRCC. Axial T2 **(e)**, T1 in phase **(f)**, T1 out of phase **(g)**, diffusion-weighted imaging (DWI) **(h)**, and post-Gad T1 **(j)** –weighted images show partially exophytic ccRCC with heterogeneous hyperintensity, drop of signal on opposed phase image relative to in phase, moderate diffusion restriction, and heterogeneous enhancement.

1 k-n. Papillary renal cell carcinoma (pRCC). Axial T2 **(k)**, DWI **(l)**, pre- **(m)** and post-Gad T1 **(n)** –weighted images show a rounded endophytic T2 low signal solid nodule with marked diffusion restriction, mild hyperintensity on precontrast T1 and hypoenhancing. These features are typical of pRCC but are not specific.

1 o-t. Lipid poor angiomyolipoma (AML). Unenhanced **(o)** and contrast-enhanced computed tomography (CT) **(p)** scans show small cortical nodule with small fat attenuation sector on left side (yellow arrow) and larger lipid poor sector on right aspect (red arrow). The former is mildy hyperdense on precontrast CT and hypointense on T2 **(q)** and shows marked enhancement mimicking a ccRCC on postcontrast images **(r)**. High signal is shown on dual T1 **(s)** with signal drop on opposed phase T1 **(t)** -weighted images.

In order to assess the degree of enhancement of a lesion, qualitative or quantitative comparison with the avid-enhancing cortex is performed. As up to 25% of resected renal lesions have been found to be benign, it is important to scrutinize the radiographic appearance of the mass, which may suggest a histospecific diagnosis (e.g., fat in an angiomyolipoma). All RCC subtypes typically present as expansive masses with rounded, lobulated, or irregular contours. ccRCC is often hypervascular and heterogeneous due to necrosis or cystic changes (**Figure 1 a-d**). On MRI, high signal intensity is typical on T2-weighted imaging, and variable degree of restriction is shown on diffusion-weighted imaging (DWI) (**Figure 1 e-j**). Chemical shift or DIXON sequences are key to demonstrating microscopic fat based on the different processional frequencies of fat and water protons.[37] Calcification and hemorrhage in the tumour are not uncommon, the former specifically shown by CT and blood products such as hemosiderin, better shown by MRI. Certain imaging features have been reported to correlate with higher grade and poorer outcomes, including the presence and amount of necrosis, retroperitoneal collateral vessels, as well as venous thrombosis, whereas serous cystic elements have been found to correlate with lower grade.[38,39]

pRCC is hypovascular with mild progressive enhancement. On unenhanced CT, pRCC is usually slightly hyperdense similar to lipid-poor angiomyolipomas. On MRI, pRCC is typically hypointense on T2 and shows restriction on DWI (higher than ccRCC) (**Figure 1 k-n**). Chromophobe RCC (chRCC) is hypervascular (less intense enhancement than ccRCC) on CT and hypointense on MRI. A central stellate scar may be present, similar to what is observed in oncocytomas. Oncocytomas are a common cause of misdiagnosis of malignancy. Imaging features usually overlap with those of ccRCC, but oncocytomas tend to be more homogeneous and usually exhibit low signal on T2 and less intense enhancement. When present, the characteristic central scar increases diagnostic accuracy. Segmental enhancement inversion pattern is characteristic of oncocytomas but not pathognomonic.[40] More recently, 99mTc-sestamibi SPECT/CT has shown promising results in differentiating oncocytomas and hybrid chRCC/oncocytomas from other renal tumours.[41]

Lipid poor AML is another potential cause of misinterpretation. It is mildly hyperattenuating on unenhanced CT. When a renal homogeneous renal lesion has a precontrast density higher than 70 HU, it is most likely a hyperdense cyst, and further workup is not warranted.[42] Precontrast densities in the 20–70 HU range are considered indeterminate, as they may correspond with any benign or malignant histology; thus, a multiphase-enhanced MSCT or MRI exam should be performed to better characterize the mass. AMLs may enhance avidly and are hypointense on T2. Chemical shift-based sequences are key to detecting small amounts of fat (**Figure 1 o-t**).

18F-FEG PET imaging is of limited value for diagnosis and staging of RCC due to its low avidity for FDG. Additionally, its urinary excretion impairs tumour visualization (**Figure 2**). 89Zr-cG250 immunoPET imaging targeting carbonic anhydrase IX (CAIX), an enzyme overexpressed in ccRCC and thus a potential powerful theranostic agent, has been reported to have high sensitivity and specificity;[43] however, it is still investigational.

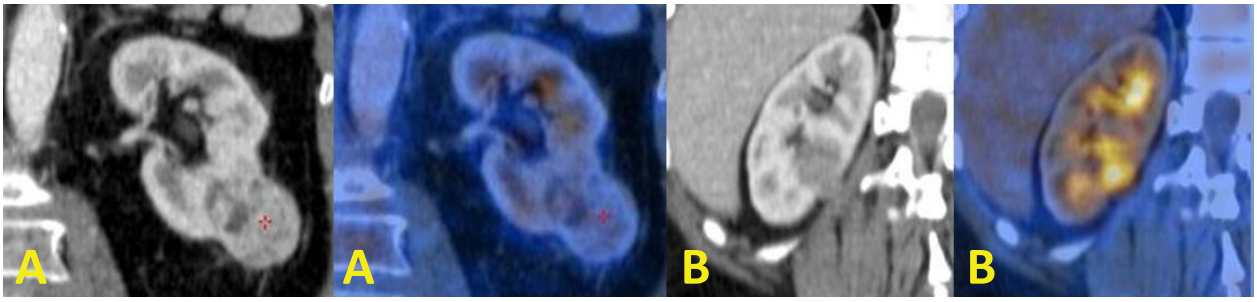
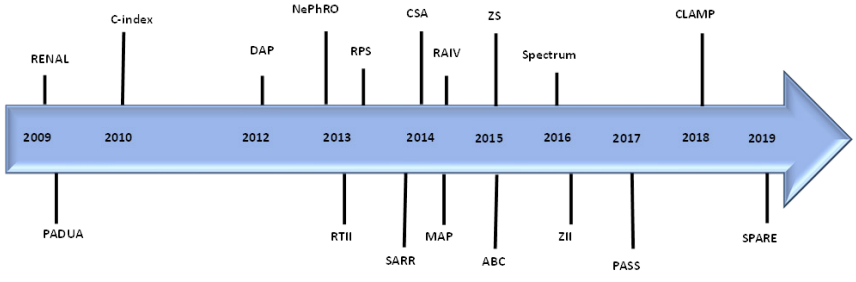


FIGURE 2 Renal cell carcinoma. Two examples of behaviour with fluorodeoxyglucose–positron emission tomography/computed tomography (FDG PET/CT).
A. Low-pole, exophytic, heterogeneous, hypervascular mass with no avidity for radiotracer.
B. Small hypovascular lesion with avid FDG uptake proven to be an aggressive tumour with sarcomatoid features.

Anatomical Complexity Models: Role and Predictive Value

Anatomical complexity models, also known as "nephrometry scores," were introduced with the common aim of objectifying the anatomical complexity of a renal mass, assisting in surgical decision-making, and facilitating outcome assessment. The RENAL and the PADUA systems were the first to be reported in 2009.[44,45] Over the past decade, several other systems have been conceptualized and proposed in the effort to improve the predictive value and clinical applicability (**Figure 3**). These can be broadly grouped into those based on a visual anatomical assessment and those based on a mathematical assessment of a renal mass (**Table 2**).

FIGURE 3 Evolution of renal mass anatomical models over time.



Abbreviations: ABC, Arterial Based Complexity; C-index, Centrality index; CLAMP, Coefficient-Location-Anterior, Multi, and Posterior boundary; CSA, Contact Surface Area; DAP, Diameter-Axial-Polar; MAP, Mayo Adhesive Probability; NePhRO, Zonal Nearness-Physical-Radius-Organization; PADUA, Preoperative Aspects and dimensions used for an anatomical classification; PASS, Peritumoral artery scoring system; RAIV, Renal and Ischemic Volume; RENAL, Radius-Exophytic-Nearness-Anterior/posterior-Location; RPS, Renal Pelvic Score; RTII, Renal Tumor Invasion Index; SARR, Surgical Approach Renal Ranking; SPARE, Simplified Padua Renal; ZII, Zero Ischemia Index; ZS, Zhongshan Score.

TABLE 2 Comparison of the American Joint Committee on Cancer (AJCC) 7th Edition and 8th Edition Renal Cell Carcinoma Tumour-Node-Metastasis (TNM) Staging Systems

	AJCC TNM 7th ed. (2009)	AJCC TNM 8th ed. (2018)	Changes
T1a	Organ confined ≤ 4 cm		None
T1b	Organ confined 4–7 cm		
T2a	Organ confined > 7–10 cm		
T2b	Organ confined > 10 cm		
T3a	Perinephric or renal sinus fat invasion, but not beyond Gerota's fascia		
	Tumour grossly extends into the renal vein or its segmental (muscle-containing) branches	Tumour extends into the renal vein or its segmental branches	Terms "grossly" and "muscle-containing" removed
		Tumour invades the pelvicalyceal system	New
T3b	Tumour extends into the vena cava below the diaphragm (without wall invasion)		None
T3c	Tumour extends into the vena cava above the diaphragm		
	Tumour invades the wall of the vena cava		
T4	Tumour invades beyond Gerota's fascia		
	Direct invasion of the adrenal gland		
N0	No regional lymph node metastasis		
N1	Metastasis to 1 or more lymph nodes		
M1	Distant metastasis or noncontiguous adrenal involvement		
	Group staging		
Stage I	T1N0M0		None
Stage II	T2N0M0		
Stage III	T1-2N1M0, T3NanyM0		
Stage IV	T4NanyM0, TanyNanyM1		

A recent systematic review and meta-analysis of 51 studies assessed the predictive role of nephrometry scores in nephron-sparing surgery.[46] The main conclusions were that available literature is mostly focused on RENAL and PADUA, which are easy to calculate and carry a good correlation with several outcome parameters. RPS, SARR, and PASS can offer a better predictive value for pelvicalyceal entry/repair and urine leak, surgical approach, and renal function variation, respectively. Not surprisingly, the implementation of nephrometry scores based on mathematical models might be limited by their complexity and limited evidence supporting their predictive value. Overall, RENAL and PADUA scores can still be regarded as the standard for reporting anatomical complexity. The latest addition is the SPARE, which was conceived as a simplified version of the PADUA.[47]

Renal Mass Biopsy

Despite the advances in imaging, accurate histological diagnosis of renal lesions remains elusive. As a result, percutaneous renal mass sampling has been proposed for the management of small renal lesions where the risk for benign histology is high (30–40%)[48] and for patients in whom up-front systemic therapy is being considered. Currently, renal mass biopsy (RMB) is discussed in most treatment guidelines.[31,49–51] RMB is recommended when the findings may have the potential to change management (primary renal lymphoma/leukemia, infections process, or metastatic foci) or prior to thermal ablation.

The adoption of RMB in the management of renal masses, especially small renal masses (SRMs), remains controversial due to concerns with diagnostic accuracy, possible post-procedure complications, and ultimate capacity to affect clinical management. Diagnostic accuracy has been improved by the use of core biopsies over the historic fine needle aspirations (FNA). A recent meta-analysis,[52] which combined more than 5,000 patients, noted an RMB diagnostic rate of 92% (interquartile range [IQR], 80–96.8%). A subsequent meta-analysis,[53] assessing 2,970 patients and 3,113 biopsy specimens, reported a diagnostic rate of 85%, which increased to 86% when limited to core biopsy specimens. In patients in whom an RMB is nondiagnostic, repeat biopsy provides a histological diagnosis in 80% of patients. Predictors for nondiagnostic RMB have been studied in SRM and noted to be smaller masses (< 2 cm), cystic lesions, nonenhancing masses, and with a skin-to-tumour distance of ≥ 13 cm.[54,55] Importantly, renal mass complexity or location near the renal hilum was not associated with nondiagnostic RMB in experienced hands.[55] While concordance has been high in regard to histological diagnosis, accurate tumour grading remains limited, with concordance rates ranging from 60% to 75%.[52,56] The decreased accuracy when assessing tumour grade stems from the significant grade heterogeneity that exists in renal cell carcinoma, especially in high-grade masses, leading to significant sampling bias.[57] Some centres[58] have advocated for multi-quadrant biopsy in large or heterogeneous masses, noting an improved diagnostic rate and increased identification of poor prognostic factors (high grade, sarcomatoid features, and necrosis).

Overall complications following RMB are rare (8%), with severe complications (Clavien Grade > 2) occurring in less than 1% of patients.[52,53] Common complications include hematoma (4.9%) and clinically significant pain (1.2%).[53] Other reported less common complications included gross hematuria (1.0%), pneumothorax (0.6%), and hemorrhage (0.4%).[53] There has been a concern for needle track seeding following RMB, but the reports remain limited to case studies with no reports in large RMB series.[59]

Advances in RMB, along with growing evidence of the indolent nature of a significant number of SRMs, has led some centres to advocate for near-universal and/or logarithmic use of renal mass biopsy in all patients prior to treatment.[59] Proponents of RMB for all suggest that universal RMB would decrease the rate of benign renal mass excisions, along with allowing for a risk-stratified approach to the management of small renal masses.[59,60] Others proposed a measured approach in which RMB is only used where the decision will impact management,[61] as it has the potential to create further uncertainty in clinical decision-making (active surveillance candidate with an RCC RMB diagnosis, young patients with oncocytic tumour RMB diagnosis, etc.) or would subject the patient to an unnecessary procedure.

The evolution of RMB over the past 20 years has been staggering. Once considered a superfluous tool, RMB is increasingly used as a central diagnostic tool in the management of the renal mass. Contemporary use of RMB shows excellent histological (malignant vs. benign & RCC subtype) diagnosis but remains limited by the tumour grade. As a result, most guidelines advocate for RMB to be used as an adjunct rather than a screening tool in the management of the renal mass.

Renal Cell Carcinoma Staging: The TNM Staging System Evolution and Pitfalls

The American Joint Committee on Cancer (AJCC) tumour-node-metastasis (TNM) staging system remains the most used one for RCC. This system includes multiple important anatomical prognostic factors, such as tumour size, extension into veins or perinephric tissues, invasion of the adrenal gland or Gerota's fascia ("T" component), as well as metastatic spread to lymph nodes ("N" component) or other organs ("M" component). Based on these TNM categories, the system categorizes RCC into stages I to IV. Since its first release in 1978, the TNM system for RCC has undergone several changes, usually every 6 to 8 years, leading to the latest 8th edition, released in late 2016 and implemented in 2017.[62] This edition incorporates minimal changes compared to the previous, the more significant being in the classification of T3a disease (**Table 3**). While the 7th edition relied on "gross" inspection for pT3a staging purposes, in the latest version, the word "grossly" to describe renal vein invasion was removed, as this could be commonly missed on the gross examination. Additionally, "muscle containing" was also removed when describing the involvement of "segmental veins," as these veins may have inconspicuous muscle. Moreover, "invasion of the pelvicalyceal system" was added.[63] Notably, no changes in the AJCC prognostic stage grouping were made, and this means the conventional prognostic stage grouping continues to be used. Thus, some pitfalls of the TNM staging system persist, and they remain to be addressed in ongoing research endeavours.[64,65]

TABLE 3 Overview of Anatomical Complexity Models and Their Predictive Value

Model	Components	Predictive value
Visual anatomical assessment-based models		
RENAL	Tumour size as maximal diameter, exophytic/endophytic tumour properties, nearness of deepest portion of tumour to collecting system/sinus, anterior/posterior descriptor, and location relative to polar line	Type of procedure (PN vs. RN), on-clamp resection, warm ischemia time, overall and major complications, conversion to RN, pelvicalyceal system entry/repair, urine leak, postoperative renal function, malignant histology
PADUA	Face of the kidney involved, longitudinal location, degree of tumour deepening into parenchyma according to exophytic rate, renal rim location, involvement of renal sinus, involvement of urinary collecting system, clinical tumour size	Type of procedure (PN vs RN), on-clamp resection, warm ischemia time, overall and major complications, conversion to RN, pelvicalyceal system entry/repair, urine leak, postoperative renal function
DAP	Diameter, axial distance, polar distance	Warm ischemia time, renal function variation
NePhRO	Nearness to collecting system, physical location, radius, and organization of the tumour	Overall complications
RPS	Percentage of renal pelvis contained inside the volume of the renal parenchyma	Overall and major complications, urine leak
SARR	Tumour size, endophytic or exophytic, longitudinal location, extent of the impairment of renal parenchyma, relationship with renal sinus, and anterior or posterior	Type of procedure (PN vs. RN)
SPARE	Tumour rim location, renal sinus involvement, exophytic rate, and maximum tumour size	Overall complications
ABC	Order of vessels needed to be transected/dissected	On-clamp resection, pelvicalyceal system entry/repair
PASS	Peritumoural artery characteristics	Postoperative renal function
MAP	Measures of perinephric fat distance and severity of perinephric stranding	Adhesive perinephric fat, on-clamp resection, conversion to RN
ZS	Maximum tumour diameter within renal parenchyma, physical location of the tumour, depth of tumour invasion	Overall complications, conversion to RN

Abbreviations: ABC, Arterial Based Complexity; DAP, Diameter-Axial-Polar; MAP, Mayo Adhesive Probability; NePhRO, Zonal Nearness-Physical-Radius-Organization; PADUA, Preoperative Aspects and dimensions used for an anatomical classification; PN partial nephrectomy; RN, radical nephrectomy; RENAL, Radius-Exophytic-Nearness-Anterior/posterior-Location; RPS, Renal Pelvic Score; SARR, Surgical Approach Renal Ranking; ZS, Zhongshan Score.

In general, tumour size is associated with more aggressive clinical behaviour,[66] and this has been traditionally reflected in determining the T stage category for T1 and T2 RCC. The 8th edition AJCC staging system continues to classify tumours >7 cm as "pT2," as this cutoff was found to be predictive of poor outcomes.[67] However, a significant number of clear cell RCCs > 7 cm will be noted to invade the renal sinus at the pathological examination, translating into a pT3a stage. Thus, it is rare for RCC at this size to be actually "confined" to the kidney. Similarly, while tumours >10 cm are classified as "pT2b," almost all of them are, in fact, invading the renal sinus, vein, or perinephric region. Thus, despite evidence that large tumours are frequently associated with renal sinus invasion, the TNM persists in classifying those > 7 cm and > 10 cm as T2a and T2b, respectively. For this reason, it has been suggested that the pT1–pT3a staging categories should be revised by defining pT1 as tumours up to 4 cm, pT2 as those between 4 and 7 cm, and pT3a as those above 7 cm.[68]

Since the incorporation of renal sinus invasion as pT3a in the AJCC staging system in 2002, several studies have confirmed the prognostic importance of this finding.[69] In the AJCC 8th edition, renal sinus and perinephric fat infiltration continue to be considered under the same category (pT3a). However, there is some evidence suggesting there may be a difference in prognosis between the two.[70] The AJCC 8th edition continues to classify both segmental or main renal vein invasion as pT3a. However, a study found that the 3-year recurrence-free survival, as well as cancer-specific survival rates for segmental vein invasion alone and main renal vein invasion, are different.[71] Thus, some argue that the current pT3a should be further substratified, as it is likely there is a prognostic difference between early and more advanced vein invasion.[64] Infiltration of the renal pelvis by RCC is uncommon (6.8–14% of cases) and, in previous studies, has been associated with aggressive tumour behaviour,[72] but without being specifically addressed in prior AJCC systems. In the 8th edition, this finding is added to the pT3a category. However, its prognostic relevance remains debatable. In a bicentre study on 671 patients, invasion of the renal pelvis was recorded in 8.8% of the cases but not found to be an independent prognostic factor on multivariate analysis.[73] On the other hand, in a follow-up study of 519 patients with intracapsular RCC, invasion of the collecting system was found in 7.5% of patients, being an independent predictor of recurrence-free survival.[74]

Prognostic group staging also remains under scrutiny, and proposals for different regrouping have been made with the aim of allowing more accurate risk stratification. For example, a retrospective analysis from the MD Anderson Cancer Center showed that patients with pT1-3N1M0 had a significant survival disadvantage compared with those with pT3N0M0, and overall and cancer-specific survival for pT1-3N1M0 patients is most similar to patients with pT1-3NanyM1 RCC, suggesting that pT1-3N1M0 disease should be considered stage IV disease.[75]

Lastly, the AJCC 8th edition also includes the World Health Organization/International Society of Urologic Pathologists (WHO/ISUP) nucleolar grade in place of the Fuhrman nuclear grade. This grading system is based on nucleolar prominence for grades 1 through 3, whereas grade 4 consists of more aggressive morphologies (rhabdoid, sarcomatoid, and anaplastic). The system correlates with prognosis in both ccRCC and pRCC but not with chRCC.[1]

RCC Prognosis and Available Models

In the absence of reliable and validated biomarkers, clinical and pathological parameters remain the primary factors in communicating prognosis. For nearly eight decades, the TNM system has been standard in risk prediction and communication.[76] Over the past 20 years, we have seen a surge in the development and implementation of clinicopathological prognostic models[77–82] aimed at providing increasingly accurate and individualized assessments.

The first of these models to be introduced was the UCLA Integrated Staging System (UISS),[77] which stratified patients based on TNM stage, nuclear grade, and Eastern Cooperative Oncology Group (ECOG) performance status, with the authors reporting a discriminatory index of 0.73 in the prediction of overall survival (OS). Currently, eight prognostic algorithms and nomograms (**Table 4**) are widely used for predicting the risk for relapse in RCC.[77–84] Each model considers clinical and/or pathologic variables but differs with regard to the number and type of covariates, tool properties (nomogram or prognostic categories), and endpoints (OS, cancer-specific survival [CSS], and disease recurrence-free survival [RFS]). The majority of these models were developed to provide a postresection prediction, and all use TNM staging as the foundation and the most important predictor of the event in question. To the TNM stage, grade, RCC histology (Kattan *et al.*[78]), symptoms on presentation (Kattan *et al.*,[78] Sorbellin *et al.*, MSKCC,[79] Yaycioglu *et al.*,[84] Karakiewicz *et al.*,[83] and Cindolo *et al.*[82]), tumour size (Frank *et al.*, SSIGN,[80] Leibovich *et al.*,[81] Yaycioglu *et al.*,[84] Karakiewicz *et al.*,[83] and Cindolo *et al.*[82]), and evidence of tumour necrosis (Frank *et al.*, SSIGN[80] and Leibovich *et al.*[81]) are added to further improve the discriminatory ability of the model (**Table 4**).

TABLE 4 Clinically Available Prognostic Models for Patients with Localized RCC

Model	UISS	SSIGN	Leibovich	MSKCC	Kattan	Yaycioglu	Karakiewicz	Cindolo	GRANT Score	ASSURE
Type	KM survival analysis	Algorithm	Algorithm	Nomogram	Nomogram	Formula	Nomogram	Formula	Algorithm	Nomogram
Outcome	OS	CSS	MFS	RFS	RFS	RFS	CSS	CSS	DFS & OS	DSF, OS, and EDP
Time period	1989–1999	1970–1999	1970–2000	1989–2002	1989–1998	1990–1999	1984–2006	1987–2003		
Original *N*	814	1,801	1,671	701	601	296	2,474	660	310	1,735
Histology	ccRCC+Pap+ Chromo	ccRCC	ccRCC	ccRCC	ccRCC+Pap+ Chromo	ccRCC+Pap+ Chromo	ccRCC+Pap+ Chromo	ccRCC+Pap+ Chromo	ccRCC+Pap+ Chromo	ccRCC+Pap+ Chromo
Inclusion criteria	RNx/PNx pTanyN(0-1)M(0-1)	RNx/PNx pTanyN(0-1) M(0-1)	RNx pTanyN(0-1) M0	RNx/PNx pTanyN0M0	RNx/PNx pTanyN0M0	RNx/PNx pT1-3cN0M0	RNx/PNx pTanyN(0-1) M(0-1)	RNx/PNx pTanyN0M0	RNx/PNx pT2-3N(0-1) M0	RNx/PNx pT1b G 3-4 pT2-3N(0-1) or pTanyN1
Model variables	3 Factors: • 1997 TNM • Fuhrman grade • ECOG PS	6 Factors: • 1997 TNM • pN+ • pM+ • Tumour size • Fuhrman grade • Tumour necrosis	5 Factors: • 1997 TNM • pN+ • Tumour size • Fuhrman grade • Tumour necrosis	5 Factors: • 2002 TNM • Tumour size • Fuhrman grade • Necrosis • Symptoms (Presentation)	4 Factors: • 1997 TNM • Tumour size • Histology • Symptoms (Presentation)	2 Factors: • Clinical tumour size • Symptoms (Presentation)	6 Factors: • 2002 TNM • Age • Gender • cM+ • Tumour size • Symptoms (Presentation)	2 Factors: • Clinical tumour size • Symptoms (Presentation)	4 Factors: • 2002 TNM • Age • Fuhrman grade • pN+	6 Factors: • Age • Histology • Tumour size • Tumour grade • Tumour necrosis • Nodal status
Median follow-up (yrs)	3.1	9.7	5.4	2.7	3.3	4	4.2	3.5	9.6	9.6
Reported C-Statistic	0.73	0.84	0.82	0.82	0.74	0.65	0.86	0.67	NA	DSF, 0.68 OS, 0.69 EDP, 0.75
Validated in contemporary data	**0.56**	**0.69**	**0.62**	**0.67**	**0.64**	**0.59**	**0.62**	**0.63**	**DFS, 0.59 OS, 0.61**	**DSF, 0.68 OS, 0.69 EDP, 0.75**

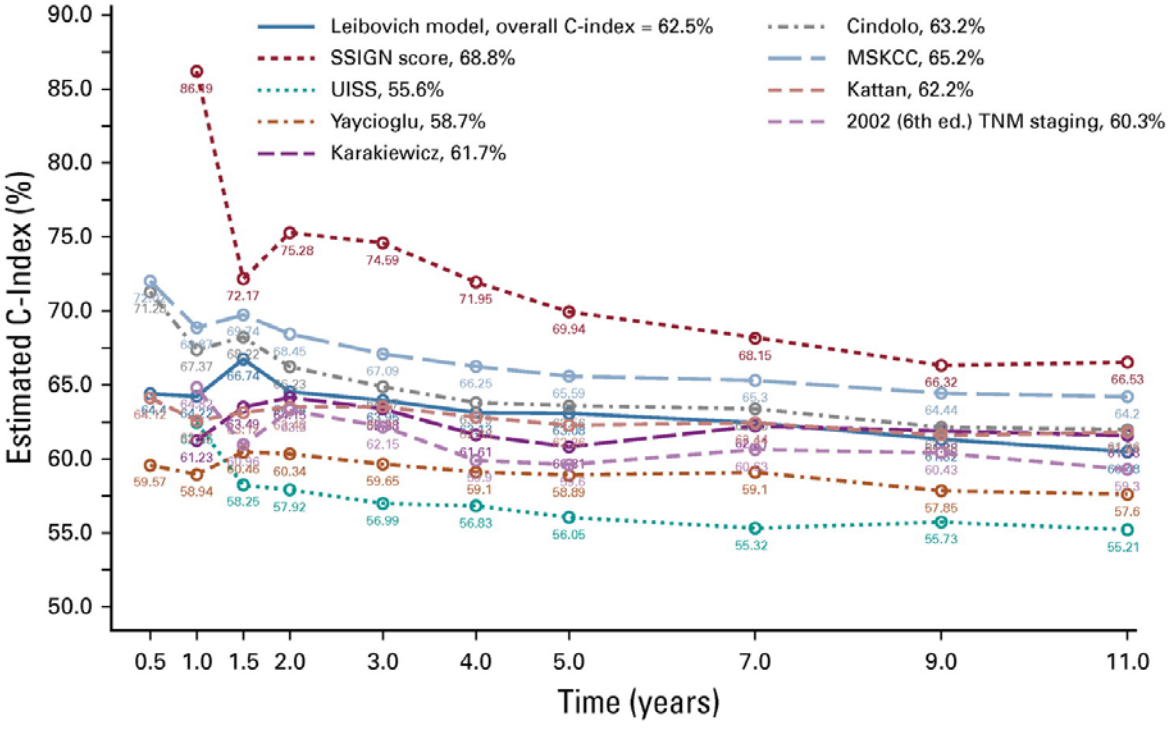
Abbreviations: ccRCC: clear cell renal cell carcinoma; Chromo, chromophobe; CSS, cancer-specific survival; ECOG PS, Eastern Cooperative Oncology Group performance status; EDP, early disease progression; KM, Kaplan–Meier; MFS, metastasis-free survival; OS, overall survival; PNx, partial nephrectomy; RFS, recurrence-free survival.

The adoption of these prognostic models in the clinical setting has been swift, with three of these models (Zisman *et al.*, UISS,[77] Leibovich *et al.*,[81] and Frank *et al.*, SSIGN[80]) rapidly becoming the pillars of risk stratification: informing risk-adapted surveillance strategies in leading guidelines,[31,48,51] selection for adjuvant therapies,[51] and enrollment into clinical trials.[51] A recent validation[85] of these models using contemporary data from an adjuvant clinical trial demonstrated a significant reduction of their previously published and validated discriminatory indices, with the majority of models barely outperforming TNM staging. An important factor often overlooked in the existing prediction models is the inherent reliance on retrospective data for model development and respective validations. The use of retrospective data is prone to significant source and reporting biases due to differences in data collection techniques, a lack of standard outcome and histological reporting, and cohorts that spanned several decades. Furthermore, the current models are limited by their reliance on a specific TNM staging version, which limits their applicability to contemporary cohorts due to evolving nature of the TNM staging system.

Two novel prognostic models, GRANT[86] and ASSURE,[87] have been developed using contemporary cohorts leveraging clinical data from clinical trials. The GRANT score,[86] introduced by Buti and colleagues, was based on 310 patients accrued as part of an adjuvant trial assessing the efficacy of low-dose interleukin-2 (IL-2) and interferon-α (IFN-α) versus observation.[88] The model includes four prognostic variables, in which the 2002 TNM staging system sets the framework for the model, to which age, Fuhrman grade, and nodal status are added. An initial discriminatory index was never published for the model, but on its validation in the ASSURE cohort, the model was calculated to have a discriminatory ability of 0.59 and 0.61 for DSF and OS, respectively.[86] The ASSURE model[87] was developed and internally validated using the ASSURE adjuvant clinical trial cohort. The model was developed with an emphasis on clinical applicability by being histology inclusive and reporting on three clinically meaningful outcome measures: DSF, OS, and early disease progression (EDP). The model was also created to be TNM stage agnostic so it can be easily transported into future clinical cohorts. The ASSURE model outperforms most of the established prognostic models (**Table 4**), with the SSIGN model providing a comparable discriminatory ability for CSS.

It is important to note that the discriminatory ability of the currently available models[77–84,87] is highest at 2 years following resection, and then it degrades rapidly over time (**Figure 4**).[85,87] The degradation in discriminatory ability is likely related to the tumour-centric nature of the currently available models, where early recurrences are largely dictated by tumour factors, whereas late recurrences are a complex interplay between tumour factors and the host's immune system.

FIGURE 4 Discriminatory ability of each validated prognostic model over time. Dashed line showed infection in the sharp decrease in discriminatory ability.



Source: Reproduced from Correa AF, Jegede O, Haas NB, et al. *Predicting renal cancer recurrence: defining limitations of existing prognostic models with prospective trial-based validation.* J Clin Oncol. *2019;37(23):2062–2072. doi:10.1200/JCO.19.00107*[85]

For patients with advanced disease, two prognostic models have been introduced (MSKCC[89] and IMDC[90]) and currently provide the framework for risk stratification. The MSKCC model[89] was the first model introduced and developed from patients treated with IFN-based regimens. The model utilizes ECOG performance status, anemia, LDH, corrected serum calcium, and time from diagnosis to metastatic disease to segregate patients into three risk groups. The IMDC model[90] builds on the variables introduced by the MSKCC model using patients treated in the targeted therapy era and adds neutrophil and platelet count to the model to further improve its discriminatory ability.[90] Both of these models continue to be used in clinical trial development and in the identification of patients for risk-based treatment options as we move toward combination treatments that include novel immunotherapy therapeutics (programmed cell death 1 receptor [PD-1], programmed cell death 1 ligand 1 [PD-L1], and cytotoxic T-lymphocyte antigen 4 [CTLA-4] inhibitors).

Update on Serum/Urine Biomarkers in RCC

While current guidelines[31,48,51] do not endorse any specific biomarker for RCC, the potential role of several biomarkers has been investigated over the past decade. "Liquid" biomarkers are those that can be measured in the "serum" and "urine," and they represent an attractive tool for clinical implementation in different settings, including screening, diagnosis, tumour characterization, and post-treatment monitoring both in localized and advanced disease.[91,92] Advantages of "liquid" over "tissue" biomarkers are: noninvasive, fast sampling, repeatability, and potential cost savings.[93]

The most promising circulating (blood-based) biomarkers for RCC to date include cell-free DNA (ccDNA) and,[94] circulating tumour cells (CTCs),[95] circulating RNAs, such as microRNAs (miRNAs)[96] and long noncoding RNAs,[97] and exosomes (extracellular vesicles secreted by tumour cells containing a concentrated number of proteins).[98] Moreover, several studies have looked at possible RCC-specific proteins and oncometabolites,[99] such as kidney injury molecule-1 (KIM-1).[100]

Urinary proteomic tests represent another attractive tool for the screening/early detection of RCC, but the evidence supporting their use remains limited, and none has surpassed the prevalidation discovery phase and have been approved for clinical use.[101] Relevant urinary proteins studied as RCC biomarkers are aquaporin 1 (AQP1) and perilipin 2 (uPLIN2), or a panel combining the two.[102] Urinary miRNA profiling has been another area of active investigation in RCC patients.[103]

Biomarkers for the prediction of response to treatment and progression of disease represent an area of active investigation as novel systemic therapies are being introduced for metastatic RCC (mRCC).[104] A correlation between ctDNA and tumour burden was found.[105] Moreover, early variations in ctDNA levels might provide an early measure of treatment response.[106] Recent studies have suggested a potential role for ctDNA testing in determining therapeutic resistance in mRCC, allowing for resistant-directed therapies.[107] The detection of ctDNA in patients with early-stage disease has been challenging due to low cfDNA shedding by RCC.[108] The measurement of cell-free tumour DNA methylomes via cell-free methylated DNA immunoprecipitation and high-throughput sequencing (cfMeDIP-seq) methylomes provides a superior technology for the measurement of cfDNA in low-shedding tumours. A recent study by Nuzzo and colleagues[109] evaluated the technology in serum and urine in patients who present with both localized and locally advanced RCC. The essay noted the highest accuracy for the detection of cfDNA in both serum (area under the curve [AUC], 0.99) and urine (AUC, 0.86) reported to date.

Overall, the actual role of "liquid" biomarkers in clinical practice for the management of RCC in different stages of the disease spectrum remains investigational. The technology has the ability to revolutionize the management of RCC, allowing for noninvasive histological assessment of the renal mass, with follow-up of patients with a high risk for recurrence and low-cost assessment of systemic treatments.

Conclusions and Future Directions

The ubiquitous use of cross-sectional imaging in modern healthcare has led to an increase in the diagnosis of renal masses. The workup of the renal mass remains nuanced mainly due to the high incidence of benign pathology in small renal masses (≤ 4 cm). Conventional imaging is limited in its ability to differentiate benign/indolent renal mass from those than are more aggressive. Several anatomical complexity models have been introduced to help clinicians and patients better risk-stratify the burden of a potential treatment. Anatomic complexity as a predictor of renal mass histology and RCC grade has been studied, but the results remain unconvincing. Molecular targeted imaging (Sestamibi and CAIX) has been introduced to aid in the diagnostic pathway, but validation studies are needed. Renal mass biopsy has been hailed as the diagnostic solution to avoid overtreatment, but its impact appears to be limited to a small subset of patients where the results actually influence patient-physician decision-making. Several serum and urine biomarkers have been proposed to aid in the renal mass diagnosis dilemma, but a clinically actionable biomarker remains elusive. Recent work on cell-free methylated tumour DNA appears promising as a potential biomarker that can be detected in both serum and urine.

For patients diagnosed with RCC, the TNM staging system remains the standard for risk stratification and communication. Several clinical prognostic models have been introduced in the hopes to individualize the risk assessment, better select patients for adjuvant therapeutic clinical trials, and introduce risk-based surveillance strategies. Recent validation of these models on contemporary data demonstrated the limitations of these models due to their development using retrospective cohorts. As a result, two models (ASSURE and GRANT) have been recently introduced; the ASSURE model is poised to become the model of choice due to its inherent applicability to future cohorts (histology inclusive and TNM agnostic). The current clinicopathological models remain limited in their ability to predict late recurrences due to their tumour-centric nature. Serum and urine biomarkers, most notably cell-free methylated tumour DNA, have been proposed to further the ability to provide individualized care and better identify patients for adjuvant therapies and clinical trials. Correlative biomarkers studies of ongoing immunotherapy adjuvant trials will likely bring a new era of RCC biomarkers that could be easily translatable to the clinical setting.

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COMMITTEE 8

Partial Nephrectomy of Renal Cell Carcinoma

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Anatomy of the Kidney

The kidneys are located in the retroperitoneum, a space demarcated by the lumbodorsal fascia posteriorly, the peritoneum anteriorly, the transversus abdominis musculature laterally, and the diaphragm cranially. Caudally, the retroperitoneum continues with the extraperitoneal pelvic structures.

The right kidney sits 1 to 2 cm lower than the left, presumably because of a downward displacement caused by the liver. Generally, the right kidney lies in the space between the top of the 1st lumbar vertebra to the bottom of the 3rd lumbar vertebra. Conversely, the left kidney occupies the space from the body of the 12th thoracic vertebra to the 3rd lumbar vertebra. Typically, kidneys are approximately 11 cm long, 6 cm wide, and 4 cm thick. The kidneys lie in a fatty cushion surrounded by Gerota's fascia.

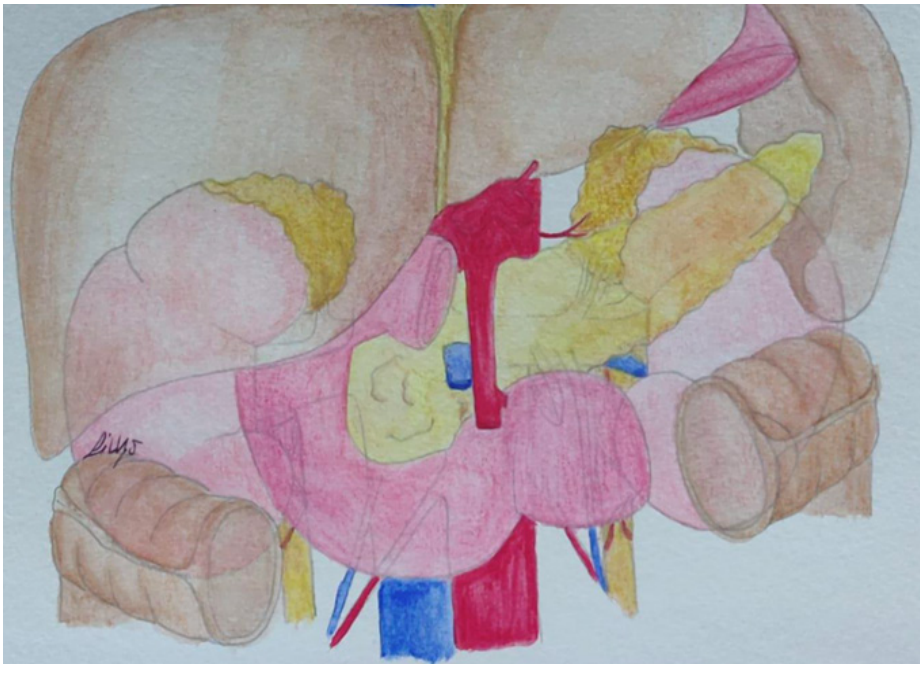
Posteriorly, the diaphragm covers the upper third part of each kidney, with the 12th rib crossing at the lower extent of the diaphragm. Notably, the pleura extends to the level of the 12th rib, posteriorly. Medially, the lower two-thirds of the kidney lie on the psoas muscle. This relation to the psoas muscle causes the upper pole of the kidneys to be situated medially and posteriorly compared to the lower pole. Moreover, the medial aspect of each kidney is rotated anteriorly at an angle of approximatively 30 degrees. Laterally, the quadratus lumborum muscle and aponeurosis of the transversus abdominis muscle are encountered.

Anteriorly, the upper pole of the right kidney is bordered by the right adrenal gland and the liver. The right kidney and the liver are separated by the peritoneum. The hepatorenal ligament bridges the upper pole of the right kidney to the posterior liver surface. The descending duodenum is in close contact with the medial part of the right kidney and hilar structures. The anterior face of the lower pole of the right kidney is covered by the hepatic flexure of the colon.

Anteriorly, the upper pole of the left kidney is bordered by the left adrenal gland, the posterior gastric wall, the tail of the pancreas, and the spleen. Notably, the splenorenal ligament attaches the left kidney to the spleen. Therefore, excessive downward pressure or traction during surgical maneuvers can be responsible for splenic capsular tears and bleeding. The lower pole of the left kidney is covered by the splenic flexure of the colon and by the jejunum (**Figure 1**).

Gerota's fascia is interposed between the kidneys and the surrounding structures. This fascial layer encloses the perirenal fat tissue, the kidneys, and adrenal glands. Superiorly and laterally Gerota's fascia is closed, while medially it extends across the midline to fuse with the contralateral side. Inferiorly, Gerota's fascia is not closed and remains an open space.

FIGURE 1 Anatomical and topographic relationship between kidneys and surrounding organs (Courtesy of Dr. Silvia Viganò).



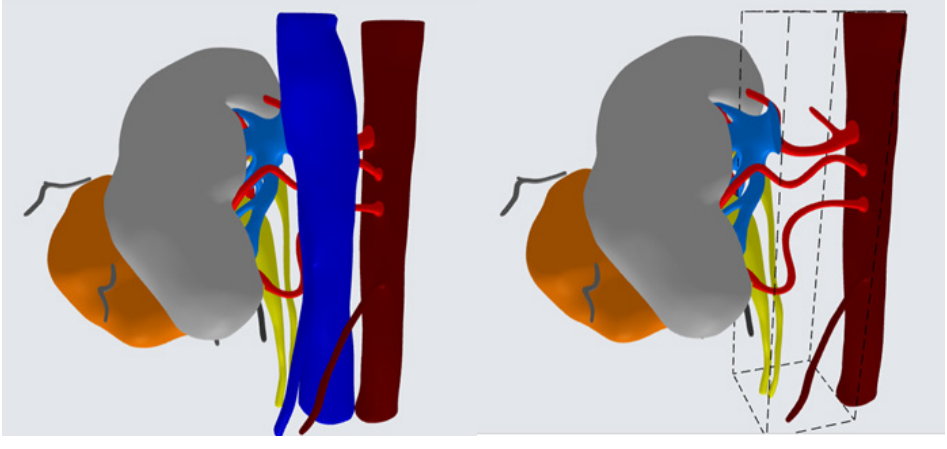
The upper collecting system is composed of minor and major calices, pelvis, and ureter. Each minor calyx narrows to an infundibulum. The infundibula combine to form three (upper, middle, inferior) major calices, further combining to form the renal pelvis. The ureter originates from the ureteropelvic junction. The proximal ureter begins posterior to the renal artery and continues along the anterior edge of the psoas muscle. From the surgical standpoint, it is important to note that gonadal vessels cross anteriorly to the ureter in this region. The ureter next crosses over the iliac vessels marking the bifurcation of the common iliac artery into internal and external iliac arteries.[1] The ureter is typically divided into an abdominal tract extending from the renal pelvis to the iliac vessels, and a pelvic tract extending from the iliac vessels to the bladder.

The renal vasculature is of relevant interest from the surgical standpoint. The renal pedicle is classically composed by a single artery deriving directly from the aorta and by a single renal vein draining into the inferior vena cava (IVC). The right renal artery runs behind the IVC, and is typically posterior and superior to the left and right renal veins. In approximately 30% of cases, the renal artery is located anteriorly to the renal vein. The left renal artery is more cranial than its right counterpart.

Both vessels enter the kidney at the level of the renal hilum. The vein is located anteriorly to the artery, while the renal pelvis and ureter are located posteriorly to the vascular structures. Usually, a single renal artery arises bilaterally from the lateral portion of the abdominal aorta immediately caudal to the origin of the superior

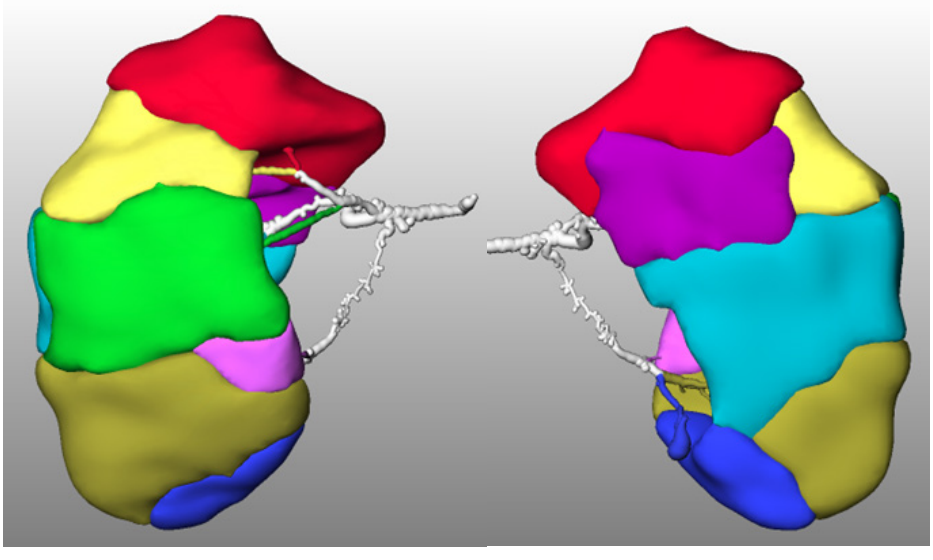
mesenteric artery. However, anatomic arterial variation can be detected in about 25% of cases. Two or sometimes three duplicate arteries can be present, above all on the right side. Supernumerary arteries can reach the kidney at the level of the hilum usually showing a similar caliber as the main renal artery, or they can enter the parenchyma at the level of a pole (aberrant arteries) (**Figure 2**). Accessory arteries directed to the upper pole are typically smaller in diameter than those to the lower pole. Approaching the kidney, the main renal artery splits outside the renal hilum into an anterior and a posterior branch. The posterior segmental branch provides the vascularization of about 25% of the renal parenchyma. The anterior branch is responsible for the vascularization of the remaining 75% of the parenchyma, and usually splits in further four segmental arteries: apical, superior, middle, and inferior.[2,3] Therefore, according to the classic Graves description, the renal parenchyma is subdivided into five segments (apical, upper, middle, lower, and posterior), each supplied by its own branch. The segmental arteries were classically considered as end arteries without an adequate collateral circulation,[2,4] and according to this paradigm, ligation of a segmental artery would cause irreversible ischemia to that segment of the kidney and subsequent segmental renal infarction. However, in 2017 Macchi *et al.* demonstrated in an experimental model obtained from human cadaveric kidneys that a single renal segment receives two or more branches originating from different segmental arteries in a significant percentage of cases.[5] Notably, overlapping branches were observed in 20% of apical segments, 33% of superior segments, 40% of middle segments, 47% of inferior segments, and 13% of posterior segments. The presence of overlapping arteries can explain the inefficacy of selective clamping observed in about 35% of the cases.[6]

FIGURE 2 Three-dimensional (3D) reconstruction showing a large right parenchymal renal tumour. A) Complete view of vascularization; B) after inferior vena cava removal. The imaging shows the presence of three right renal arteries.



In an anatomical study performed using the 3D model obtained from high-resolution computed tomography (CT) scan images of arterial vascular cast, Macchi *et al.* described for the first time the presence of a higher number of parenchymal segments compared to the classical Graves description in a high proportion of cases. In detail, a mean value of 7.3 segments (range, 5–9) were identified. Interestingly, the volume of each perfused segment can be calculated using the CT scan imaging (**Figure 3**).[7] Further studies should clarify the potential clinical application of this novel anatomical observation.

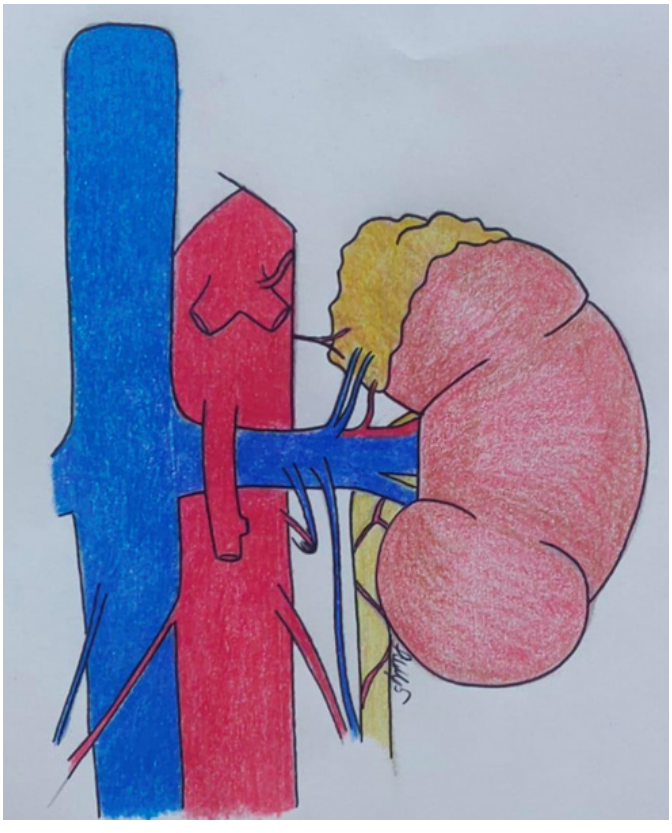
FIGURE 3 Parenchymal renal segments identified according to volume of each perfused segment calculated using the computed tomography (CT) scan imaging. A) Anterior view; B) posterior view.



The right renal vein is generally 2–4 cm in length, it does not receive any branches, and enters the right lateral to posterolateral edge of the IVC. Rarely, the right gonadal vein may drain into the right renal vein. Renal vein duplications are found in 15–20% of cases, but isolated accessory polar veins are a rarity.

The left renal vein is 6–10 cm in length and enters the left lateral aspect of the IVC running posteriorly to the superior mesenteric artery and anteriorly to the aorta. Differently from its right counterpart, the left renal vein receives the left adrenal vein superiorly, the lumbar vein posteriorly, and the gonadal vein inferiorly (**Figure 4**).

FIGURE 4 Renal left venous vasculature (Courtesy of Dr. Silvia Viganò).



Indications for Partial Nephrectomy

The aim of partial nephrectomy (PN) is to completely remove the renal tumour while preserving the largest possible part of healthy renal parenchyma. Over the past decades, indications for PN have been classified as 1) imperative, 2) relative, and 3) elective. Imperative indications are finalized to avoid hemodialysis and, therefore, are applied to patients with renal tumours in anatomical or functional solitary kidney, bilateral synchronous renal tumours, or with multiple tumours in the context of von Hippel-Lindau (VHL) disease. Relative indications are represented by any medical condition that might impair the function of the contralateral kidney (e.g., hypertension, diabetes, pyelonephritis, preexisting chronic kidney disease, urolithiasis). Elective indications are applicable to unilateral renal tumours with a contralateral healthy kidney.

Indications for elective PN have changed significantly over time. Currently, PN is strongly recommended as the preferred treatment option for localized renal tumours ≤ 7 cm in size (cT1). If technically feasible, PN might be offered also to patients with localized renal tumours larger than 7 cm (cT2). However, the strength rating assigned

to PN for cT2 renal tumours is weak. Therefore, PN in this latter category should be still considered suitable for patients with imperative or relative indications.[8,9] Moreover, the amount of parenchymal volume preserved to allow sufficient postoperative renal function should be strongly considered. Notably, in this subgroup of large tumours, surgical feasibility might not be matched by oncologic safety. Indeed, larger tumours are associated with a higher risk for fat tissue and/or peritumoural vein involvement and/or high nuclear grade and/or unfavourable histologic subtypes at final hystopathological examination.[10] Similarly, PN should be preferable for well-circumscricted lesions instead of those with an infiltrative growth pattern.[11] Surgical or technical feasibility is not yet standardized, and strongly related to the surgeon's experience and preferences. Moreover, beyond surgeon experience, hospital volume is a further key factor to be considered in the decision-making process to select candidates for PN.

TABLE 1 Factors considered in the decision-making process to select patients suitable for PN instead of RN. *Modified from Chandrasekar T, Boorjian SA, Capitanio U,* et al. *Collaborative review: factors influencing treatment decisions for patients with a localized solid renal mass*. Eur Urol. *2021;80(5):575–588. doi:10.1016/j.eururo.2021.01.021*[11]

Categories	Factors
Patient related	Younger age Familial/genetic syndromes
Kidney related	Reduced baseline eGFR Baseline proteinuria Atrophic/absent contralateral kidney Comorbidities that impact renal function
Tumour related	Tumour size/clinical stage (cT1a; cT1b; cT2 with caution) Well-circumscribed tumours Benign mass or positive sestamibi scan
Provider related	Surgeon experience Medical centre experience

Abbreviations: eGFR, estimated glomerular filtration rate; PN, partial nephrectomy; RN, radical nephrectomy.

Factors influencing the decision-making process for PN versus radical nephrectomy (RN) are summarized in **Table 1**.[11] Indications for PN in the case of solid tumours are also applicable to cystic lesions classified as category III or IV according to the modified Bosniak classification.[12]

Partial Nephrectomy Versus Radical Nephrectomy

The choice of PN over RN should be strongly based on careful evaluation of oncological, functional, and perioperative outcomes. In detail, PN should offer equivalent oncological outcomes to RN, better renal function preservation (prevention of chronic kidney disease [CKD]), and overall survival (OS) as consequence of a reduction in cardiovascular events due to CKD. Moreover, also health-related quality of life (HRQoL) can represent an important discriminant between PN and RN in patients with localized renal cell carcinoma (T1-2 N0M0).

Oncological outcomes

The highest level of evidence in the choice of PN versus RN is represented by the European Organisation for Research and Treatment of Cancer (EORTC) randomized controlled trial (RCT) 30904 published in 2011.[13] This RCT was designed as a noninferiority study between the two surgical procedures in terms of overall survival. Cancer-specific survival (CSS) was considered as a secondary endpoint. The trial started in April 1992, and it was prematurely closed because of poor accrual in January 2003. In detail, 268 patients were randomized to PN and 273 to RN. Median follow-up was 9 years. Notably, only solitary, clinically organ-confined renal tumours equal or inferior to 5 cm in size were included. Median clinical and pathological tumour size was 3 cm (T1a). During follow-up, 12 (2.2%) renal cancer–related deaths were observed, 4 (1.5%) in the RN group and 8 (3%) in the PN group. Therefore, the estimated risk for death from renal cancer was not significantly higher in the PN arm (HR, 2.06), with a very wide CI (95% CI, 0.62–6.81; Gray's test p=0.23). Looking at the progression of disease, the 10-year progression rate was 4.1% (95% CI, 1.7–6.5) after PN and 3.3% (95% CI, 1.2–5.4) after RN (p=0.48), confirming the oncological equivalence between PN and RN.[13]

The oncological findings provided by the EORTC 30904 trial were widely confirmed by several retrospective studies comparing PN and RN in the setting of localized cT1a and cT1b renal tumours, thus supporting the expanding indications for PN to the setting of patients with tumours larger than 4 cm (**Table 2**).[14–16]

TABLE 2 Oncologic outcomes reported in studies comparing PN versus RN in the setting of cT1 tumours.

			Cases (*n*)		CSS (5-yr) [10-yr]		OS (5-yr) [10-yr]	
Authors, year	**Setting (cT)**	**Follow-up (months)**	**PN**	**RN**	**PN**	**RN**	**PN**	**RN**
Patard *et al.* 2004[14]	cT1b	62.5	65	576	6.2%*	9%*		
Leibovich, 2004	cT1b	48	60	534	96.2%	86%†		
Mitchell, 2006	cT1b	44	33	66	96.2%	97.8%		
Antonelli, 2008	cT1b	43	52	277	93%	92.5%		
Antonelli, 2011	cT1b	47	198	1,426	90% [90%]	92.6% [87%]		
Badalato, 2012	cT1b	33–41	1,047	10,209			82.5%	85%
Simmons, 2009	cT1b	57	35	57	97%	97%	89%	89%
Thompson, 2009	cT1b	56	286	873	97% [90%]	91%† [85]†	80% [51%]	79% [58%]
Iiuzuka, 2012	cT1b	NR	67	195	100% [100%]	86% [67%]		
Roos, 2012	cT1b-cT2	55	101	146	94% [91%]	97% [95%]	83% [64%]	86% [76%]
Jang, 2015	cT1b	42–48	100	477	[85.7%]	[84.4%]	[85.7%]	[73.3%]†
An, 2017	cT1b-2	36	437	350	100% [100%]	87.5%† [80.2%]†	80.2% [60.6%]	65.4%† [35.1%]
Cai, 2018	cT1b	67–70	39	160	96% [88%]	91% [82.8%]	93.3% [85.5%]	85.6% [73.4%]
Gershman *et al.* 2018[30]	cT1	132	919	690	RN vs. PN HR, 1.08 (0.64–1.81)		RN vs. PN HR, 1.14 (0.94–1.38)	
Yang *et al.* 2020[35]	cT1b	55	177	154	RN vs. PN HR, 2.867 (1.309–6.277)‡		RN vs. PN HR, 2.129 (1.211–3.743)‡	

*Cancer-specific mortality rate; †statistically significant; ‡confirmed at multivariable analysis.

Abbreviations: CSS, cancer-specific survival; HR, hazard ratio; NR, not reported; OS, overall survival; PN, partial nephrectomy; RN, radical nephrectomy.

A potential oncological issue with PN could be represented by the risk for clinical tumour downstaging.

In their meta-analysis including 7,406 patients collected in 12 selected articles related to upstaged pT3a, Chung *et al.* did not report any differences in recurrence-free survival (RFS) and CSS between the PN and RN groups. Conversely, patients who underwent PN showed a significant longer OS compared with those who received RN.[17] Recently, Liu *et al.* analyzed the clinical records of a total of 3,196 patients who underwent PN or RN for clinical T1 RCC and resulted pT3aN0 (perirenal fat tissue invasion) on final pathology. This population-based study using data of the Surveillance, Epidemiology, and End Results (SEER) database between 2010–2017 showed that PN provides similar CSS and OS as RN in the previous setting of patients, confirming the oncologic safety of PN in cT1a RCCs that are proved to be pT3a on final pathology.[18] A more recent study published by Tian *et al.* in 2022 confirmed that patients with pT3a RCC who underwent PN achieved comparable oncologic outcomes with those receiving RN. In particular, these SEER database data demonstrated that PN and RN had comparable CSS both in the fat invasion cohort (p=0.075) and the venous invasion cohort (p=0.190).[19] These studies demonstrated that PN can be considered a safe oncologic procedure for selected T3a tumours.

In 2014, Kopp *et al.* published a very interesting study showing an equivalent CSS in a series of patients who underwent PN or RN for localized cT2 renal tumours.[20] A systematic review of studies comparing PN and RN in the setting of patients with cT1b or cT2 renal cell carcinoma showed statistically significantly higher CSS rates after PN in comparison with RN.[21] Previous results have been confirmed by a more recent multicentre study including clear cell RCC larger than 7 cm in size followed for a median time of 102 months. In detail, the authors reported a statistically significantly better CSS in patients who underwent PN in comparison with RN (median survival not reached for PN vs. 164 months for RN; p=0.04).[22] A recent meta-analysis of studies comparing PN and RN in the setting of cT2 RCC showed worse recurrence rates in patients who underwent RN and equivalent CSS and CSM between the two surgical treatments. Moreover, no differences in oncological outcomes were observed in sensitivity analyses considering nuclear grading and histological subtypes.[23] Data of a previous meta-analysis were confirmed in a further comparative study between PN and RN in patients with cT2 tumours. In detail, overall, metastases-free, and cancer-specific survival were not significantly different between PN and RN considering a 7.1-year median survivor follow-up.[24] **Table 3** summarizes oncological data of available studies comparing PN and RN in patients with cT2 tumours.

TABLE 3 Oncologic outcomes reported in studies comparing PN versus RN in the subgroup of cT2 tumours.

			Cases (*n*)		CSS (5-yr) [10-yr]		OS (5-yr) [10-yr]	
Authors, year	**Setting (cT)**	**Follow-up (months)**	**PN**	**RN**	**PN**	**RN**	**PN**	**RN**
Margulis, 2007	cT2	62–43	34	567	78%	74%		
Jeldres, 2009	≥cT2	48	17	45	67%	87%*		
Breau, 2010	≥cT2	38	69	207	RN vs. PN HR, 0.96 (0.50–1.82)		RN vs. PN HR, 1.01 (0.63–1.62)	
Hansen, 2012	cT2	NR	245	8,602	96%	88%		
Kopp *et al.* 2014[20]	cT2	41	80	122	86.7%	82.5%	83.3%	80%
Janssen *et al.* 2018[22]	cT2	102	18	105	[88.9%]	[74.6%]*	[75%]	[60%]*
Reix, 2018	cT2	24	91	176	80.2%	85%	78.7%	76.2%
Shum, 2018	cT2	49	137	226			RN vs. PN HR, 5.289 (4.137–6.762)†	
Klett *et al.* 2021[24]	cT2	84	72	379	RN vs. PN HR, 1.32 (0.61–2.82)		RN vs. PN HR, 0.51 (0.28–0.93)*	

*Statistically significant; †all-cause mortality.

Abbreviations: CSS, cancer-specific survival; HR, hazard ratio; NR, not reported; OS, overall survival; PN, partial nephrectomy; RN, radical nephrectomy.

Although promising, oncologic data reported for cT2 tumours are likely affected by a high risk for selection bias in favour of the PN group including patients and tumours with more favourable characteristics. Therefore, further data from high-quality studies are needed to support the expanding indications of PN to the challenging setting of cT2 tumours.

Renal function and overall survival

One of the main arguments for preferring PN over RN is the decreased impact on developing CKD. In 2004, Huang *et al.* published an interesting retrospective study showing that patients who underwent a PN for renal tumours inferior or equal to 4 cm in size had a significantly lower probability of freedom from new onset of estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or < 45 mL/min/1.73 m^2 compared with patients treated with RN. Patient age, preoperative eGFR value, and performing a PN were shown to be independent predictors of postoperative renal function preservation.[25]

The best available evidence concerning the comparison between PN and RN is still represented by the EORTC 30904 trial. At a median follow-up of 6.7 years, PN decreased the percentage of subjects reaching at least moderate CKD stage A (eGFR <60 mL/min) and stage B (eGFR <45 mL/min) in comparison with RN. Moreover, also the percentage of subjects with advanced CKD (eGFR <30 mL/min) was lower in the PN arm, although the difference between the two treatment arms was relatively small for this subgroup. Conversely, no differences between the two treatments were detected in terms of incidence of end-stage renal disease (GFR <15).[26]

A significant lower decline in eGFR and a minor risk of developing CKD were observed also in patients who underwent PN in comparison with RN for localized cT1b-T2 tumours.[21] Previous data were recently confirmed in a meta-analysis including only studies comparing PN and RN in the setting of cT2 RCC.[23] Moreover, in 2021, Klett *et al.* confirmed in a series of cT2 tumours that eGFR rate change at 1 and 3 years was more pronounced with RN in comparison with PN.[24] Previous data suggested that in patients with preexisting CKD, PN is the treatment of choice to reduce the risk for further development of CKD, which may require hemodialysis.

An interesting study published in 2004 highlighted the strong correlation between CKD and risk for death, cardiovascular events, and hospitalization in the general population.[27] Therefore, we can hypothesize that in patients who underwent surgical treatment for renal tumour, PN could be strongly associated with a reduction in the risk for cardiovascular events, and, consequently, with a prolonged overall survival in comparison with those who underwent RN. However, conflicting data were later reported. While some population-based studies failed to show differences in terms of cardiovascular events between PN and RN, other studies showed a decreased cardiovascular-specific mortality and an improved overall survival in patients who underwent PN in comparison with those treated with RN.[28,29] More recently, the Mayo Clinic published a large study including patients with localized cT1 RCC who underwent PN or RN. In this study, the authors observed a significant reduction in the risk for CKD after PN compared with RN.[30]

Concerning the overall survival endpoint, the EORTC trial 30904 showed a noninferiority of PN in comparison with RN. When considering the targeted population of RCC patients only and clinically and pathologically eligible patients, the 10-year OS rates after PN and RN were 75.2% and 79.4%, respectively, for RCC patients and 78.0% and 79.6%, respectively, for clinically and pathologically eligible patients.[26]

Equivalence in terms of overall survival between PN and RN was reported also by Gershman *et al.* analyzing a very large series of cT1 renal tumours surgically treated at the Mayo Clinic.[30]

Conversely, a meta-analysis of studies comparing PN and RN for cT1b and cT2 tumours showed a significant lower risk for all-cause mortality in patients who underwent PN in comparison with those receiving RN.[21]

A recent meta-analysis including only cT2 tumours treated with PN or RN showed a significant advantage in favour of PN in terms of overall survival and all-cause mortality.[23]

Therefore, the OS advantage suggested for PN versus RN is still questionable. While the OS advantage seems to hold for younger patients and/or those without significant comorbidities, the point remains substantially questionable for patients older than 75 years with or without comorbidities.[31,32] Moreover, the lower OS in patients with preoperative lower eGFR values does not seem a consequence of a renal function impairment due to surgery, but rather the consequence of medical comorbidities responsible for presurgical CKD.[33] These data reinforce the indications for PN in patients with presurgical CKD to minimize the risk for subsequent end-stage renal disease and hemodialysis.[8]

Perioperative outcomes and quality of life

It is generally accepted that a procedure such as PN is associated with a higher likelihood for postoperative complications and blood loss compared to RN.[13,21] Hemorrhagic complications and urinary fistulas are the most frequent and typical postoperative complications observed in patients undergoing PN.[34] Conversely, RN can be complicated with damage to the surrounding organs (spleen, lung, liver, and bowel).[13] However, a meta-analysis showed an equivalent risk of spleen damage in patients who underwent PN or RN.[35] The risk for complications is strongly related to the surgery complexity and clinical stage both for PN and RN.

The EORTC 30904 RCT including cases of small, incidentally detected RCC showed only slightly higher complication rates in the PN group in comparison with RN.[13]

Conversely, in T1b and T2 renal tumours, available retrospective studies showed a significantly higher risk for blood loss and postoperative complications after PN in comparison with RN.[21] Notably, previous data are mainly reported for clinical series including patients receiving an open approach.[21] A recent meta-analysis comparing patients who underwent PN versus RN confirmed that patients treated with PN were associated with a greater risk for overall postoperative complications (OR, 1.40; 95% CI, 1.17–1.68; $p<0.001$), postoperative hemorrhagic complications (OR, 1.92; 95% CI, 1.28–2.87; $p=0.002$), and urinary fistula (OR, 17.65; 95% CI, 5.35–58.30; $p<0.001$) in comparison with RN.[35] Similar results were reported by Huang *et al.* in 2021 analyzing studies with cT2 cases only.[23] Conversely, although Klett *et al.* reported more common overall and severe complications for PN compared with RN, this difference was not statistically significant.[24]

The risk of developing a cardiovascular event (CE) after RN in comparison with PN is non-negligible. Huang *et al.* reported a CE risk that was 1.4 times more frequent in patients who underwent RN (HR, 1.37; $p<0.001$) compared with those who received PN. However, the cardiovascular-related death score was equal for both treatments.[28] These findings were confirmed in a multicentre study, showing a lower risk of developing CEs following PN compared with RN (HR, 0.57; 95% CI, 0.34–0.96; $p=0.03$), after adjusting for patients' cardiovascular profile. Interestingly, the authors observed a trend toward a higher incidence of CEs in PN patients with a postoperative GFR < 60 mL/min/1.73 m^2 compared with those with a GFR ≥ 60 mL/min/1.73 m^2.[36] However, a recent meta-analysis including eight comparative studies showed that cardiovascular complications were equivalent after the two surgical treatments.[35]

Only a few studies assessed the impact of PN and RN on quality of life (QOL). In 2009, Novara *et al.* analyzed 129 consecutive patients who underwent PN or RN for RCC. Interestingly, they noted a significant worsening in physical domains and significant improvement in the emotional ones after surgery (all $p<0.05$). Moreover, only 50–80% of patients returned to baseline scores 6 months and 12 months after surgery. Age, body mass index (BMI), educational level, occupational status, New York Heart Association (NYHA) functional class, tumour mode of presentation, pathologic stage, size, and histological subtype were associated with 6-month and 12-month return to baseline HRQoL scores. Notably, no differences in analyzed HRQoL domains were detected between PN and RN.[37] Other authors reported a proportional correlation between tumour size and HRQoL. Indeed, patients treated with PN for a tumour less than 4 cm with a normal contralateral kidney reported a significantly better HRQoL than those treated for larger tumours.[38] In a recent systematic review of the literature, Junker *et al.* analyzed three studies and investigated HRQoL in studies comparing PN and RN, showing higher QoL scores after the conservative surgical management.[39]

Preoperative Management

The multiphasic contrast-enhanced abdominal CT is still the reference standard for the diagnosis, staging, and preoperative surgical planning of renal tumours. However, an abdominal contrast-enhanced CT angiography should be considered in cases requiring detailed information on the renal vascular supply.[40] Three-dimensional CT reconstructions are needed to display the vascular and renal mass anatomy in a visual form that is familiar to surgeons and to guide the surgical strategy during PN, especially in complex cases.[41] Indeed, abdominal CT imaging provides essential information regarding the anatomical and topographical characteristics of the tumour as well as information regarding the relationship between the kidney and surrounding organs and its vasculature. Abdominal magnetic resonance imaging (MRI) could be the only imaging available in patients who are allergic to intravenous CT contrast medium or are pregnant without renal failure.[8]

Some anatomical and topographical characteristics of renal tumours can help urologists evaluate the surgical complexity of PN. In 2009, first-generation nephrometry systems were proposed with the aim to standardize the description of renal tumours beyond the traditional clinical size and to predict the potential morbidity of PN in different clinical scenarios. Nephrometry scoring systems were soon applied to clinical practice because they were found to provide useful data for treatment planning, patient counselling, and comparison between different PN series.

The RENAL nephrometry (Radius/maximal tumour diameter, Exophytic/Endophytic properties, Nearness to the collecting system or renal sinus, Anterior/posterior descriptor, and Location relative to the polar lines), the Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification, and the Centrality Index (C index) represent the first-generation nephrometry systems.[42–44] Although in the following years several second-generation nephrometry systems have been proposed, the RENAL and PADUA systems are still the most common tools used to objectify tumour anatomy and complexity.[1] Indeed, both the RENAL and PADUA scoring systems have been widely externally validated as predictors of overall complications, warm ischemia time

(WIT), estimated blood loss (EBL), and renal function impairment in patients who underwent PN, regardless of the approach used.[1,45–48] Moreover, a recent comprehensive systematic review and meta-analysis, evaluating the impact of host factors on robot-assisted partial nephrectomy (RAPN), confirmed the ability of both the RENAL and PADUA nephrometry systems to predict the most important intra- and postoperative outcomes.[49] Notably, in 2019, Ficarra *et al.* proposed a simplified version of PADUA classification including only four of the original variables (rim location, exophytic rate, clinical size, and renal sinus involvement), which was able to reach the same performance as the first-generation and more complex RENAL and PADUA systems (**Table 4**).[50] Nephrometry scores can therefore be a helpful tool for preoperative decision-making, counselling, and patient selection. Besides nephrometry systems, a parameter of interest to estimate the functional impairment after PN is represented by the Contact Surface Area (CSA).[51] A simplified formula to calculate this interesting parameter was proposed by Hsieh *et al.* in 2016 and externally validated by Haifler *et al.* in 2018.[52,53] In 2019, Ficarra *et al.* showed than while CSA was not a predictor of overall complications, it was an independent predictor of renal function impairment after PN.[54]

TABLE 4 Parameters and scores included in the first generation of nephrometry scores.

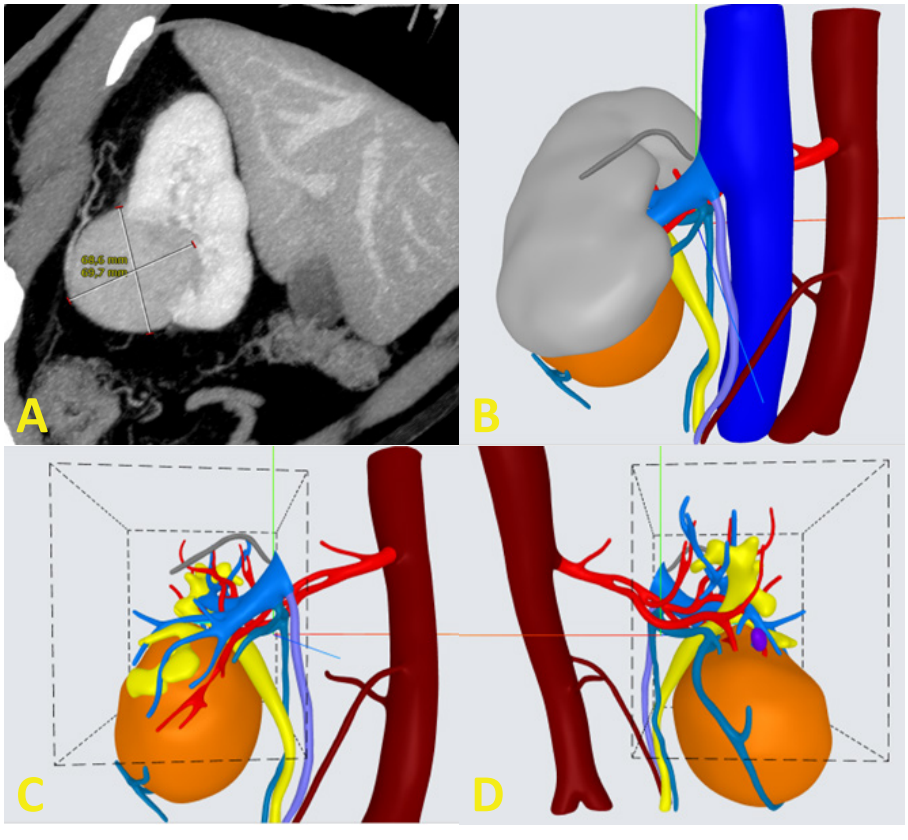
	RENAL Nephrometry Score	**PADUA score**	**SPARE system**
	Variables included or not included		
Tumour size (cm)	≤4 (1), 4–7 (2), >7 (3)	≤4 (1), 4–7 (2), >7 (3)	≤4 (0), 4–7 (2), >7 (4)
Exophytic rate (%)	≥50% (1), <50% (2), endophytic (3)	≥50% (1), <50% (2), endophytic (3)	≥50% (0), <50% (1), endophytic (2)
Polar location	Superior vs. inferior vs. middle (1–2–3)*	Superior/inferior (1) vs. middle (2)	Not Included
Medial/lateral location	Not evaluated	Lateral (1) vs. medial (2)	Lateral (0) vs. medial (2)
Anterior/posterior location	Included (a/p)	Included (a/p)	Included (a/p)
Renal sinus involvement	≥7 mm (1), 4–7 mm (2), <4 mm (3)	Not involved (1) vs. involved (2)	Not involved (0) vs. involved (3)
Collecting system involvement		Not involved (1) vs. dislocated/infiltrated (2)	Not included
	Subgroup stratification		
	4–6 vs. 7–9 vs. 10–12 (no criteria specified)	6–7 vs. 8–9 vs ≥10 based on multivariate analysis	0–3 vs. 4–7 vs. 8–10 based on OR binary logistic regression analysis

*1) Entirely above the upper or below the lower polar line; 2) lesion crosses polar line; 3) >50% of mass is across polar line, or mass crosses the axial renal midline, or mass is entirely between polar lines.

Abbreviations: PADUA, Preoperative Aspects and dimensions used for an anatomical classification; RENAL, Radius-Exophytic-Nearness-Anterior/posterior-Location; SPARE, Simplified Padua Renal.

Another interesting parameter not included in the classical nephrometry scoring system, but with a potential interest in the preoperative imaging evaluation is represented by perirenal fat tissue status. Indeed, in 2014, Davidiuk *et al.* proposed the Mayo Adhesive Probability (MAP) score, an accurate image-based scoring system to predict the adherent perirenal fat tissue in patients suitable for PN.[55] The score was based on thickness of lateral and posterior perirenal fat measured at the level of the renal veins as well as on grading of perinephric stranding. The MAP score was shown to be a predictor of operative time and EBL during PN.[56,57]

FIGURE 5 Traditional CT scan imaging (A) and 3D reconstruction of renal vasculature, collecting system, kidney shape, and tumour characteristics, anterior vision (B-C); posterior vision (D).



Hyper-accuracy three-dimensional (HA3D) reconstruction of the anatomical structures from CT scan images represents an interesting new tool for assessing surgical complexity and plan surgical treatment. A 3D virtual model of the affected kidney is created on the basis of high-resolution abdominal CT (angio-CT) scans. It is focused on the renal vasculature (both arterial and venous), collecting system, kidney shape, and tumour characteristics. The 3D images allow for reconstructing the renal pedicle, and the extra- and the intrarenal arteries, with the possibility of seeing the segmental arteries and their relationship with the renal tumour (**Figure 5**). Notably, in 2019 Porpiglia *et al.* showed that 3D virtual imaging of renal tumours helped surgeons improve the accuracy of nephrometry scoring systems for predicting both overall and major complications.[58] Moreover, this new technology may maximize the efficacy of selective clamping technique during RAPN for complex renal tumours.[59] Features such as 360-degree rotation along all axes, changing the view from solid phase to transparency mode, and establishing a resection plane with possibly adequate safety margins even before resection can further aid surgeons to optimally plan for the different steps of the operation. In robotic platforms, these reconstructions can be imported to complete the virtual surgery and intraoperative navigation.[59,60]

Surgical Approaches

PN can be performed using either open, pure laparoscopic, or robot-assisted approach based on the surgeon's expertise and skills as well as the hospital's surgical volume.[61–64] However, according to most representative international guidelines, minimally invasive surgery should not be taken into consideration if this approach may compromise oncological, functional, and perioperative outcomes of PN or significantly increase the risk for intraoperative conversion to RN. Conversely, it is not acceptable to perform a laparoscopic RN instead of an open PN in patients with cT1 tumours suitable for nephron-sparing surgery (NSS) in experienced hands.[8]

For many years, the open approach had been the only option available to perform NSS in patients with parenchymal renal tumours. Urologists have performed open partial nephrectomy (OPN) through a retroperitoneal approach using a flank/subcostal incision or transperitoneally using a median xifo-ombelical incision or a bilateral subcostal Chevron incision according to their preference and tumour location at the level of posterior or anterior face, respectively.

Over the past decades, conventional and robot-assisted laparoscopy have been proposed as minimally invasive alternatives to OPN. According to the literature, pure laparoscopic partial nephrectomy (LPN) is considered a technically challenging procedure requiring a steep and long learning curve to reach acceptable WIT and perioperative morbidity.[65] Robot-assisted partial nephrectomy (RAPN) has been introduced as the natural evolution and simplification of traditional LPN. Specifically, 3D vision, optical magnification up to 12x, and the patented EndoWrist (Intuitive Surgical, Sunnyvale, California, United States) technology allow surgeons to perform a very precise tumour resection and a very accurate and simplified renorrhaphy.[66] The advantages of robotic technology have facilitated the expanding indications of minimally invasive PN for the management of large and/or very complex parenchymal renal tumours. Recent data has confirmed that hospital RAPN volume is a predictor of the most important perioperative outcomes as well as positive surgical margins (PSMs).[61–63]

Notably, more than 60 PN/year were shown to be an independent predictor of PSMs in a large series of 2,060 patients who underwent OPN, LPN, or RAPN.[67]

A potential issue with NSS is the risk for PSMs. In a recent systematic review of the literature, Ficarra *et al.* reported a 6.7% PSM rate in a total of 45,786 PN cases included in the analysis, with a mean PSM rate ranging from 0.7 to 10.1% of cases. According to the different approach used, mean PSM rate ranged between 0 and 8.5% in the 26,606 RAPN cases analyzed; between 1 and 12% in the 2,013 LPN cases included in the systematic review, and between 1.8 and 18% in the 7,126 OPN cases analyzed. Notably, the risk for PSMs was not correlated with the tumour complexity.[68] Conversely, the risk for PSMs was inversely correlated with hospital volume.[62]

Similarly to open surgery, laparoscopic procedures can also be performed using a transperitoneal or retroperitoneal approach, according to tumour location and surgeon preferences. Posteriorly located tumours may be approached in an easier manner using a retroperitoneal approach. Moreover, this approach allows for direct access to the renal hilum without the need for bowel mobilization. Conversely, the small operation field and the lack of anatomical landmarks are potential disadvantages of this approach.[69] A recent study comparing transperitoneal with retroperitoneal RAPN showed advantages in favour of the retroperitoneal approach in terms of lower EBL. Conversely, no differences in terms of postoperative complications, PSM rate, length of hospital stay, WIT, and postoperative kidney function were observed. Moreover, this study failed to demonstrate any significant advantages in favour of the retroperitoneal approach in the management of posterior tumours.[70] Therefore, surgeon preference represents the main factor influencing the choice between the transperitoneal and the retroperitoneal approaches.

Open partial nephrectomy versus robot-assisted partial nephrectomy

In the past decade, the number of RAPN cases significantly increased, exceeding the number of NSS procedures still performed using the open approach in several countries. Currently, RAPN should be considered as the reference standard for NSS in patients with renal tumours, with the exception of centres without the robotic platform where LPN remains the main alternative to OPN.

In 2013, Masson-Lecomte *et al.* compared prospectively collected clinical data of 58 patients who underwent OPN and 42 who received RAPN by the same experienced surgeon between 2008 and 2010. The authors reported a statistically significant advantage in favour of RAPN only in terms of EBL and length of hospital stay. Conversely, overall complications, WIT, PSM rate, and effect on renal function were similar.[71] In 2014, Ficarra *et al.* published a multicentre, multi-surgeon, matched pair-analysis comparing 200 OPN with 200 RAPN cases. The authors showed a significantly shorter WIT in patients who underwent OPN and a significantly lower EBL in those who underwent RAPN. No differences were observed in terms of operative time and intraoperative complications. However, RAPN was associated with a shorter in-hospital stay and a significantly lower postoperative complications rate. No differences in terms of PSM rate were reported in the two groups.[72] In 2016, Peyronnet

et al. published a multicentre, retrospective French study comparing 1,800 patients who underwent OPN or RAPN in 6 academic departments. The results of this study confirmed that RAPN was associated with lower complications, lower EBL, and a shorter hospital stay. Although the median follow-up was short, the oncologic outcomes were similar in the two compared groups.[73] Comparable results with the two techniques in terms of PSM rate were also reported in another meta-analysis.[68]

Previous oncologic data were confirmed by Garisto *et al.* in a series of patients receiving OPN or RAPN for highly complex renal masses. Indeed, the authors reported comparable recurrence- and cancer-specific mortality rates between the two approaches.[74] Similarly, in the subgroup of complex tumours, Wang *et al.* reported 5-year RFS and CSS rates for RAPN versus OPN of 95.1% versus 92.7% (p=0.48) and 98.7% versus 97.6% (p=0.12), respectively.[75] Previous data were confirmed by Larcher *et al.* in a propensity observational study comparing 170 OPN with 302 RAPN cases. In detail, the study showed equivalent 5-year rates of local recurrence-free, distant progression-free, and cancer-free survival between the two groups. Moreover, patients who underwent PN showed a lower rate of overall and major complications. Notably, this advantage was confirmed also in more complex cases characterized by high PADUA scores, high CCI, large tumours, and low preoperative eGFR.[76]

In 2019, Grivas *et al.* published a systematic review of the literature including 22 studies comparing OPN and RAPN, showing that the last approach was superior to OPN in terms of complication rate in 11 included studies while similar results were observed in 9 studies. Positive surgical margins were similar in 13 studies while RAPN had lower surgical margins in 6 studies. Looking at perioperative outcomes, most of the retrieved studies showed equivalent or longer OR and WIT in RAPN. Moreover, most studies showed that EBL and length of hospital stay were equivalent or in favour of RAPN. Overall and major postoperative complications were equivalent or in favour of RAPN. Both eGFR decline and CKD upstaging were similar in the majority of studies.[77]

More recently, Zeuschner *et al.* in a comparison of 313 OPN and 500 RAPN cases confirmed that RAPN beyond the learning curve was associated with fewer complications, less blood loss, and shorter length of hospital stay compared with OPN, even for more complex tumours.[78]

Some studies compared RAPN and OPN in specific settings of patients. Takagi *et al.* compared RAPN and OPN in a cohort of patients with CKD. Performing a propensity score–matched analysis comparing 40 RAPN with 40 OPN cases, the authors observed that EBL was significantly lower and length of hospital stay was significantly shorter in the RAPN compared with the OPN group. Conversely, major complications, PSM rates, and preservation of the eGFR did not differ between the two groups.[79]

The potential role of RAPN in obese patients was evaluated by Malkoc *et al.* in a study comparing 180 RAPN with 207 OPN cases. Perioperative outcomes were in favour of RAPN. In this study, obesity and OPN turned out to be independent predictors of postoperative complications.[80]

Yerram *et al.* investigated 110 patients who underwent RAPN or OPN for multifocal tumours located in the same kidney. RAPN achieved equivalent rates of trifecta as open surgery. The equivalence persisted on subgroup analyses of patients with two and more than two tumours.[81]

Laparoscopic partial nephrectomy versus robot-assisted partial nephrectomy

Most studies comparing LPN and RAPN were performed at the beginning of the robotic era, and therefore they are not representative of the current clinical practice, where virtually all surgeons proficient in traditional laparoscopy have embraced the robotic approach. First, the robotic approach offers better ergonomics to surgeons, and it has been associated with a shorter learning curve in comparison with pure laparoscopy.[66] More controversial is the cost analysis between the two techniques. Usually, the robotic approach is considered more expensive in comparison with traditional laparoscopy. However, in 2018, Camp *et al.* showed lower postoperative costs for RAPN compared with LPN, as RAPN was associated with fewer complications in the first 90 postoperative days and lower total costs one year after surgery.[82] A meta-analysis including 23 cohort studies comparing LPN and RAPN showed a significantly lower risk for conversion to RN or open surgery in patients who underwent RAPN. Moreover, RAPN cases were associated with shorter WIT, lower decline in eGFR, and shorter in-hospital stay in comparison with LPN cases. No differences between the two techniques were recorded in terms of overall complications, operative time, EBL, and PSM rate.[83] These findings were confirmed in a prospective, multicentre study including the 50 latest patients having undergone LPN or RAPN in the participant institutions. In detail, LPN was associated with a longer WIT and longer hospital stay in comparison with RAPN. Conversely, there were no differences in terms of transfusion rates, perioperative complications, and change in renal function between the two approaches. Moreover, PSMs were observed in 2% of RAPN versus 6% of LPN cases. This difference was not statistically significant.[84] Conversely, a cumulative analysis of five studies comparing LPN and RAPN showed an increased risk for PSMs in patients who underwent LPN (OR, 3.02; 95% CI, 2.05–4.45).[68]

In 2018, Chang *et al.* performed a propensity score–matching analysis comparing 122 patients with parenchymal renal tumours each treated with OPN, LPN, or RAPN. At a 5-year median follow-up, the authors reported similar local recurrence, distant metastasis, and cancer-related death rates. However, RAPN was associated with a lower incidence of CKD upstaging compared with OPN and LPN.[85] The association between RAPN and early recovery of renal function was demonstrated also by Choi *et al.* in a study evaluating the preoperative and 1-year postoperative renal scan of a series of patients who underwent OPN or LPN or RAPN. Indeed, RAPN turned out to be an independent predictor of 1-year eGFR reduction.[83]

Previous data were confirmed by a recent systematic review of the literature showing a 5-year CSS ranging between 90 and 98%, 86 and 87%, and 88 and 96% after RAPN, LPN, and OPN, respectively.[86]

Surgical Technique

Regardless of the different approaches used to perform PN, the main steps of the procedure are represented by 1) isolation of the renal hilum; 2) mobilization of the kidney and tumour identification/demarcation; 3) clamping (or not) of renal artery(ies) with or without clamping of the renal vein; 4) tumour excision; and 5) renorrhaphy.

Isolation of the renal hilum

Although some surgeons proposed to avoid the isolation of the renal hilum as a preliminary step of PN in order to avoid potential damage at the level of major renal vessels, the majority of surgeons perform this step of the procedure regardless of the decision to perform an off-clamp or on-clamp technique. Psoas muscle, ureters, and gonadal vessels represent important landmarks for identifying the renal vein. The renal artery usually lies behind the vein, and the pulsations can lead to its location. Preoperative CT scan imaging on axial and coronal planes is necessary to have a detailed preliminary knowledge of the unique vasculature of each kidney. 3D reconstruction of the anatomical structures from CT scan may play an important role in the identification of the main renal artery, its relationship with venous vessels, and in the identification of segmental arteries, which could be of interest when a selective clamping strategy is considered. Usually, the isolated renal vessels are suspended using vessel loops.

Kidney mobilization and tumour identification

Once the hilar vessels are identified, Gerota's fascia is opened and perirenal fat is removed to identify the exophytic portion of the tumour. Posterior and lateral fat thickness measured on CT scan at the level of the renal vein and the grade of perinephric stranding may help surgeons to predict adherent perinephric fat in patients scheduled for PN.[55] Adherent perinephric fat could be due to inflammatory reaction more frequently in patients with diabetes, cardiovascular diseases, and/or elevated BMI. Adherent fat may render the parenchyma isolation very difficult, thus increasing the operative time and the intraoperative blood loss.[87–89] Appropriate parenchymal isolation and renal mobilization is a key step of the procedure for placing the kidney in the best position to perform tumour excision and renorrhaphy.

Ultrasound examination can be performed intraoperatively to identify entirely endophytic tumours or to better define the deepness of the partially exophytic ones and/or to better identify the limits between the renal tumour and the healthy parenchyma (**Figure 6**). Moreover, ultrasound may also be helpful during selective ischemia using Doppler or contrast-enhanced ultrasound.[90,91] The capsule of the kidney can be superficially cauterized close to the tumour margins to demarcate it from the healthy parenchyma (**Figure 7**).

FIGURE 6 Intraoperative ultrasound examination (Tilpro option) during robot-assisted partial nephrectomy.

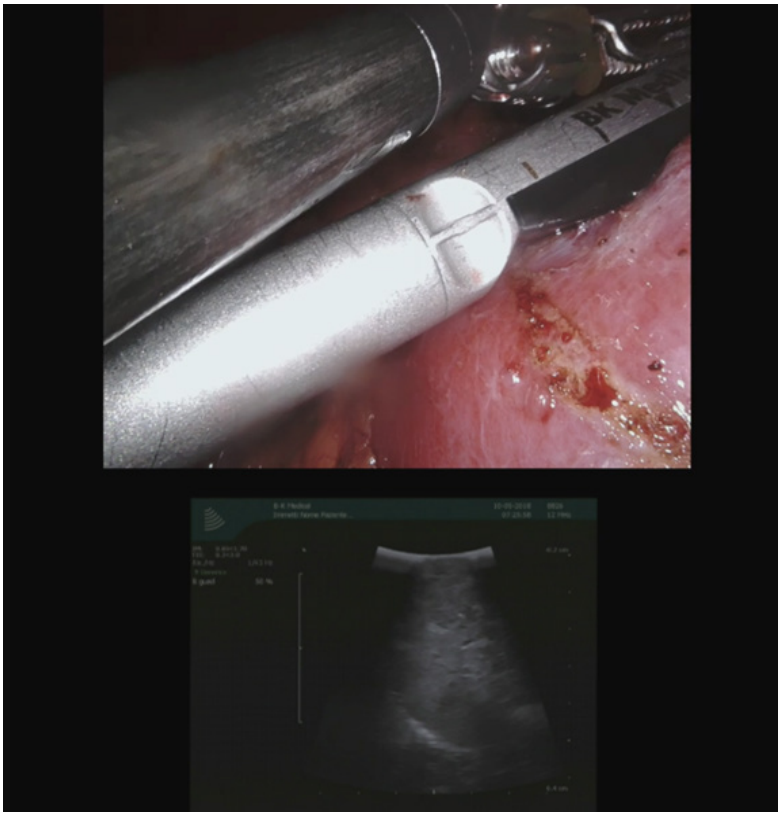
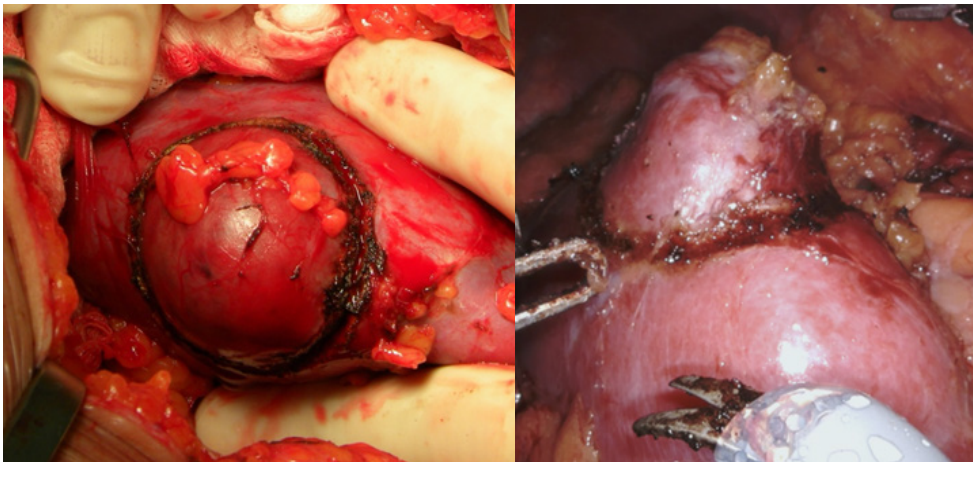


FIGURE 7 The renal tumour is identified, and its margins demarcated from the healthy parenchyma. A) Open surgery; B) robotic surgery.



Clamping techniques

Once the tumour is well identified and correctly demarcated from the surrounding healthy parenchyma, there are several options:

1) clamping the main renal artery (on-clamp technique) with or without early unclamping at the body temperature (warm ischemia) or after induction of hypothermia (cold ischemia); 2) clamping only the pertinent segmental artery(ies) (selective clamping); 3) performing a zero-ischemia technique consisting in a superselective clamping of tumour-specific tertiary or quaternary artery branches; 4) not clamping the renal artery (off-clamp technique) and performing the entire procedure while the tumour and the renal parenchyma remain vascularized.

The on-clamp technique minimizes blood loss during tumour excision, allowing for a relatively bloodless field during tumour excision and parenchymal reconstruction. However, long ischemia time could be responsible for renal damage, leading to acute renal failure or CKD. Ischemia time is therefore one of the most important surgical factors influencing postoperative renal function. Indeed, clamping of the main renal artery induces a circulatory arrest at the level of renal parenchyma, with consequent hypoxia and potential acute tubular necrosis.

Although there is no general agreement, the ideal cutoff of WIT is currently considered 20 min, with values ranging from 20 to 30 min being traditionally considered safe.[92] Notably, in 2010 Thompson *et al.* published a seminal study clearly demonstrating that every minute counts when the renal artery is clamped.[93] Therefore, it is widely accepted that the shorter the WIT, the lesser the negative impact on renal function after PN. Conversely, some studies showed that a healthy kidney can cope with even more prolonged ischemia time.[94,95] Notably, elderly patients with comorbidities and preoperatively compromised kidneys are probably more susceptible to even shorter ischemic damage compared to healthy younger patients with normal baseline kidney function. Interestingly, a recent retrospective study analyzing 147 patients who underwent PN and subsequent RN due to tumour recurrence showed that in the context of conventional ischemia time, histological deterioration of the preserved parenchyma after PN is related mainly to preexisting medical comorbidities rather than ischemia.[96]

To limit the ischemic damage, some authors have proposed using cold ischemia when the time of arterial obstruction is expected to be more than 30 minutes. Putting an ice slush around the kidney decreases renal energy expenditure and partly ameliorates the adverse impact of warm ischemia and reperfusion injury.[97,98] In 2011, Lane *et al.* compared cold and warm ischemia techniques during PN in a nonrandomized study of patients with solitary kidney. They showed a similar decrease in eGFR at 3 months, although median cold ischemia time was significantly longer than median warm ischemia time (45 vs. 22 min).[99]

In open surgery, ice slush can be easily applied around the organ to accomplish temperature cooling. Conversely, this technique is rarely used during minimally invasive surgery due to technical difficulties.[100] Retrograde cooling through the ureter,[101] cold saline surface irrigation,[102] and intra-arterial cold perfusion[103] have been proposed as alternative options to achieve cold ischemia.

Global renal ischemia time can be significantly shortened by early unclamping of the main artery. This technique was proposed in 2008 by Nguyen and Gill in a series of patients who underwent LPN.[104] The early unclamping maneuver is typically performed immediately after placement of the inner renorrhaphy suture, with the remaining parenchymal suturing performed in the revascularized kidney. In their initial experience, Nguyen and Gill reported a reduction of the WIT higher than 50% in the early-unclamping group in comparison with the standard one (14 vs. 31 min). This technique has been widely used both in open and robotic PN. In a study evaluating the impact of the early-unclamping technique during RAPN, the authors reported a short WIT without significant differences in terms of postoperative renal function.[105] A recent systematic review of the literature showed that early unclamping was associated with a higher EBL compared with the on-clamp technique even if transfusion rates were similar. Moreover, no differences were recorded in terms of in-hospital stay, overall and major complications, and PSM rate.[106]

Clamping of the pertinent segmental artery(ies) can reduce the greatest renal ischemic insult caused by clamping of the main renal artery.[107] Although this clamping technique is done mainly during the minimally invasive approach, some authors have described its application also in OPN.[108] Interestingly, in 2011 Gill *et al.* described the "Zero ischemia" technique, consisting of a superselective clamping of tumour-specific tertiary or quaternary artery branches, avoiding the interruption of arterial blood flow to the healthy parenchyma and the consequent global renal ischemia.[109] Selective and superselective clamping techniques can be associated with greater blood loss but better renal function at 3 to 6 months in comparison with clamping of the main artery.[110–112]

Some authors have proposed performing PN without any vascular clamping. Small tumours with favourable anatomical and topographical characteristics and/or in solitary kidney could be considered as the ideal cases for this option.

In 2019, Greco *et al.* performed a systematic review and meta-analysis of ischemia techniques in NSS. They selected 156 studies including 22,622 patients who underwent OPN, LPN, or RAPN. All the included studied reached a level 4 of evidence. When comparing cold ischemia, warm ischemia, and zero ischemia, this meta-analysis showed no differences in terms of EBL, local recurrence rates, and renal function impairment. Conversely, patients treated with cold ischemia showed a higher risk for complications in comparison with warm and zero ischemia. Notably, the PSM rate was significantly higher in patients treated with zero ischemia in comparison with those receiving cold or warm ischemia.[113] Previous functional data were recently confirmed by two RCTs comparing patients treated with off-clamp or on-clamp RAPN.[114,115] In 2019, Anderson *et al.* performed an RCT comparing off-clamp with on-clamp techniques in patients who underwent RAPN. The study showed that EBL, rates of pyelocalyceal repair, postoperative complications, and PSM rate were similar in the two arms. Moreover, the study did not show any difference between both groups in terms of 3-month change in postoperative eGFR or percent split renal function.[115] In 2021, Antonelli *et al.* failed to find any significant difference between on- and off-clamp in terms of 6-month absolute variation in eGFR as well as absolute variation in ipsilateral split renal function. Interestingly, in this RCT, a 14% and 43% crossover in the on- and off-clamp arms, respectively, was observed.[114] The use of off-clamp techniques might have limited advantages in healthy individuals with normal

kidney function. However, these techniques may be helpful in patients with a solitary kidney, preoperative CKD, or other medical comorbidities threatening long-term renal function. Unfortunately, studies evaluating these subgroups of patients are lacking.[114,115]

Although historically both the renal vein and artery were clamped, currently most surgeons perform an artery-only clamping to prevent renal damage in the long term.[116] Usually, additional clamping of the renal vein can be done to reduce the backflow from the IVC, especially for complex renal tumours located at the level of the right kidney. A recent meta-analysis including two retrospective and three prospective studies showed no difference in terms of WIT, transfusion rate, EBL, and early postoperative renal function between the renal artery–only and renal artery plus vein–clamping group during PN. However, a higher percentage decrease in eGFR at last follow-up was observed in the artery plus vein–clamping group.[116]

Most authors do not favour arterial reclamping during PN in order to avoid ischemia-reperfusion injury (IRI). IRI is, in fact, associated with an inflammatory and oxidative stress response caused by temporary obstruction of blood flow. Formation of reactive oxygen species released during the reperfusion phase initiates a cascade causing inflammation, cell death, and acute kidney injury (AKI). The pathophysiology of IRI is not completely understood but is known to play an important role in the genesis of AKI.[117]

Resection techniques

Maximization of volume preservation during PN is the most important surgical factor for optimizing post-PN functional outcomes, especially in healthy patients with normal function at baseline.[1]

Simple enucleation, standard enucleoresection, polar resection of tumours located at the level of the upper or lower pole, and wedge resection of tumours located at the level of the mid pole represent the most common resection techniques used to perform NSS in patients with renal parenchymal tumours.[118] The choice of the most appropriate technique is usually based on tumour dimension and location as well as on surgeon preference. Over the past decades, standard enucleoresection and simple enucleation have represented the most commonly adopted techniques regardless of the approach used (**Figure 8**). Standard enucleoresection is typically performed by sharp dissection through the parenchyma removing few (1–3) mm of healthy tissue surrounding the tumour. Some studies showed a consistent variability of the safety margins from the external area of the renal capsule to the deeper bottom of the tumour. Of course, thickness of safety margins around the tumour is also strongly influenced by several anatomical and topographical tumour characteristics.[119] Conversely, simple enucleation consists of blunt dissection along a plane between the pseudocapsule of the tumour and the normal renal tissue without inclusion of any visible normal renal parenchyma in the removed tissue.[120] A retrospective, multicentre, national study in 2011 demonstrated similar oncologic outcomes between simple enucleation and standard enucleoresection both for cT1a and cT1b tumours.[121] These findings were recently corroborated by a multicentre, prospective study comparing simple enucleation versus enucleoresection. This study showed that simple enucleation was associated with lower PSM rate, postoperative surgical complications, and AKI rate in comparison with standard PN.[122] The Surface Intermediate Base (SIB) protocol was proposed to standardize the

definition of the resection technique used based on the visual inspection of the gross pathological specimen.[123] However, it could be easier to group in two categories the enucleoresection techniques including 1–2 mm around the more cortical portion of the tumour, and the simple enucleation techniques including 0–1 mm of healthy parenchyma around the tumour. The so-called "minimal partial nephrectomy" could simplify this scenario respecting the concept that the extent of normal parenchyma removed around the tumour should be determined by surgeons according to individual clinical situation, tumour location, its topographical characteristics, and its interface with normal tissue (**Figure 9**).[9]

FIGURE 8 Enucleoresection technique with minimal amount of healthy parenchyma removed around the tumour. A) Open surgery; B) robotic surgery.

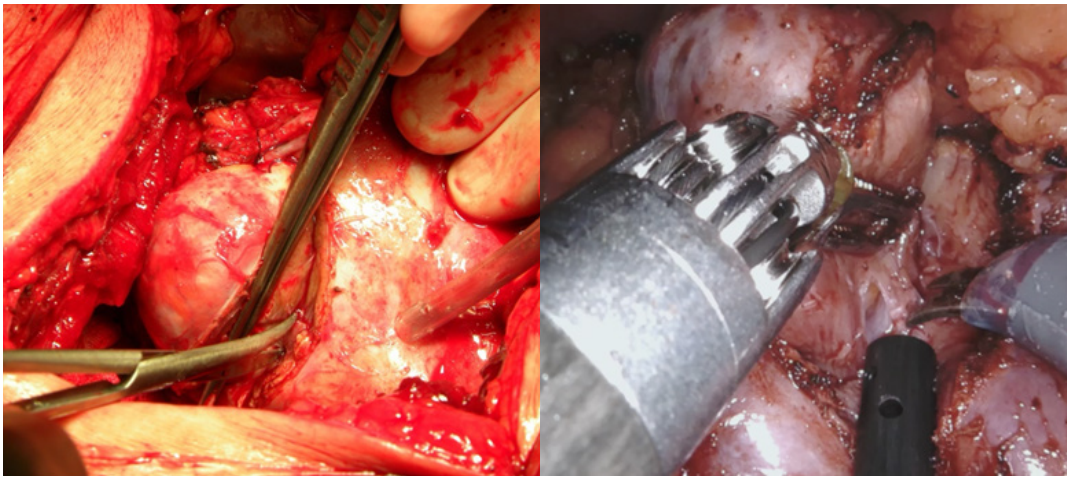
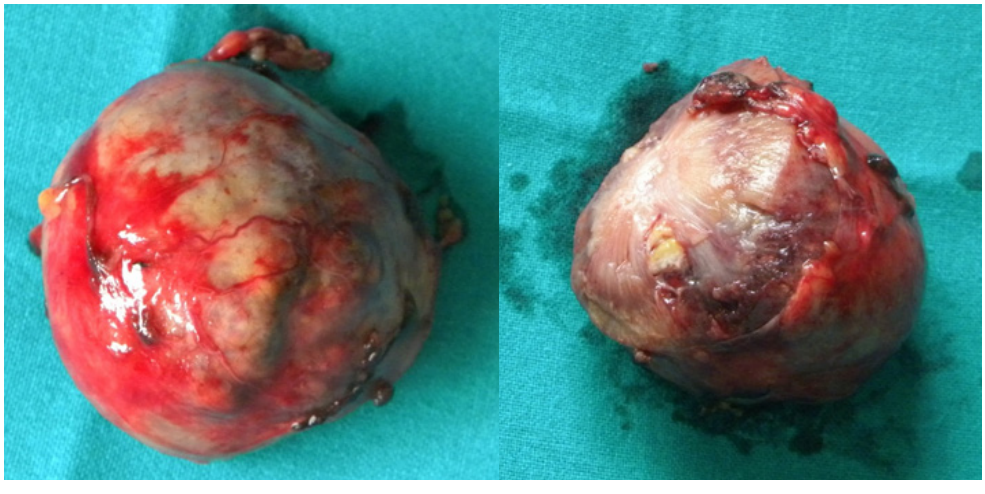


FIGURE 9 Parenchymal renal tumour 4 cm in size removed using minimal robot-assisted partial nephrectomy (RAPN): A) View from the exophytic portion; B) view from the tumour contact surface with the kidney.



Suturing techniques

After complete tumour resection, a renorrhaphy is usually performed to optimize hemostasis and to ensure closure of the urinary collecting system (UCS). There are no current guidelines on reconstruction techniques and most studies in this field are limited by short-time follow-up.[124]

When the UCS is opened during tumour resection, it should be closed separately with single re-absorbable clips (Absolok) or a 4-0 monofilament suture (**Figure 10**). Standard renorrhaphy consists of an inner (medullary) and an outer (cortical) suture (**Figure 11**).

FIGURE 10 Upper collecting system repair during open partial nephrectomy.

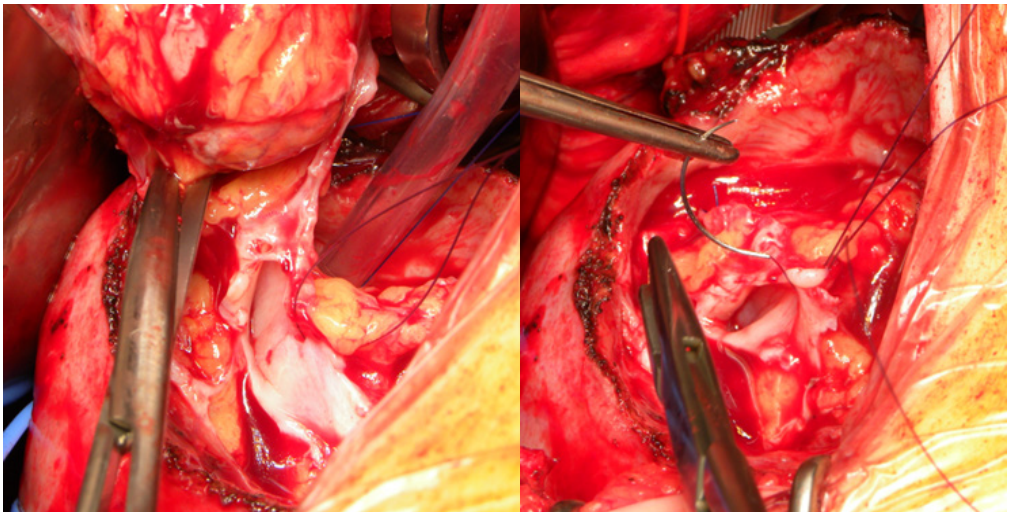
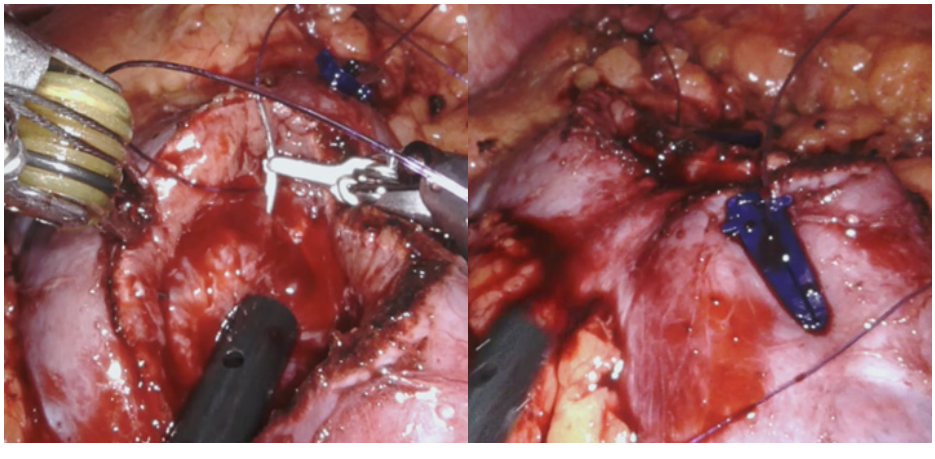


FIGURE 11 Inner (medullary) renorrhaphy performed by sliding clip technique and using Absolok clip.



The interlobar arteries could be injured during the inner suture, while the arcuate arteries could be damaged during the cortical sutures. The sliding clip technique is mostly used to secure the sutures.[125] Notably, in one study, the use of the sliding-clip technique during OPN was associated with better intraoperative and postoperative outcomes in comparison with the standard technique.[126] This technique has some advantages, such as a more precise control and readjustment of tension along the sutures, dividing pressure points.

A single-layer suture omitting the outer renorrhaphy can be considered in an attempt to preserve renal function. In a recent systematic review and meta-analysis, three studies comparing single- versus double-layer suture were considered.[127] This meta-analysis showed significantly shorter operative time and WIT in the single-layer group. However, EBL, perioperative complications, and rate of urinary fistula were similar in the two groups.[128]

Only selective sutures are applied where arterial bleeding is observed at the cortical level. Hypoperfusion can occur during cortical suturing, resulting in renal volume loss.[124] With the same rationale, interrupted sutures were proposed instead of running sutures. A recent meta-analysis showed that running sutures were associated with shorter OR, shorter WIT, and lower complication rates in comparison with interrupted sutures.[128]

Finally, the use of barbed sutures in comparison with no-barbed sutures was associated with significant advantages in terms of OR, EBL and WIT. No differences were observed in terms of rates of transfusion, postoperative complications, and urinary fistulae.[128]

A sutureless technique is sometimes performed to preserve the renal parenchyma and minimize any further damage during suturing. After tumour resection, bipolar or monopolar coagulation is used, combined with selective suturing if needed. A propensity-score–matched analysis comparing 29 patients who underwent sutureless RAPN with their counterparts receiving standard RAPN showed a similar rate of 30-day postoperative complications, trifecta outcome, and postoperative AKI. Conversely, sutureless RAPN showed better results in comparison with standard RAPN in terms of OR, length of stay, and 6-month renal function decline.[129] However, well-designed prospective studies are required to better assess the appropriate indications and perioperative outcomes of this technique.

Hemostatic agents can be used after renorrhaphy or after a sutureless technique to ensure adequate hemostasis. Human fibrinogen/thrombin-based collagen fleece (TachoSil®, Nycomed) and gelatin-based seals (Veriset™, Medtronic; FloSeal®, Baxter Healthcare) are some examples.[130] However, these hemostatic agents are expensive and are not always associated with lower rates of bleeding complications. Careful use in a case-by-case manner can therefore be important to limit potentially unnecessary operative costs.[131]

Follow-Up

Oncological follow-up after PN should be finalized mainly to rule out local recurrence or recurrence in the contralateral kidney as well as disease progression at the level of regional nodes or other organs (lung, liver, contralateral adrenal gland, bone, brain). Follow-up schedule following PN is mainly on the estimated risk for local and/or distant recurrence based on pathological stage or prognostic algorithms or nomograms.[8] The European Association of Urology (EAU) guidelines have adopted the Leibovich risk stratification algorithms distinguishing patients in three different categories: low, intermediate, and high risk for recurrence.

For tumours with low risk for recurrence (ccRCC Leibovich 0–2; non-ccRCC T1a or T1b grade 1 or 2), a first postoperative CT scan is scheduled 6 months after surgery and afterwards yearly up to 3 years after surgery. This protocol is further intensified for intermediate-risk tumours (ccRCC Leibovich score 3–6, non-ccRCC T1b grade 3 or 4), performing CT scans at 6 and 12 months, and then yearly up to 5 years postoperatively. In cases with high risk for recurrence (ccRCC Leibovich ≥ 6; non-ccRCC T2a - T4 or N1 disease), CT scans are performed 3, 6, 12, 18, and 24 months after surgery, and afterwards yearly until 5 years postoperatively.[8,132] Follow-up should be intensified in patients who have undergone PN for tumours larger than 7 cm or in patients with PSM at the final histopathologic examination.

During follow-up, patients who have undergone PN should be carefully evaluated also from the functional point of view by monitoring renal function and cardiovascular events, similarly to those who have undergone RN.

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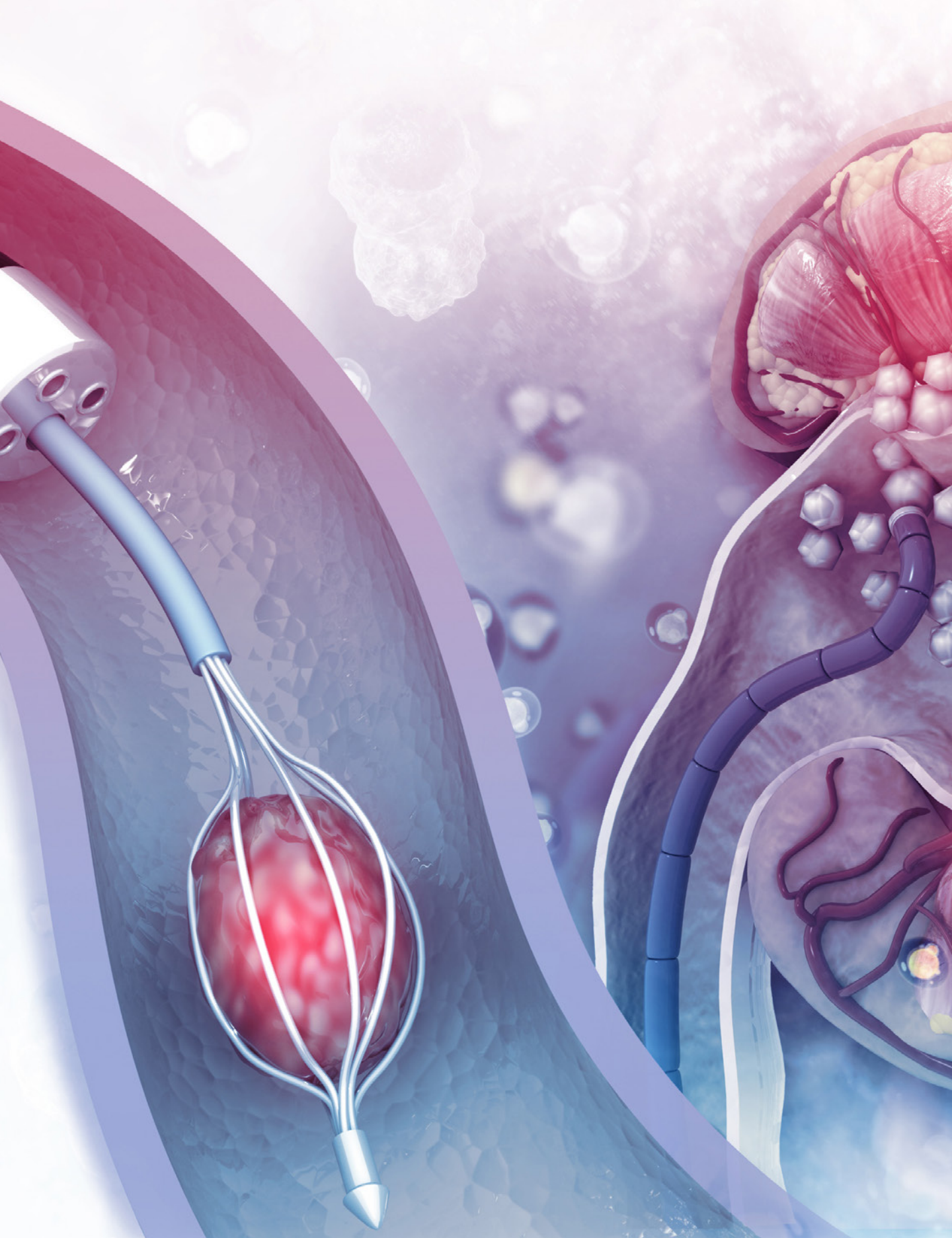

COMMITTEE 9

Ablative Therapies Including Stereotactic Ablative Body Radiotherapy (SABR) for Localized Kidney Cancer

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Introduction

Renal cell carcinoma (RCC) predominantly affects older adults, with a median age at diagnosis of between 60–65 years.[1,2] Surgery is the standard of care for primary RCC; however, a significant proportion of patients in this population have comorbidities that render them high risk from both anesthesia and surgical perspectives. Resection of the RCC, via either partial (PN) or radical nephrectomy (RN) is associated with varying degrees of postoperative nephron loss, with potential risk for long-term impairment of renal function, chronic kidney disease (CKD), and several other medical complications.[3–5] These risks are higher in patients with RCC involving a solitary kidney, those with increased risk for multifocal RCC tumours (for example, von Hippel-Lindau syndrome), and in patients with baseline CKD.

Active surveillance (AS) of small renal masses (SRMs) refers to routine radiologic assessment of the renal mass so that timely surgical intervention can be carried out in the case of rapid tumour growth. The current American Urological Association (AUA) guidelines recommend AS in cases where the anticipated risk for intervention or competing risks for death outweigh the potential oncologic benefits of active treatment, specifically in patients with limited life expectancy (less than 5 years), multiple competing comorbidities, poor baseline renal function, tumour size of less than 2 cm, and tumour growth kinetics of less than 5 mm/year.[6] Of the 785 patients enrolled to the prospective Delayed Intervention and Surveillance for Small Renal Mass (DISSRM) registry, 348 (44.3%) elected primary intervention while 437 (55.7%) elected AS. The 10-year cancer-specific survival (CSS) was not significantly different between the two arms (primary intervention, 99.2% vs. AS, 99.7%).[7] Over a median 3.3 years of follow-up, 67 (15.3%) patients in the AS cohort ultimately underwent delayed intervention.

In a retrospective study, involving 457 patients with 544 lesions, McIntosh *et al.* reported that SRM growth in up to one-third of patients may require delayed intervention.[8] In a large population-based cohort from the National Cancer Database, surgery, tumour ablation, and stereotactic ablative radiotherapy (SABR) were associated with significantly decreased risk for all-cause mortality, when compared to observation, with hazard ratios of 0.25 (95% confidence interval [CI], 0.24–0.26, $p<0.001$), 0.36 (0.35–0.38, $p<0.001$), and 0.56 (0.39–0.79, $p<0.001$), respectively.[9] Given the potential for aggressive behaviour as demonstrated by rapid increases in tumour size[10] and higher risk for cancer-specific mortality for early-stage RCC in older populations,[11] AS is not universally recommended for all patients with SRMs. Readers are advised to consult the chapter on AS for a detailed review of patient selection, recommended protocols, and outcomes.

For patients with SRMs who are not suitable for surgery, thermal ablation (TA) of their tumour can be considered. This approach leverages the physical cell–destroying properties of extreme temperature (either hot or cold) to incite necrosis in cancer cells. Over the past two decades, TA has been endorsed by multiple international guidelines for patients who are not suitable for surgery or have declined surgery.[12,13] The most frequently used TA technologies include radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation (CA), which use heat (RFA, MWA) and cold (CA), respectively, to induce lethal damage in tumour cells.

More recently, SABR, a form of hypofractionated radiation, which delivers high doses of radiation over a single fraction or a few fractions, has emerged as an alternative noninvasive treatment option for patients who are not suitable for surgery. Biological mechanisms likely responsible for the increased sensitivity of RCC to large fractional doses of radiation include novel apoptotic pathways, such as translocation of ASMase and production of proapoptotic ceramide, which result in rapid endothelial cell death within 1 hour of radiotherapy.[14–16] Recent European Society of Medical Oncology (ESMO) guidelines have endorsed SABR as a treatment option for patients considered unsuitable for TA.[12] The 2022 National Comprehensive Cancer Network (NCCN) version 1.0 Kidney Cancer guidelines state that "SABR may be considered for medically inoperable patients with stage I kidney cancer (category 2B) [and patients] with stage II/III kidney cancer (category 3).[17]

Thermal Ablation

Thermal ablation refers to the local application of thermal energy to a tumour with curative intent.[18] In TA of a renal tumour, the thermal energy is delivered directly into the tumour via an image-guided antenna/probe that is inserted percutaneously or delivered directly in cases performed via open or laparoscopic surgical exposure. Small (T1) localized renal tumours are well suited for ablation because of their generally rounded shape and relative isolation from temperature-sensitive structures in the retroperitoneum.[19] Given the *in-situ* nature of treatment, evaluation of treatment efficacy is determined by post-treated interval surveillance imaging via computed tomography (CT) or magnetic resonance imaging (MRI).

Since it was first described in the 1990s, single electrode RFA has demonstrated high efficacy in the treatment of SRMs less than 3 cm in maximal diameter. While initial reports demonstrated lower efficacy in tumours greater than 3 cm in size, subsequent technical advances such as the use of ablation probe arrays, coalescing ice balls, MWA, and embolization/ablation techniques have resulted in successful ablation of >3 cm renal masses.[19–24] While TA has traditionally been reserved for the treatment of patients who have contraindications to surgical extirpation via PN or RN, this approach is increasingly being adopted in selected patients as a primary treatment strategy in some tertiary care centres with established multidisciplinary teams. Over the past two decades, there have been significant advancements in TA technologies and techniques, resulting in improved oncologic outcomes, reductions in treatment-associated complications, and greater understanding of post-treatment surveillance following this approach.[19]

Indications and patient selection

Ubiquitous use of cross-sectional imaging has contributed to the increased detection of incidental localized SRMs.[25] These relatively indolent masses are commonly identified in older patients with multiple other medical comorbidities and CKD; conditions that may preclude surgical excision of the mass under general anesthesia.[25,26] Currently, the standard of care for patients with localized RCC is excision via PN or RN; however, international guidelines[27–29] support consideration of TA in the treatment of patients with a renal tumour <3 cm as a primary treatment modality.

Image-guided percutaneous techniques have been reported as the preferred treatment compared to laparoscopic approaches due to a lower risk for associated complications, shorter hospitalization and operative times, reduced morbidity, reduced opioid analgesic requirement, and faster recovery time.[30–34] This approach generally requires moderate sedation alone, rather than general anesthesia, and can be performed as an outpatient procedure in select patients, thereby providing a treatment alternative for patients who would otherwise be considered unfit for surgery. The average length of hospital stay following percutaneous TA is usually shorter (reported around 1–2 days) than traditionally reported for patients treated with radical or partial nephrectomy, especially via an open approach (mean 3–5 days) and similar to that of patients treated with contemporary minimally invasive partial and radical nephrectomies.[32,33,35] In a retrospective review involving 166 patients, Chen *et al.* reported a readmission rate of only 1% in patients who were discharged on same day post-ablation.[33,36] This finding has encouraged some centres to consider same-day discharge as a feasible approach.

Historically, TA has been reserved for patients that are poor surgical candidates due to renal insufficiency or comorbid conditions. However, TA has been found to be an effective treatment modality for patients with a solitary kidney, renal insufficiency, multiple tumours, or hereditary tumours (e.g., von Hippel-Lindau syndrome). Appropriate patient selection for TA is associated with oncologic outcomes that appear comparable to those observed with nephron-sparing surgery, albeit in the absence of randomized evidence.[30,34,37,38] Recent AUA and American Society of Clinical Oncology (ASCO) guidelines present TA and PN as potential alternatives for tumours <3 cm.[27,28] During patient counselling, the merits and risks of each treatment alternative must be compared, taking tumour morphology, local expertise, and patient preference into account.

Optimal tumour characteristics for ablation

The ABLATE score

The ABLATE score was developed to define patient-selection criteria for renal tumour TA and is specific to image-guided TA, incorporating salient anatomic renal tumour characteristics. These factors include (A) axial tumour diameter; (B) bowel proximity; (L) location within the kidney; (A) adjacency to the ureter; (T) touching renal sinus fat; and (E) endophytic or exophytic position.[39]

Axial tumour diameter (A)

Tumour size is one of the most important indicators for ablation outcome. Radiofrequency ablation and MWA have good oncologic outcomes for masses less than 3 cm. Masses measuring 3 to 4 cm may require repeated treatment or multiple probes and are highly operator dependent.[20–22,40] Microwave ablation should theoretically be able to treat larger tumours efficiently given the physics behind the larger active heating zone. Although T1b tumours have been treated with secondary efficacy rates up to 95%, current reports[40–43] are limited by small samples (the largest series included 56 patients).[44] High output centres have reported significant tumour control with single-session treatment for larger tumours using CA.[45–47] However, the upper size limit at which complete ablation can be expected remains to be defined. Moreover, larger tumours also have an increased risk for hemorrhage with TA modalities.[20,24]

Tumour location (BLAT)

The location of the tumour relative to adjacent viscera including the intestine, ureter, adrenal gland, liver, stomach, and pancreas should be ascertained to minimize unintended collateral thermal injury. Hydrodissection via instillation of saline and intentional patient positioning can move adjacent structures away from the tumour target to limit such damage.[39]

Tumours located in the upper pole can potentially result in thermal damage to the ipsilateral adrenal gland, resulting in a hypertensive crisis.[48] Conversely, when treating lower-pole tumours, proximity to the psoas muscle should be considered to avoid injury to the adjacent genitofemoral or lateral femoral cutaneous nerves.[39] Retrograde pyeloperfusion can be used to protect the ureter and pelvo-ureteric junction as the relatively cooler (RFA and MWA) or warmer (CA) solution perfusing through the collecting system minimizes the risk for thermal-associated ureteral injury.[39]

Due to their proximity with the larger renal vessels, centrally located tumours abutting the renal sinus fat are at increased risk for treatment failure.[20,49] The "heat sink effect" caused by these vessels, results in more rapid dissipation of the extreme temperature associated with the ablation procedure, thereby reducing its efficacy. Cryoablation provides better outcomes for centrally located tumours than RFA. For example, treatment of central tumours measuring 3 cm or less demonstrate a 3-year local tumour control rate of 98% with CA compared with only 78% with RFA.[50] Cryoablation has also been postulated to be less damaging to the collecting system than RFA in the case of central tumours.[51,52] Nevertheless, continuous irrigation of the collecting system and pelvis is recommended to provide additional protection against thermally induced injury.[53]

Exophytic or endophytic tumour (E)

Exophytic tumours are frequently surrounded by retroperitoneal fat, which insulates the temperature change within the tumour following ablation. In addition, their increased distance from central vessels mitigates any heat sink effect. Therefore, depending on size, exophytic tumours can be successfully ablated in a single session.[20,21] Endophytic tumours, on the other hand, are surrounded by renal parenchyma through which temperature gradients may dissipate more rapidly, leading to an association with increased treatment failure.[39,54]

Other tumour considerations

The effect of ablative therapies on tumours varies and is partially explained by differences in tissue perfusion, electrical conductivity, impedance, heat sensitivity in different cells, and the heat sink effect.[20,55–57] For example, less-vascularized tumours (papillary RCC, oncocytomas) may theoretically be easier to ablate in comparison to highly vascularized tumours (clear cell RCC).[49,57,58]

Percutaneous TA is an accepted treatment for solid renal neoplasms,[27–29] but the published experience on ablating cystic renal tumours is limited.[59–61] The theoretical potential risk for cyst puncture and spillage of contents resulting in tumour seeding in the ablation tract are cited as reasons why percutaneous TA is less frequently undertaken for the treatment of cystic renal masses.[62] This concern was challenged by two small cohort studies (n=40 and n=23) in which cystic renal masses were successfully treated with no observed tumour seeding.[60,62] Critics of these studies cite the studies' modest follow-up (median < 3 years).[59–62]

To summarize, small (<3 cm) exophytic solid renal masses, with a minimum of 1 cm distance from adjacent anatomic structures, represent an ideal morphologic candidate for percutaneous tumour ablation.

Renal tumour scoring systems

Several cross-sectional imaging-based classification systems have been developed to describe renal tumours in a standardized quantitative manner and are predictive of complications and recurrence as well as tumour histopathological features following PN.[63–68] These scoring systems allow comparison between tumour populations, aid tumour demarcation for treatment, and facilitate communication between clinicians and patients. Although initially used to inform surgical indications and characterize tumours in surgical outcome studies, renal tumour scoring systems are now also widely used to plan ablative treatment strategies.

Tumour size and location within the kidney relative to other structures are the most common features incorporated in scoring systems to communicate the tumour's complexity. The most commonly used scoring systems are the R.E.N.A.L nephrometry score (RNS)[64] (**Table 1**) and PADUA classification.[69]

TABLE 1 Points Assigned to Each Parameter According to the (Modified) R.E.N.A.L Nephrometry Score

R.E.N.A.L nephrometry score			
	1 point	**2 points**	**3 points**
(**R**)adius	<4 cm	4–7 cm	>7cm
(**E**)xo-/endophytic location	≥50% exophytic	<50% exophytic	Entirely endophytic
(**N**)earness of the tumour to the collecting system/sinus (mm)	≥7	>4 but <7	≤4
(**A**)nterior/posterior location	No points given; tumour is assigned a suffix according to location relative hilar vessels A = anterior, P = posterior, X = midline		
(**L**)ocation relative to the polar lines	Entirely above the upper or below the lower polar line	Lesion crosses polar line	>50% of mass is across polar line; or mass crosses the axial renal midline; or mass is entirely between the polar lines
Modified R.E.N.A.L nephrometry score (As above but with modified size limits for the Radius parameter)			
(**R**)adius	<3 cm	3–4 cm	>4 cm
Interpretation Score of 4–6: low complexity Score of 7–9: moderate complexity Score of 10–12: high complexity			

The RNS has been revised in the modified R.E.N.A.L nephrometry score (m-RNS)[70] and is now adapted to smaller-sized T1 tumours, normally considered for ablation. In these scoring systems, different anatomical tumour parameters are assigned points and summed to a total score. A higher score reflects greater tumour complexity.

RENAL nephrometry score has the advantage of high interobserver reliability across specialties and various levels of training.[71,72] A higher RNS score is associated with increased risk for local treatment failure and treatment-associated complications.[73–75] However, the E and N parameters are not fully independent of each other, as an endophytic tumour is more likely to be closer to the collecting system than an exophytic one. Thus, a purely endophytic small lesion above the polar line would have the same total RNS as an exophytic lesion between the polar lines; however, the latter would be expected to be easier to ablate.

The PADUA classification is based on a similar principle, providing a general assessment of the tumour's growth pattern in relation to the collecting system and sinus, rather than measuring the distance between the two as in the RNS. The polar lines are evaluated on axial images alone, while the RNS also requires coronal views.

While the RNS and PADUA systems correlate to different surgical outcomes, the m-RNS may be a better choice for predicting outcomes post-ablation.[70] These scoring systems are not specific for ablation and warrant further validation. Interestingly, Maxwell *et al.* observed that maximum tumour size alone outperformed both RNS and PADUA for prediction of local tumour recurrence after renal tumour ablation.[76] Nevertheless, the use of classification systems in a multidisciplinary setting permits description of SRMs in a standardized fashion and has the potential to improve communication and decision-making, and may facilitate patient education regarding treatment expectations and complication risks. These systems are also helpful from a research standpoint, permitting more granular quantitative characterization of tumours.

Procedure and technical consideration

Pre-procedure planning

Prior to TA, a patient should undergo a standard evaluation including a detailed history particularly documenting relevant comorbidities and functional status, physical examination, documentation of any known risk factors for RCC, and family history of hereditary RCC syndromes. Relevant laboratory work should be obtained including evaluation of coagulative profile and renal function.[77] The AUA/SUO guideline for the management of SRMs recommends that all patients who elect TA for the management of their renal mass should undergo a biopsy prior to TA to obtain a histologic diagnosis of the tumour to inform post-treatment surveillance.[27]

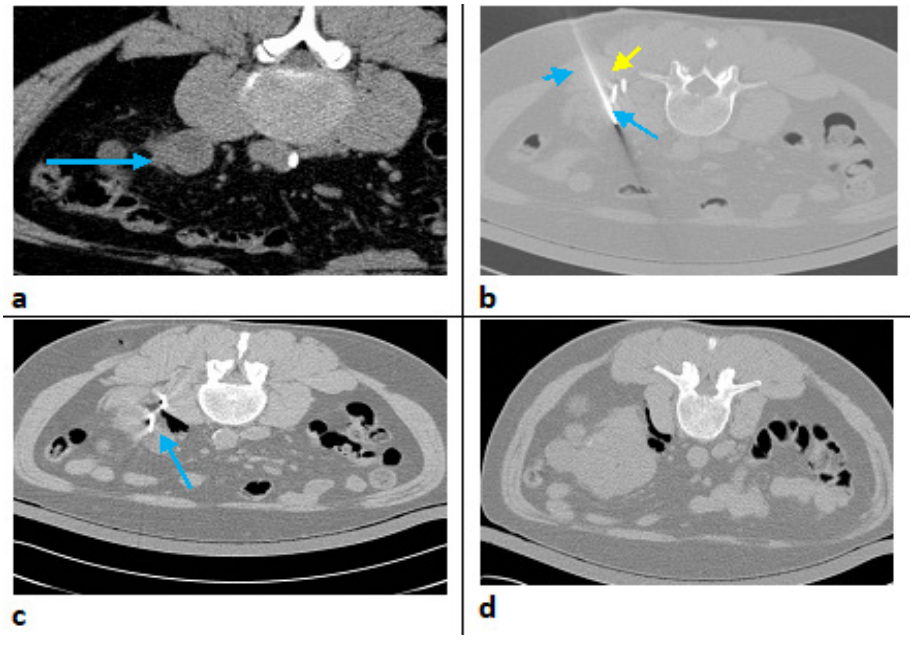
There are several tumour and patient-related factors associated with successful TA of a renal tumour with minimal complications in a single session. Careful pre-procedural imaging guides a feasibility of the procedure, and informs decision regarding the access site, number of probes needed, location of the tumour relative to other structures, and the need for any ancillary procedures.[18,78] The choice of imaging modality relies on the operator's preference. Computed tomography is normally the modality of choice for procedural planning and

guiding. Although MRI can be used, it is more expensive and time-consuming, is not always available, and is more technically demanding. Ultrasound alone allows direct monitoring during probe placement; however, visualization of adjacent structures can be limited with ultrasound evaluation, and upon initiation of TA, loss of visualization of the target is common because of gas formation. Thus, it is commonly used in combination with CT.[78,79]

Other technical considerations

Percutaneous ablation can be performed under either general anesthesia or conscious sedation. As renal tumour ablation is usually performed with the patient in the lateral, semi-prone, or prone position, careful monitoring of the airway during conscious sedation is necessary. Tumours close to the bowel or ureter may increase the risk for pain or require techniques such as tissue displacement through hydrodissection and injection of gas (**Figure 1**).[80] Choice of ablation technique may be influenced by patient comfort. Cryoablation is associated with less patient-reported discomfort than RFA,[81] and RFA is associated with less discomfort than MWA.[82] General anesthesia may be employed in situations that require a controlled environment for the operator or according to patient preference.

FIGURE 1 Example of patient requiring tissue displacement prior ablation. A 43-year-old woman with prior history of von Hippel-Lindau syndrome and polycystic kidneys was treated for a 2.6-cm exophytic tumour in the lower pole of the left kidney. On the day of the procedure, the tumour (arrow) is seen in contact with the psoas muscle when the patient is examined in the prone position (a). Two microwave ablation (MWA) probes are inserted in the tumour (blue arrows), and through a spinal needle (yellow arrow) (b) carbon dioxide (c, arrow) is insufflated and the tumour is displaced from the psoas muscle (c, d).



Source: Images courtesy of A/Prof Shankar Siva, Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria; Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia.

Conscious sedation is generally preferred for patients with severe cardiopulmonary dysfunction to avoid the physiologic stresses of intubation; however, insufficient pain control may result in procedure interruptions resulting in incomplete ablation.[80,83] Selective nerve blocks of the quadratus lumborum can mitigate intra- and post-procedural pain.[82] Finally, local expertise, resources, and experience will influence the choice of anesthesia method.

Tumour biopsy prior to ablation

Although some guidelines recommend renal tumour biopsy prior to ablation,[27,29] others recommend biopsy only when it may alter the course of management.[28] Different strategies are applied in clinical practice; renal biopsies can be performed as a separate event, prior to ablation, or immediately prior to ablation. Obtaining the biopsy prior to treatment avoids overtreatment and minimizes uncertainties regarding follow-up in the case of nondiagnostic results. On the other hand, obtaining a biopsy subjects the patient to the risks associated with the procedure including pain, bleeding, infection, and injury to surrounding organs, as well as risks associated with anesthesia, if it is used. There is also a risk for an indeterminate biopsy in up to approximately 10% of patients[84] or a false-negative biopsy due to sampling error. Performing the biopsy immediately before the ablation is advantageous in that both procedures are performed in one session. Regardless of when the biopsy is performed, a balanced discussion of the risks and benefits of biopsy should be had when obtaining informed consent.

Common thermal ablation techniques

Radiofrequency ablation (RFA)

RFA transmits a high-frequency (300–500 kHz) alternating electrical current that induces ionic agitation resulting in frictional heat within the targeted tissue. The vibrating molecules are the source of heat.[85] The heat accumulation due to the frictional force adjacent to the electrode propagates radially, resulting in tissue death immediately adjacent to the electrode. Tissue destruction and subsequent coagulative necrosis occur at temperatures above 55°C, with immediate cell death occurring at 60°C. Temperatures above 100°C result in tissue vaporization and carbonization, which act as an insulator impairing heat propagation thereby limiting the ablation zone. It is therefore optimal to maintain a constant temperature of 60–100°C in the target tissue throughout the procedure.[77,85,86] Variations in tissue impedance can result in variability in the size and shape of the ablation zone. Ablating near vascular structures is associated with heat loss in the adjacent ablation zone, which induces a heat sink effect that can minimize the ablation efficacy through dissipation of the temperature gradient.

Microwave ablation (MWA)

In MWA, cell death is achieved through a heat-based mechanism like in RFA. The oscillating microwave electromagnetic field radiating from the antenna forces polar molecules, such as water, to rotate billions of times per second, increasing their kinetic energy and temperature. Microwaves can propagate through high-impedance tissues, allowing larger zones of active heating. Compared to RFA, MWA is less affected by the heat sink effect and can achieve faster ablation over large ablation zones.[77,85] Subjectively, due to the efficiency of the heat generation, patients undergoing MWA may experience more pain and require more analgesia during treatment.[87]

Cryoablation (CA)

Cryoablation relies on low temperatures to achieve cell death. Expanding gases within the needle-like cryoprobe leads to rapid cooling of the probe. A drop in temperature is achieved close to the tip of the antenna, which cools the probe to −160°C or lower. Ice-ball formation can be visualized during treatment, giving a rough estimate of the ablation zone that assists in avoidance of inadvertent treatment of critical structures and complete treatment of the tumour. Rapid ice formation in the centre of the ice ball causes direct cell injury. The slower extracellular ice formation in the periphery results in an osmotic denaturation of the cells. Freeze-thaw cycles induce microvascular injury and endothelial damage. Multiple cryoprobes can be used simultaneously to sculpt the ablation zone to the shape of the tumour. The disadvantages to this approach include an increased risk for hemorrhage upon the melting of the frozen tissue and the requirement of medical-grade argon gas canisters to facilitate the exothermic reaction.[19,87,88]

The key advantages and disadvantages between ablative techniques are summarised in **Table 2**.

TABLE 2 Advantages and Disadvantages Between Ablative Technologies

	Advantages	Disadvantages
RFA	• Most commonly used system • Short treatment time (12–30 min ablation time)	• Treatment of maximum 3-cm tumours • More affected by heat sink effect • RF current may be redirected to high electrolyte content of urine
MWA	• Achieves larger ablation zones than RFA • Quicker than RFA (5–8 min ablation time) • Less affected by heat sink effect	• Newer system, needs further validation but principles of thermal coagulation same as RFA • More painful than RFA
CA	• Can treat larger tumours (>4 cm) • Can treat central tumours • Real-time monitoring of ice ball (however not reflective of the zone of cell death)	• Requires several probes, increased risk for post-procedural hemorrhage • Argon (and possibly helium) canister required • Time-consuming (30–40 min ablation time)

Abbreviations: CA, cryoablation; MWA, microwave ablation; RFA, radiofrequency ablation.

Clinical outcomes

Local tumour control

Current literature suggests that careful patient and tumour selection can result in successful ablation of nearly all tumours, with low tumour recurrence rates over short and intermediate follow-up. To date, TA has not been

compared to surgery in the randomized controlled trial setting. As such, the available (retrospective) data is potentially limited by selection bias, unmeasured confounding, institution-specific practices, and expertise with the potential for limited generalizability across centres. Indeed, surgery is stereotypically favoured for healthier patients while ablation is traditionally preferentially offered to patients with a high burden of comorbidity or limited projected life expectancy, who therefore would be at greater risk for adverse events following surgery and/or general anesthesia. The sum of the comparative efficacy data to date suggests comparable oncologic and safety outcomes between TA and RN or PN for T1a disease.[89]

Long-term studies

The largest cohort of patients treated with TA has been reported by Andrews *et al.* (2019). After their retrospective review of 367 sporadic cT1 renal ablation-treated tumours, (180 RFA, median follow-up, 7.5 years; 187 CA, median follow-up, 6.3 years), the 5-year local recurrence-free survival rate was 95.9% and 95.9%; and the CSS rate was 96% and 100%; for RFA and CA, respectively.[37]

Psutka *et al.* (2013) retrospectively reviewed a cohort of 185 sporadic T1 RCC patients treated with percutaneous RFA. After a median follow-up of 6.43 years, only 12 (6.5%) local recurrences were observed. For T1a tumour, the 5-year recurrence-free and disease-free survival (DFS) was 96.1% and 91.5%, respectively. Higher tumour stage was independently associated with poor DFS.[38]

Georgiades *et al.* (2014) prospectively followed 134 biopsy-proven RCC patients, treated with percutaneous CA. The median tumour size was 2.8cm ± 1.4 cm. The 5-year efficacy and CSS were 97% and 100%, respectively, while the overall complication rate was only 6%.[47] In another retrospective study, Yu *et al.* (2021) reviewed 323 patients with 371 biopsy-proven RCC, with a mean diameter 2.9 cm ± 1.2 cm. The patients were treated with ultrasound-guided percutaneous MWA and followed for a median of 5 years. Only 7 (2.2%) cases of local tumour progression were found at a median of 20 months. The 5-year DFS was 85.2% and 69.1% for cT1a and cT1b tumours, respectively.[41]

Comparative studies

Multiple authors have attempted to characterize the comparative effectiveness of TA versus PN in retrospective cohorts. Zangiacomo *et al.* (2021) reported treatment outcome in 85 biopsy-proven T1a RCC surgical candidates who were treated with percutaneous TA. With median follow-up of 56 months, the authors observed only four (4.7%) local recurrences with no distant metastasis.[90] In a retrospective review, Andrews *et al.* (2019) compared outcomes for 1,424 RCC patients of whom 367 were treated with percutaneous ablation (RFA or CA), and the remaining 1,055 underwent PN. There was no difference in CSS for patients with T1a disease, with 5-year CSS of 96%, 100%, and 99% for RFA, CA, and PN, respectively. For the 376 patients with cT1b disease, 5-year CSS was 91% for CA and 98% for PN. However, higher RCC mortality was observed for CA compared to PN in this subset. The authors noted that there was increased risk for cancer-specific mortality with CA in patients with cT1b RCC and that further work was needed to appropriately characterize the oncologic efficiency of CA in pT1b disease. Acknowledging the limitations inherent in this retrospective analysis including selection bias and unmeasured

confounding, the authors concluded that any clinically significant difference between ablation and PN of cT1a tumours is unlikely and that treatment selection should be performed following shared decision-making.[37]

In a systematic review and meta-analysis of 107 studies (the majority being retrospective studies), Pierorazio *et al.* (2016) summarized the comparative effectiveness of AS, TA, and RN or PN for primarily T1 tumours. The authors noted a higher risk for local recurrence following TA; however, they noted no significant difference when including secondary ablations. They also noted that TA was associated with less perioperative morbidity and complications compared to PN. There was no difference in the CSS across the different management options.[89] Similar findings were reported in another systematic review and meta-analysis of surgery and ablative techniques for T1 tumours.[30] Thus, contemporary retrospective data supports consideration of TA as an effective alternate approach to surgery.

Post-treatment renal function

The aim of nephron-sparing approaches to RCC is successful resection or ablation of the tumour while preserving normal renal parenchyma and therefore, renal function (glomerular filtration rate [GFR]) to minimize the risk of end-stage renal disease (ESRD) and the potential risk of need for renal replacement therapy.[29,91] Renal parenchymal volume preservation is one of the most important determinants of renal function, while ischemia time during surgical resection plays a secondary role.[92,93] Percutaneous TA has the advantage that it does not require temporary vascular clamping, which is commonly required during PN.[92,93] Furthermore, the sphere-shaped ablation zone can be tailored to the size of the tumour, with the goal of minimizing collateral damage to the adjacent normal renal parenchyma.

Studies assessing GFR and creatinine values to compare renal function following surgical resection and TA have conflicting results. These can partially be explained by renal compensatory mechanisms and differences in pretreatment characteristics between treatment arms.[94–97] Conversely, studies assessing renal function using techniques such as radioisotope renography or split renal function based on contrast-enhanced CT have reported results favouring ablation.[34,98] This has led some authors to conclude that TA is the treatment of choice in the patients with compromised renal function where dialysis and/or nephrectomy is not desired.[27,29]

Peri- and post-procedural complications

Thermal ablation is generally considered a safe procedure with a low risk for major complications. A systematic review and meta-analysis reported a lower complication rate for TA (7.4%) compared to surgery (11%).[30] Similarly, the post-ablation incidence of major complications was lower compared to that observed following PN (2.3 vs. 5%).[30,99] Centrally located tumours near the renal pelvis or a major calyx are prone to a higher risk for postoperative complications from thermal injury, with the most observed complications including ureteral strictures, hydronephrosis, urinomas, or perinephric abscesses.[99,100]

Complications during ablation of renal tumours may include:

1. **Constitutional Symptoms:** During recovery, patients can experience a post-ablation syndrome that is characterized as a transient and self-limited period of fevers, nausea, vomiting, and malaise. Larger volumes of necrosis are associated with prolonged symptoms. Less than 10% of patients experience the full spectrum of symptoms, while up to 60% report flu-like symptoms within the first 10 days following ablation.[101]
2. **Bleeding:** The most common complication following TA is minor bleeding. The incidence of hematomas is around 6%, while massive hemorrhage requiring transfusion is extremely rare (<1% of cases).[20,24,78] Some cases may require embolization for bleeding, which is often related to treatment of highly complex tumours.[24,47,78]
3. **Hematuria:** The incidence of post-ablation hematuria is rare, with reported incidence of 0.5–1%.[78] It often resolves within 12–24 hours, but if persistent then thermal damage to the pelvicalyceal system should be suspected. In the case of persistent hematuria causing hydronephrosis due to clot obstruction, placement of a ureteric stent and/or manual irrigation of the bladder may be necessary.
4. **Ureteric/Collecting System Injury:** Careful planning is needed to avoid ureteric thermal injury when ablating central tumours close to the ureter or pelvicalyceal system, as mentioned previously. Although rare (1–3%),[78] injury can result in ureteric strictures, urine leak, urinoma, or formation of a urinary fistula.[24,32,78] Such injuries may not be apparent until weeks or months after treatment. Strictures may result in obstructive uropathy, hydronephrosis, and renal atrophy if undiagnosed. Prolonged obstruction may also predispose patients to developing pyelonephritis or chronic infections ultimately leading to need for nephrectomy. Pelvicalyceal urinary leaks and urinomas may require maximal urinary decompression with placement of a urinary stent and Foley catheter or percutaneous nephrostomy tube as well as perinephric drainage. Chronic leaks may require nephrectomy.
5. **Neuropraxia:** Nerve injury (1–3%) can occur following ablation of tumours close to the psoas muscle, or intercostal or lumbar nerves.[78] Such injuries may manifest as changes in sensation, paresthesia, pain, or numbness, following the dermatomal pattern of the affected nerve. One study found that nerve injury resolved in 90% of affected patients within 6 months.[24]
6. **Infection:** Infectious complications are uncommon (<1%),[78,102] and prophylactic antibiotics are routinely recommended prior to renal tumour TA. However, prophylactic antibiotic use can be considered for patients with diabetes, with a prior urinary diversion using a segment of intestine or in patients requiring ureteric stent for pyeloperfusion.[78]
7. **Bowel injury/perforation/ureteroenteric fistula:** This is an extremely rare but potentially life-threatening complication (<1%),[78] resulting from thermal damage to the adjacent bowel (commonly the colon or duodenum. Injury to the bowel can be prevented by hydrodissection or CO_2 dissection to displace the at-risk bowel segment away from the renal tumour.[20,55] Surgical consultation and resection of the affected bowel segment is generally indicated if bowel injury is suspected or detected.

Other complications include pneumothorax, skin burn or freeze at the site of entry, and tumour seeding along the entry site.[19,24,33]

Post-ablation imaging and monitoring

The aim of post-procedural surveillance is to assess tumour response, exclude any immediate or late complications, and to evaluate renal function. There is no universally recommended surveillance plan. ESMO and the European Association of Urology (EAU) recommend follow-up 3–6 months for the first 2 years and every 6–12 months for the subsequent 3 years.[29,103] At each visit, clinical evaluation includes an assessment for pain, the ability to pass urine, presence of hematuria and/or fever, evaluation of kidney function, and examination of the skin entry point.[78]

As treatment with percutaneous ablation is *in situ*, ongoing oncologic surveillance imaging is required to assess the cancer control and rule out local recurrence post-procedure. Generally, patients are followed using analogous protocols to those followed after PN, but with additional imaging during the first year.[104] A follow-up contrast CT at 1 and 3 months after ablation evaluates for residual disease and need for retreatment. If no evidence of residual disease is detected after the first scan, follow-up scans should be performed at intervals including 1, 3 and 5 years. Computed tomography protocols should include non-contrast, arterial, nephrographic, and delayed (10 min) excretory phase images. There should be no contrast enhancement in the treated lesion; any nodular enhancement of ≥15 HU is concerning for residual disease (or disease progression).[78] Contrast-enhanced ultrasound can be performed when CT with contrast is contraindicated. In the case of contraindications to contrast-based CT, MRI can be considered as an alternative modality. On MRI, the successfully ablated tumour maintains T1 signal hyperintensity (associated with coagulative necrosis) and is non-enhancing, while it will appear hypointense compared to normal renal parenchyma T2-weighted images.[78,105]

Due to the possibility of delayed post-ablation recurrence, some authors advocate for lifelong imaging after treatment. One study reported local tumour progression 5 years post-treatment.[106] The frequency and duration of imaging should be planned with due consideration of the patient's radiation exposure while taking the oncologic potential of the tumour into account. Surveillance protocols can also be adapted to each patient's competing risks for other-cause mortality, as has been recommended following surgical treatment of RCC.

A benign "halo sign" comprising a thick rind of fat and then a thin rim of fibrous tissue is seen in up to 75% of lesions following treatment. This is more commonly seen in patients with exophytic tumours. This appearance is generally observed approximately 6 months after treatment and may persist on subsequent imaging.[78]

After ablation, the tumour often gradually decreases in size, with the greatest size decline during the initial 6 months.[105] Any increase in the size of the treated zone on immediate post-treatment imaging should raise suspicion for local recurrence or persistence of tumour.[105] Persistent contrast enhancement suggests presence of residual tumour. However, benign peri-ablative enhancement, due to the reactive hyperemia and granulation reaction in the surrounding tissues, can be seen for up to 3–6 months after ablation. Conversely, any nodular enhancement developing within or at the margin of the ablation zone that persists beyond 3 months should raise suspicion for residual tumour.[105]

A few different definitions of treatment success have been suggested; therefore, the Society of Interventional Radiology (SIR) has proposed a standardized terminology and reporting criteria for image-guided tumour ablation.[18] This terminology (**Table 3**) helps to facilitate communication and comparisons among different treating physicians.

TABLE 3 Definitions of Ablation Treatment Outcome According to the Society of Interventional Radiology (SIR)[18]

Term (unit)	Definition
Technical success	Whether the tumour is completely covered by the ablation zone during treatment and treated according to protocol
Technique efficacy	Refers to treatment outcome demonstrated with appropriate clinical follow-up. It is assessed at a prospectively defined time point (e.g., 1 week or 1 month after ablation) at which complete ablation, as evidenced by follow-up, has been achieved.
Primary efficacy rate (%)	The percentage of tumours successfully ablated after the initial procedure (or defined course of treatment)
Secondary efficacy rate (%)	Includes tumours that have been successfully ablated after retreatment of identified local tumour progression
Residual unablated tumour	Any residual tumour found at the ablative margin at the time of initial follow-up
Local tumour progression	Found at the edge of the ablation zone, when at least one contrast-enhanced study has documented absence of viable tumour within the treated area
Local tumour recurrence	The presence of new tumour foci at the ablative margin after successful complete tumour eradication with ablation

Stereotactic Ablative Radiotherapy (SABR)

Renal cell carcinoma was historically considered as one of the most radioresistant tumours when treated with conventional fractionation. However, *in vitro* cell culture studies revealed that ablative doses of radiation can effectively eradicate RCC cells with an exponential decrease in survival observed at doses over 6 Gy.[107] This finding was supported by further work in mouse models with implanted human RCC cell lines.[108] Similarly, a systematic review on clinical outcomes associated with the use of SABR in extracranial metastatic RCC reported a weighted crude local control (LC) of 89%.[109]

Over the past decade, multiple, retrospective, and prospective phase 1 and 2 studies have demonstrated demonstrating feasibility, safety, and efficacy of SABR.[110–121] In 2016, eight different institutions with prior published experience in kidney SABR from Australia, Germany, Japan, Sweden, Canada, and the United States

collaborated to form the International Radiosurgery Oncology Consortium for Kidney (IROCK). This group provided a consensus statement for SABR in localized primary RCC.[122] The results of selected published studies are summarised in **Table 4**.

TABLE 4 Summary of Prospective and Retrospective Studies Evaluating SABR for the Definitive Treatment of Small Renal Masses

Author/ year	Type of study	Inclusion criteria/ Tumour size	Number of patients	Dose/ fraction	Local control*	Median follow-up
Grubb *et al.* (2021)[120]	Prospective clinical trial (phase 1)	Localized RCC, poor surgical candidates due to medical comorbidities/median maximum tumour diameter 3.7 cm (range, 1.7–9.5 cm)	11	48 Gy/3 fractions 54 Gy/3 fractions 60 Gy/3 fractions	3-year local control, 90%	34.3 months
Tetar *et al.* (2020)[121]	Retrospective cohort study	High surgical risk due to comorbidity, Patient preference, CKD/median tumour size 5.5 cm (2.4–9.3)	36	40 Gy in 5 fractions	1-year local control, 95.2%	16.4 months
Siva *et al.* (2017)[113]	Prospective clinical trial (phase 1)	ECOG 0–2, single lesion, medically inoperable or high risk for surgery due to likelihood of dialysis or refused surgery/ median tumour size 4.8 cm (range 2.1–7.5)	33	26 Gy/1 fraction for tumours ≤5 cm 42 Gy/3 fractions for tumours >5cm	2-year local control, 100%	24 months
Kaidar-Person *et al.* (2017)[119]	Retrospective cohort study	Non-surgical candidates/ tumour size >4 cm	6	39 Gy in 3 fractions	100% local control	NA†
Chang *et al.* (2016)[111]	Retrospective cohort study	Any primary tumour treated with SABR/ median tumour size 4.0 cm (range, 1.0–14.6 cm)	16	30–40 Gy in 5 fractions	100% local control	19 months

TABLE 4 Summary of Prospective and Retrospective Studies Evaluating SABR for the Definitive Treatment of Small Renal Masses *(Cont'd)*

Sun *et al.* (2016)[118]	Retrospective cohort study	Any primary tumour treated with SABR/mean maximum tumour diameter 3.9 cm (range, 1.6–8.3 cm)	40	21–48 Gy in 3 fractions	92.7% local control	NA†
Ponsky *et al.* (2015)[117]	Prospective clinical trial (phase 1)	Poor surgical candidates, KPS >60/median tumour volume was 57.9 cm (range, 13.8–174.7 cm)	19	24–48 Gy in 4 fractions	No evidence of local progression in 15 evaluable patients	14 months
Staehler *et al.* (2015)[114]	Prospective case-control study	Unable to spare kidney during surgery/size <4 cm	40	25 Gy/1 fraction	9-month local control, 96%	28 months
Pham *et al.* (2014)[116]	Prospective clinical trial (phase 1)	ECOG 0–2, single lesion, medically inoperable or high risk for surgery due to likelihood of dialysis or refused surgery/ NA†	20	26 Gy in 1 fraction	Not reported	NA†

*Local control is defined as absence of progression.

†Not available.

Abbreviations: CKD, chronic kidney disease; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Status; SABR, stereotactic ablative radiotherapy.

Indications and patient selection

Chronic kidney disease and high-risk patients for surgery

Current published studies have evaluated the safety and efficacy of SABR in patients with localized RCC who are inoperable, those who refuse surgery, and those with baseline CKD and high risk for renal replacement therapy with PN or RN, as well as in patients with bilateral renal tumours. In a prospective case-control study, Staehler *et al.* treated 40 patients with renal masses who were anticipated to require dialysis if they underwent nephrectomy, with single fraction 25 Gy SABR.[114] After a median follow-up of 28 months, the authors reported good local tumour control, with minimal decline in renal function. In another study of 21 patients of whom 9 were considered high risk for end-stage renal failure if treated with surgery, researchers observed only a

moderate decline in renal function post-SABR, with mean change in GFR of +0.6 ± 11.3, +3.2 ± 14.5 and −8.7 ± 13.4 mL/minute (p=0.03) at 2 weeks, 3 months, and 1 year, respectively (123). While these studies are limited by small sample size, the preliminary results suggest that SABR is a safe alternative to surgery in patients who are at high risk for dialysis following surgical resection of their renal mass.

Of note, in patients with preexisting stage 4–5 CKD, progressive renal dysfunction has been observed following treatment with SABR.[111] The ongoing, large, phase 2 study TROG 15.03 (FASTRACK II) limits inclusion of patients to those with estimated GFR (eGFR) of ≥30 mL/minute.[124] Ultimately, post-treatment renal function reflects the underlying disease processes responsible for CKD, baseline renal function, as well as the tumour volume and location, and the amount of surrounding parenchyma at risk for radiation-related damage. As the exact safety-threshold level has yet to be determined, patients with CKD 4–5 at baseline undergoing SABR should be counselled regarding the risk of ESRD following treatment and potential need for renal replacement therapy.

Solitary kidney

Treatment of RCC in a patient with a solitary kidney is a challenging clinical scenario. The aim of treatment is to maximize tumour control, with minimal impact on renal function while minimizing the need for possible lifelong dialysis, which has significant implications for quality of life and longevity. Partial nephrectomy, if feasible, remains the standard of care for renal masses in patients with a solitary kidney. However, ablative treatments are a good alternative for patients where PN is not possible due to tumour location or size. While reported outcomes are similar between TA and PN for cT1a renal masses,[125] oncologic outcomes and safety of TA are less favourable than PN for the treatment of larger tumours, particularly in a solitary kidney. For the centrally located large tumours in a solitary kidney, SABR represents a potentially attractive alternative.

In one prospective study, Svedman *et al.* reported the results of SABR in patients with a single kidney with median tumour size of 5.5 cm (range, 2.3–6.8) and found that none of the seven patients evaluated required dialysis post-treatment.[110] Similarly, none of the patients from the IROCK pooled analysis required dialysis, including 81 patients with RCC in the solitary kidney.[126] The median tumour size in this cohort was 3.7 cm (range, 2.5–4.3), with 37% of tumours 4 cm or greater. Though the short-term results are encouraging, long-term follow-up on this cohort with respect to both post-SABR LC and renal function is awaited.

SABR for small renal masses (T1a disease)

Optimal management plan for SRMs depends on a complex calculus weighing oncologic risk, competing risks related to comorbidities, and therapy-associated risks, incorporating patient- and tumour-related features as well as patient preferences.[127] Available treatment modalities include surgical resection, AS, and TA.[12,29] As there are no randomized trials to directly compare the outcomes between these modalities, treatment decisions should optimally involve multidisciplinary discussion and shared decision-making with patients. In the pooled analysis of IROCK involving 223 patients, of whom 113 (50.7%) patients had tumour size of less than 4 cm in diameter, the 4-year LC rate was 97%.[128] In another retrospective review of 347 patients with median tumour size of 3.8 cm (range, 2.8–5.2 cm) with 46% patients with tumour size of less than 3.5 cm,

median overall survival (OS) was 92 and 88 months for primary tumours ≤2.5 cm and 2.6–3.5 cm, respectively (median follow-up, 36 months).[129] Results of an ongoing Prospective Randomized Pilot Trial of SABR Versus RFA for the management of SRMs (NCT03811665) are eagerly anticipated to further define optimal selection criteria and outcome for SABR versus TA.

Most common acute side effects post-SABR are minor and include acute nausea, fatigue, and dermatitis. Severe toxicities reported include renal toxicity, duodenal ulcer, and skin ulceration, although the overall rates were low.[117,130,131] Taken together, these early data suggest that, for patients unable or unwilling to undergo surgery, TA, or AS for an SRM, SABR is an acceptable alternative treatment strategy resulting in good oncologic outcomes and minimal treatment-related toxicity.

SABR for large renal masses (T1b+)

Surgical extirpation via PN, if feasible, or RN if nephron-sparing surgery is not feasible, is recommended for patients with cT1b tumours measuring 4 to 7 cm in maximal diameter.[12,29] The treatment options are limited for patients with larger tumours who are not surgical candidates. Ablation with TA is not routinely considered for patients with a larger tumour size of ≥ 4cm due to increased risk for local recurrence and treatment-associated complications.[132] In this subset of patients, SABR may be an attractive approach.

In a prospective phase 1 trial (FASTRACK) of 33 patients, the median tumour size was 4.8 cm (range, 2.1–7.9) with 20 patients with tumours of >4 cm.[113] In this study, freedom from local or distant progression and OS at 2 years were 100%, 89%, and 92%, respectively. Treatment-related grade 1 to 2 toxicities occurred in 26 of 33 patients (78%) and grade 3 toxicity occurred in only one patient. A recently published retrospective analysis including 95 patients with tumours > 4 cm (median, 4.9 cm) showed promising LC with an acceptable toxicity profile.[133] In this study after a median follow-up of 2.7 years, local failure rate was only 2.9%. After treatment, mean eGFR decreased by 7.9 mL/minute and three patients (3.2%) required dialysis. Thirty-eight patients (40%) experienced a grade 1 to 2 toxicity. No grade 3 to 5 toxicities were reported.

Another retrospective review of 36 patients treated with stereotactic MR-guided radiotherapy (MRgRT) reported 1-year LC of 95.2% despite most patients having either a T1b or T2 renal mass with a median tumour size of 5.6 cm.[121] The tumour size limit at which SABR is no longer safe or effective remains to be established. Thus, the relatively limited data to date supports consideration of SABR in patients with larger tumours if an acceptable tumoricidal dose can be delivered in conjunction with adherence to tolerance limits of adjacent organs at risk (OARs).[134]

Patients with multiple comorbidities and challenging tumour location

In contrast to surgical approaches or TA, SABR has the advantage of being a noninvasive outpatient procedure that does not require anesthesia or sedation. Therefore, it may be a more suitable option for patients who are frail, those on long-term anticoagulation therapy, or those with multiple competing comorbidities in whom anesthesia is contraindicated.

From a technical perspective, SABR can also be used to treat tumours located near the hilum or ureter, permitting treatment of tumours at any location within the affected kidney. For example, one study examined outcomes in 15 patients with urothelial carcinomas of the renal pelvis treated with single-fraction SABR.[114] One patient developed acute kidney injury in the setting of pretreatment gross hematuria, which subsequently resolved 2 days following SABR. No patients subsequently developed ESRD requiring dialysis, and no treatment-related late complications were observed. Conversely, treatment of anterior exophytic or left laterally located tumours that abut the bowel, which is a dose-limiting organ for SABR, is technically challenging and is associated with an increased risk for complications.[122] For anterior tumours, positioning the patient in a lateral decubitus position may be helpful in reducing proximity of the tumour to the intestine and may permit safe treatment.

Different scoring systems including RNS and ABLATE score are used in clinical practice to estimate local failure and complications post-surgery and TA.[135,136] Higher RNS score is predictive of poor LC and higher complication rates following TA.[137,138] To date, no validated scoring system has been developed to predict treatment outcomes in terms of LC and complications post-SABR. In one prospective case-control study of single-fraction SABR, the R.E.N.A.L complexity score for 30 patients with RCC was moderate in 16 and high in 14 patients.[114] Despite the high complexity score, there were no reported local progression events or grade 3/4 treatment-related toxicities following SABR.

Procedure and technical consideration

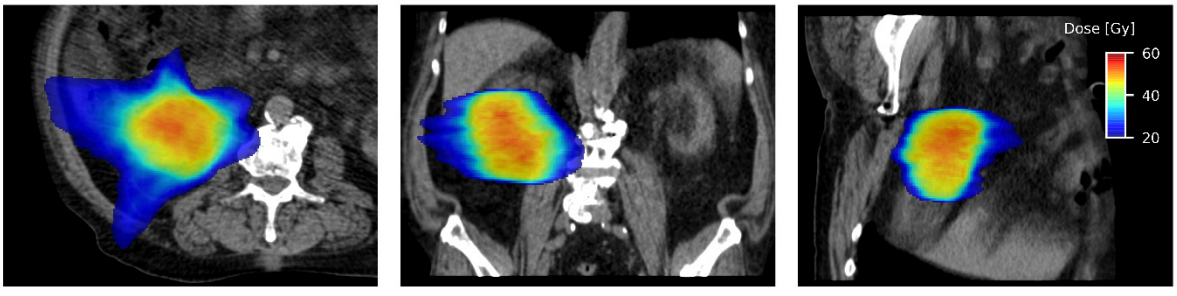
A summary of the salient technical considerations is given in this section. However, a comprehensive review of the technical considerations involved in SABR is beyond the scope of this chapter. Readers are advised to consult radiation oncology textbooks for a more detailed review. A typical dose distribution with a SABR plan is shown in **Figure 2**.

Simulation/Planning and contouring

Treatment units used to deliver SABR include gantry-operated linear accelerators, CyberKnife, robotic radiosurgery system, helical TomoTherapy, carbon ion therapy, proton therapy, and MRgRT.[113,114,117,121,130] Planning techniques used by gantry-operated linear accelerators include 3-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiation therapy (IMRT), volumetric-modulated arc therapy (VMAT), and dynamic conformal arcs.

Irrespective of the treatment system used, the most important consideration in treatment planning and delivery is respiratory motion. This is because the mean displacement of the kidneys with respiration is 0.75 cm, with a range of 0.10 to 2.15 cm for the left kidney and 0.11 to 1.92 for the right kidney.[139] One review of kidney motion reported that, counterintuitively, the kidneys moved the least in free-breathing patients while a greater range of movement was observed in patients that either had a compression device or were placed in the prone position.[140]

FIGURE 2 Axial (left), Coronal (middle), and Sagittal Sections (right) Showing Highly Conformal Radiation Dose Distribution with a Typical SABR Plan



Source: Images courtesy of A/Prof Shankar Siva, Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria; Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia.

Given the wide range of observed motion between patients and the difficulties with limiting free-breathing motion, different measures are used in clinical practice to mitigate this challenge. The most common used technique in linear accelerator-based treatment is to use the internal target volume (ITV) concept, where a thin-cut 4-dimensional CT (4D-CT) with or without abdominal compression is obtained during simulation. Respiratory gating or tumour tracking using implanted fiducial markers may be used to allow for a reduction in ITV, and this is usually incorporated into the delivery of SABR using CyberKnife.

TABLE 5 Volumes as Defined by the International Commission on Radiation Units and Measurements (ICRU)[141]

Gross tumour volume (GTV)	Gross demonstrable extent of tumour on available planning CT and diagnostics imaging
Internal target volume (ITV)	Generated to encompass GTV motion on the 4D-CT scan if not treating with respiratory tracking or gating techniques
Planning target volume (PTV)	ITV to PTV margins must take into consideration setup uncertainties, and a 3–10 mm isotropic expansion from ITV to PTV is recommended based on centre-specific confidence in motion management.
Planning organ at risk volume (PRV)	Any movements of the organs at risk (OARs) during treatment as well as uncertainties in the setup during the whole treatment course should be addressed by adding a suitable margin to the respective OAR. This margin can be 2–3 mm for hollow organ viscus.

To aid in contouring, treatment planning scans can be fused with the diagnostic CT and/or MRI of the abdomen with contrast, if the patient has adequate renal function. Target volumes are defined as per the International Commission on Radiation Units and Measurements (ICRU) report 91,[141] which has been endorsed by the IROCK consensus statement as well;[122] these are summarised in **Table 5**.

Organs at risk with acceptable dose constraints were suggested by the IROCK group in their consensus statement on SABR and are summarised in **Table 6**.[122]

TABLE 6 Suggested SABR Dose Constraints

Organ at risk	1 fraction	3 fractions	5 fractions
Spinal cord	<1 cc to 8 Gy <0.03 cc to 12 Gy	<0.03 cc to 18 Gy Max 22.2 Gy	<0.5 cc to 23 Gy <0.03 cc to 27.5 Gy
Small bowel	<20 cc to 14 Gy Full circumference <12.5 Gy PRV, D0.03cc < 26 Gy	<10 cc to 11.4 Gy <1 cc to 24 Gy PRV, D0.03cc < 30 Gy	<5 cc to 20 Gy Max. 30 Gy
Stomach	<10 cc to 11 Gy <5 cc to 22.5 Gy	<10 cc to 16.5 Gy 5 cc to <22.5 Gy Max 30 Gy	<5 cc to 18 Gy Max. 30 Gy
Large bowel	PRV, D1.5cc< 26 Gy	PRV, D1.5cc < 42 Gy	Max. 38 Gy <20 cc to 25 Gy
Chest wall	N/A	<700 cc to 30 Gy	<70 cc to 37 Gy
Skin	Max. 24 Gy	<10 cc to 30 Gy	<10 cc to 15 Gy <0.03 cc to 30 Gy
Liver	N/A	<700 cc to 15 Gy V17 < 66%	<700 cc to 15 Gy
Heart	15 cc to <16 Gy	Max 27.9 Gy	<15 cc to 32 Gy Max. 38 Gy
Contralateral kidney	ALARA	V10 < 33% V5 < 14 Gy	ALARA
Ipsilateral kidney	ALARA: minimize volume receiving >50% isodose	ALARA: minimize volume receiving >50% isodose	ALARA: minimize volume receiving >50% isodose

Abbreviations: ALARA, amount of radiation dose is as low as reasonably achievable; N/A, not applicable; PRV, planning organ at risk volume.

Source: Adapted from Siva S, Ellis RJ, Ponsky L, et al. *Consensus statement from the International Radiosurgery Oncology Consortium for Kidney for primary renal cell carcinoma.* Future Oncol. *2016;12(5):637–645. doi:10.2217/fon.16.2.*[122]

Optimal dose fractionation

A range of dose fractionation regimens have been used in prospective studies to date. Most reported trials evaluated cohorts of 10 to 40 patients treated with doses of 25 to 26 Gy in 1 fraction, 24 to 48 Gy in 4 fractions, or 21 to 60 Gy in 3 fractions as outlined in **Table 4**. In a study of 40 patients (75% of whom had biopsy-proven RCC), Staehler *et al.* showed acceptable toxicity with good LC with single fraction of 25 Gy.[114] Similarly, other published studies reported acceptable toxicity with 26 Gy in single fraction for tumours measuring less than 5 cm.[113,116]

The prospective dose-escalation studies evaluated doses ranging from 21 to 48 Gy in 3 fractions[131,142] and 24 to 48 Gy in 4 fractions[117] and showed dose escalation to 48 Gy in 4 fractions without dose-limiting toxicity. This group subsequently reported safe dose escalation to 60 Gy in 3 fractions without any dose-limiting toxicity.[120] A dose-response relationship may exist in RCC but there is no data to guide the maximum safe dose level that optimizes LC rates while minimizing dose-limiting toxicity. The phase 2 study TROG 15.03 (FASTRACK II) is evaluating 26 Gy in 1 fraction for tumours ≤4 cm and 42 Gy in 3 fractions for tumours >4 cm in size.[124] The study has completed accrual of 70 patients and results are anticipated in early 2023.

In clinical practice outside of clinical trials, optimal dose fractionation depends on the tumour size and tumour proximity to adjacent normal tissues. The IROCK consensus statement recommended the following dose fractionation approaches.[122]

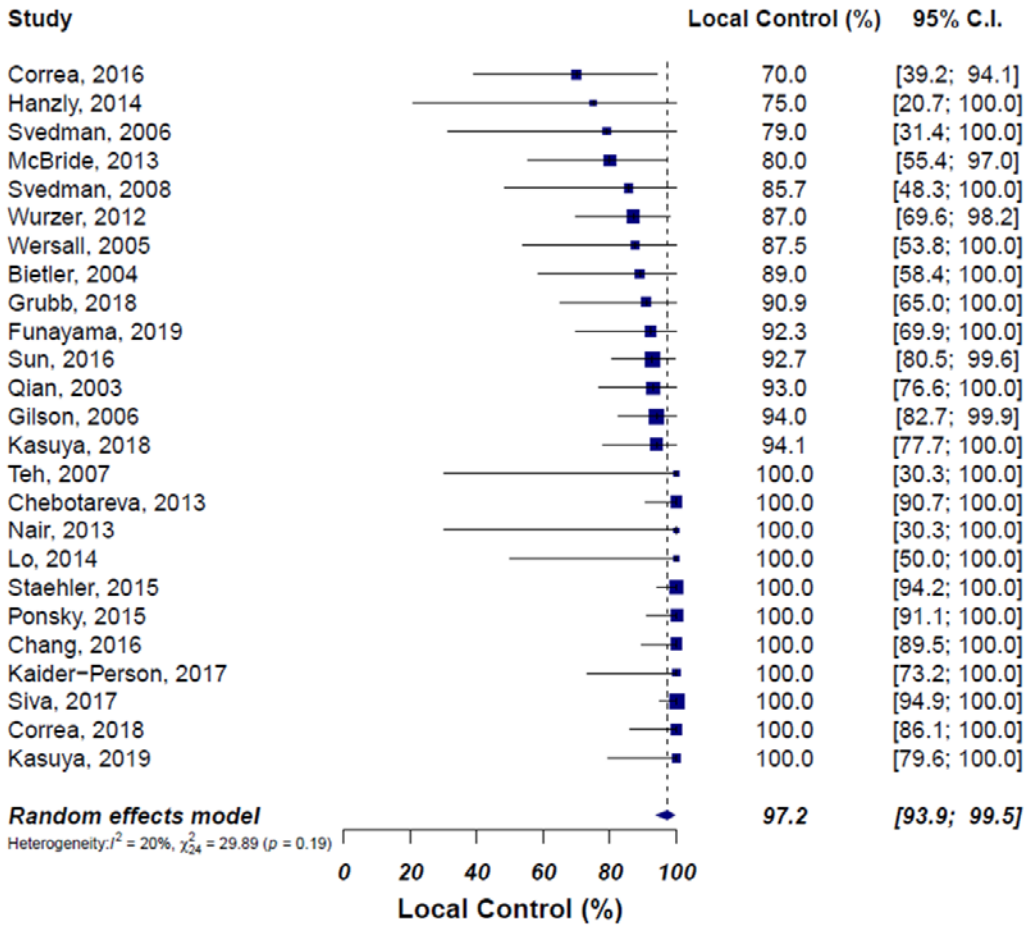
- 1 fraction of 25–26 Gy
- 35–45 Gy in 3 fractions
- 40–50 Gy in 5 fractions

Clinical outcomes

Tumour-related outcomes

As summarized in **Table 4**, several retrospective and prospective studies have demonstrated promising LC rates. In a pooled analysis involving 223 patients with median tumour size of 3.6 cm, the IROCK group reported LC, CSS, and PFS rates of 97.8%, 91.9%, and 65.4% at 4 years.[128] A systematic review and meta-analysis published in 2019, involving 372 patients with localized RCC (median size, 4.6 cm) involving 26 studies (11 of which were prospective) reported that the random effect estimates for LC was 97.2% (**Figure 3**).[143]

FIGURE 3 Local Control Post-SABR



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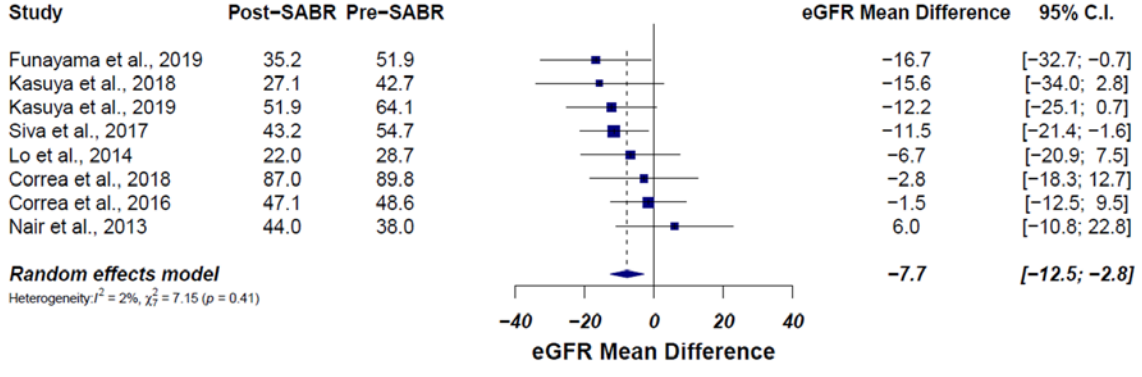
These reported outcomes are comparable to those observed with TA. While tumour size of more than 4 cm is associated with higher local recurrence post-TA, published LC rates with SABR for primary RCC are encouraging.[133,143] In a series of 95 patients with cT1b (>4 cm tumour size) localized RCC treated with SABR, Siva *et al.* (2020) reported CSS, OS, and PFS rates of 96.1%, 83.7%, and 81.0% at 2 years and 91.4%, 69.2%, and 64.9% at 4 years, respectively. Local, distant, and any failure rates at 4 years were 2.9%, 11.1%, and 12.1%, respectively.[133] Similarly, a retrospective review involving 36 patients with T1b or T2 disease stage and a median tumour size of 5.6 cm, who received treatment with MRgRT, reported 95% LC at 1 year.[121]

Post-SABR renal function outcomes

Given that many patients with RCC are at risk for long-term CKD following treatment, concerns exist regarding the impact of SABR on renal function. The literature demonstrates a mild-to-moderate decrease in baseline renal function following SABR. In the IROCK pooled analysis of 223 patients treated with renal SABR, the average GFR decreased by ~5.5 mL/minute after SABR, with 6 patients requiring dialysis.[128] Similarly, a systematic review and meta-analysis involving 372 patients showed a post-SABR eGFR change of –7.7mL/min from baseline (**Figure 4**).[143]

Additionally, SABR appears safe in patients with localized RCC in a single functioning kidney with a low risk for dialysis following treatment. In a study of SABR in patients with a single kidney, Svedman *et al.* reported that none required dialysis during subsequent follow-up.[110] In the IROCK pooled analysis of 81 patients with solitary kidney, a modest decline of 5.8 mL/min in eGFR post-SABR was observed, with no patient requiring dialysis.[126]

FIGURE 4 Renal Function Change Post-SABR



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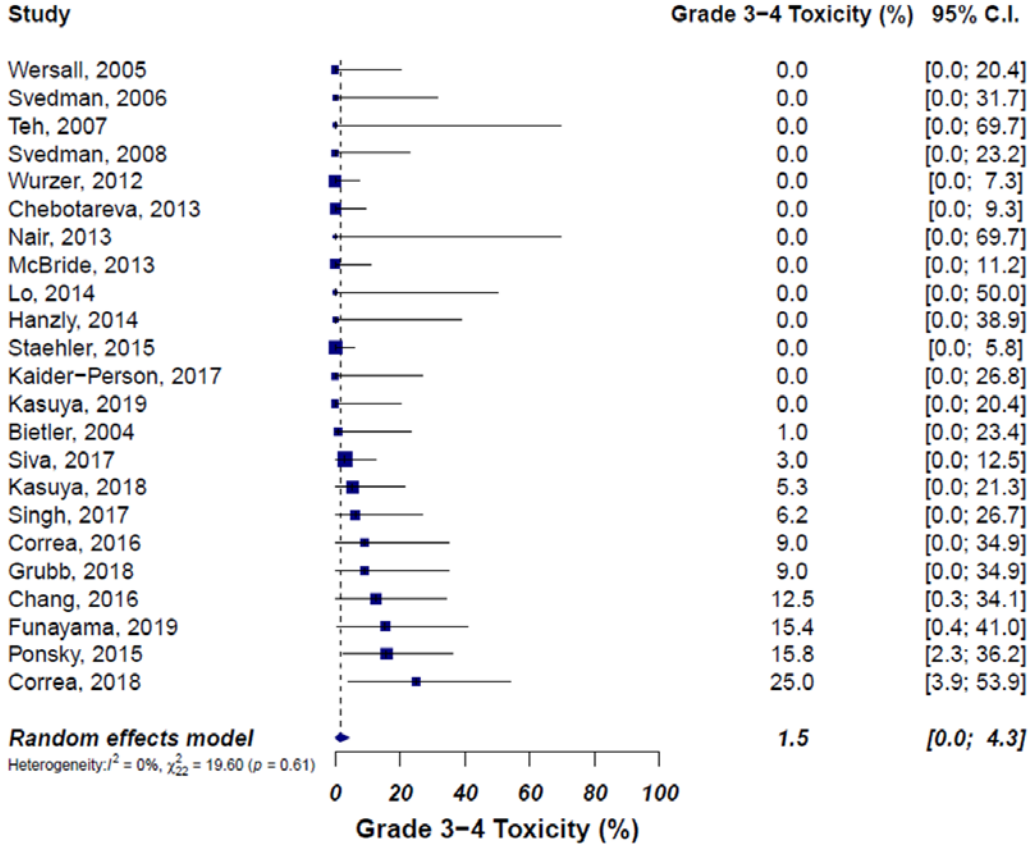
A prospective clinical trial suggested an exponential decline in affected kidney GFR with subsequent decline in renal function of 39% for 26 Gy in 1 fraction and 25% for 42 Gy in 3 fractions for every 10 Gy of physical dose delivered.[123,144] The authors concluded that sparing the functional kidney from high-dose regions (>50% isodose) may help reduce risk for functional loss. Another study of 14 patients receiving SABR for RCC (50–70 Gy in 10 fractions) showed significant renal atrophic change.[145] The dose distribution of SABR at 20 to 30 Gy in 10 fractions had a strong correlation with renal atrophy. However, there were no observed grade 2 or greater renal toxicities and no patients developed ESRD.

Treatment-related toxicity

In general, SABR is well tolerated with low reported rates of post-treatment toxicity. The most reported toxicities include fatigue, nausea, vomiting, radiation dermatitis, and enteritis. Severe reported toxic effects include renal dysfunction, duodenal ulcer, and adverse skin reactions, but the overall rates are low.[117,130,131] In the FASTRACK study, a prospective phase 1 trial of 33 patients, treatment-related grade 1–2 toxicities occurred in 6 patients (78%) with 1 patient developing grade 3 fatigue, and no patients developing grade 4–5 toxicities.[113] Similarly, the largest reported prospective study to date including 40 patients (75% RCC) reported no treatment-related grade 3 or 4 adverse events.[114] In the IROCK pooled analysis, there were 83 patients who experienced grade 1–2 toxicities (35.6%) and 3 (1.3%) with grade 3–4 toxicities.[128]

Results from these studies are further supported by a systemic review and meta-analysis involving 372 patients in which the rate of grade 1, 2, and 3–4 toxicity was 37.5%, 8.8%, and 1.5% (95% CI, 0–4.3%), respectively (**Figure 5**).[143]

FIGURE 5 Toxicity Post-SABR



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Response assessment post-SABR

Local control post-SABR is measured using the Response Evaluation Criteria in Solid Tumors (RECIST) by imaging modalities either CT or MRI. However, there are some limitations of this assessment tool, as it does not specifically reflect the area being treated or modality of the given treatment. Due to the different mechanisms involved in cell kill, complete response following SABR is a rare event, and some persistent post-SABR stable masses are common findings. Staehler *et al.* reported RECIST criteria–based complete, partial, and stable disease in 6, 5, and 19 of 30 RCC patients, respectively.[114] However, there were no reported cases of progressive disease after a median follow-up of 28 months. Similarly, the so-called reported phenomenon of initial "pseudo-progression" after SABR in patients with RCC has been found to subsequently shrink over time.[111,119,130]

Treatment failure after ablative techniques is identified as a "visually enlarging neoplasm or new nodularity in the treatment area." It presents as enhancement of the mass on post-treatment contrast imaging; development of new satellite or port site soft tissue nodules; or biopsy-proven recurrence.[146] Unlike TA, the radiotherapy does not result in immediate physical tissue destruction, as it involves a different mechanism of cell sterilization and kill, post-SABR; therefore, imaging-based contrast enhancement does not indicate treatment failure. In a study of 40 patients, Sun *et al.* reported an average regression of 0.37 cm in maximum dimension of RCC per year and observed no significant changes in contrast enhancement after SABR.[118] Interestingly, the authors reported that clear cell RCC exhibited increased enhancement following SABR. There was no clinical progression identified despite persistent contrast enhancement.

Novel imaging modalities including but not limited to multi-parametric MRI and Prostate-specific membrane antigen-based (PSMA) PET are being explored in ongoing studies for RCC. Functional MRI sequences show promise in detecting early response to therapy. The early changes in diffusion and perfusion following renal SABR have been shown to correlate with the later development of anatomic CT changes.[147] Dynamic contrast-enhanced (DCE) MRI acquires a timed series of images to measure the uptake and removal of the intravenous contrast agent. Treatment-related changes in tumour vasculature are assessed with perfusion maps generated from a DCE image series. Diffusion weighted imaging (DWI) is a measure of water mobility and has been correlated to cellularity in several tumour types.[148]

Given the uncertainties mentioned above, the following imaging strategy is currently recommended for post-SABR surveillance to evaluate for response:

- If not contraindicated, CT or MRI with contrast are considered the modalities of choice.
- The first scan to assess response should be performed at 6 months after treatment. This helps to avoid confusion with pseudo-progression.[111] Lack of growth and subsequent slow regression on size criteria is considered a successful response to treatment.
- Ongoing surveillance imaging is recommended every 6 months for the first 2 years and then yearly thereafter.
- In the absence of size progression, contrast enhancement alone should not be considered as treatment failure.

Routine post-SABR biopsy should be considered experimental. In their initial study of dose escalation up to 48 Gy, Ponsky *et al.* observed that, while 64% of biopsies post-SABR were positive for neoplastic cells, there was no progression of disease on subsequent follow-up imaging studies.[117] In their most recent prospective study involving 11 patients with further dose escalation to 60 Gy in 3 fractions, 5 of 5 post-treatment biopsies in the expansion cohort were positive by hematoxylin and eosin staining. Three of the 5 patients with positive biopsies have been observed for 1.2 to 3.9 years without evidence of progression.[120]

Follow-up

Post-SABR surveillance evaluates for disease recurrence and/or metastasis as well as treatment-related toxicity. The IROCK consensus statement recommends a follow-up interval of 3 to 6 months for the first 2 years and 6 to12 monthly for the subsequent 3 years.[122] At each follow-up visit, a comprehensive history is obtained; specifically inquiring regarding details of any treatment-related toxicity, and performing clinical examination and serum laboratories including a complete blood count, serum blood urea nitrogen, creatinine levels with estimated GFR, and serum electrolytes. Imaging for response assessment and ongoing surveillance should be obtained as summarised in above section. Chest imaging can be considered annually in patients who are deemed high risk for systemic relapse.

Future Directions

Both TA and SABR are associated with favourable clinical outcomes, with minimal toxicity in carefully selected groups of patients with RCC. However, there is no data to compare these two ablative modalities. Data from randomized trials comparing SABR with TA, or SABR with surgery is lacking. There is at least one ongoing, prospective, randomized, pilot trial (https://clinicaltrials.gov/show/NCT03811665) comparing SABR with RFA for the management of SRMs. There are always challenges to complete large, randomized trials comparing different interventional modalities. A previous trial sponsored by the University of Michigan Cancer Centre (NCT02138578), comparing SABR with RFA, was terminated after 4 patients due to a poor accrual rate. One way to counteract these difficulties can be to conduct comparative studies using existing datasets and establishing prospective registries.

Combining SABR with other ablative treatments has shown improved outcomes in patients with hepatocellular carcinoma.[149] This approach has potential in RCC, particularly for complex lesions with poor outcomes. One retrospective review involving 7 patients treated with a combination of SABR and MWA reported 100% LC with acceptable toxicity.[150] Another clinical trial (https://clinicaltrials.gov/show/NCT02782715) aimed at determining usefulness of the SABR and MWA combination for RCC measuring more than 4 cm has, unfortunately, been suspended due to poor accrual. Combined SABR and TA represents a potentially interesting strategy that warrants further exploration in RCC.

As immunotherapy is increasingly being used in the management of localized RCC, the role of TA and SABR in this context should be explored. The recently reported KEYNOTE-564 randomized phase 3 clinical trial showed significant and clinically meaningful improvement in disease-free survival with adjuvant pembrolizumab compared with placebo in patients with locoregional RCC who underwent nephrectomy.[151] There is now a significant body of evidence supporting the fact that radiation therapy also has potent immunomodulatory effects, orchestrating a spectrum of cellular and molecular alternations culminating in the potentiation of the systemic immune response.[152–154] Similarly, the different TA modalities have been variably shown to trigger an immune response.[155,156] Future studies should focus on combining ablative treatments, SABR or TA, with immunotherapies with the aim of optimising immune response to improve long-term outcomes. One such trial, Neoadjuvant Pembrolizumab and Stereotactic Radiotherapy Prior to Nephrectomy for Renal Cell Carcinoma (NAPSTER), is assessing this approach in patients with T1B-T3, N0 or N1, 0 or low-volume M1 RCC before nephrectomy (https://clinicaltrials.gov/show/NCT05024318).

Take-Home Messages

There are multiple management options available for patients with SRMs and localized RCC, spanning from AS to extirpation by PN or RN, TA, and SABR. We currently lack high-level prospective comparative effectiveness contrasting these modalities. Based on our review of the available data and experience, we will conclude this chapter by the following take-home messages:

- Patients with a newly diagnosed SRM or localized renal mass should undergo a detailed pre-procedure assessment including history with particular focus on comorbidity burden, physical examination, renal function assessment, and appropriate comprehensive tumour staging imaging. An assessment of patient-reported priorities and goals of care should be solicited.
- Each case should be discussed in a multidisciplinary team meeting consisting of a urologist, interventional radiologist, and radiation oncologist, including central imaging review.
- Ablative treatments, including TA or SABR, can be considered in patients who are at high risk for adverse outcomes following surgery who decline surgery and in whom AS is not optimal. Local expertise should be considered for decision-making.
- Patients should be counselled in a balanced fashion regarding the risks and benefits of available treatment options.

- SRMs less than 4 cm (ideally <3 cm), predominantly exophytic and distant to the renal hilum, should be considered for TA preferentially to SABR.
- Tumours measuring more than 4 cm (ideally >3 cm), predominantly endophytic and centrally located, should be considered preferentially for SABR over TA.
- Post-treatment follow up should include regular renal function assessment.
- Ongoing imaging at regular specified intervals is important to monitor the treatment outcome.

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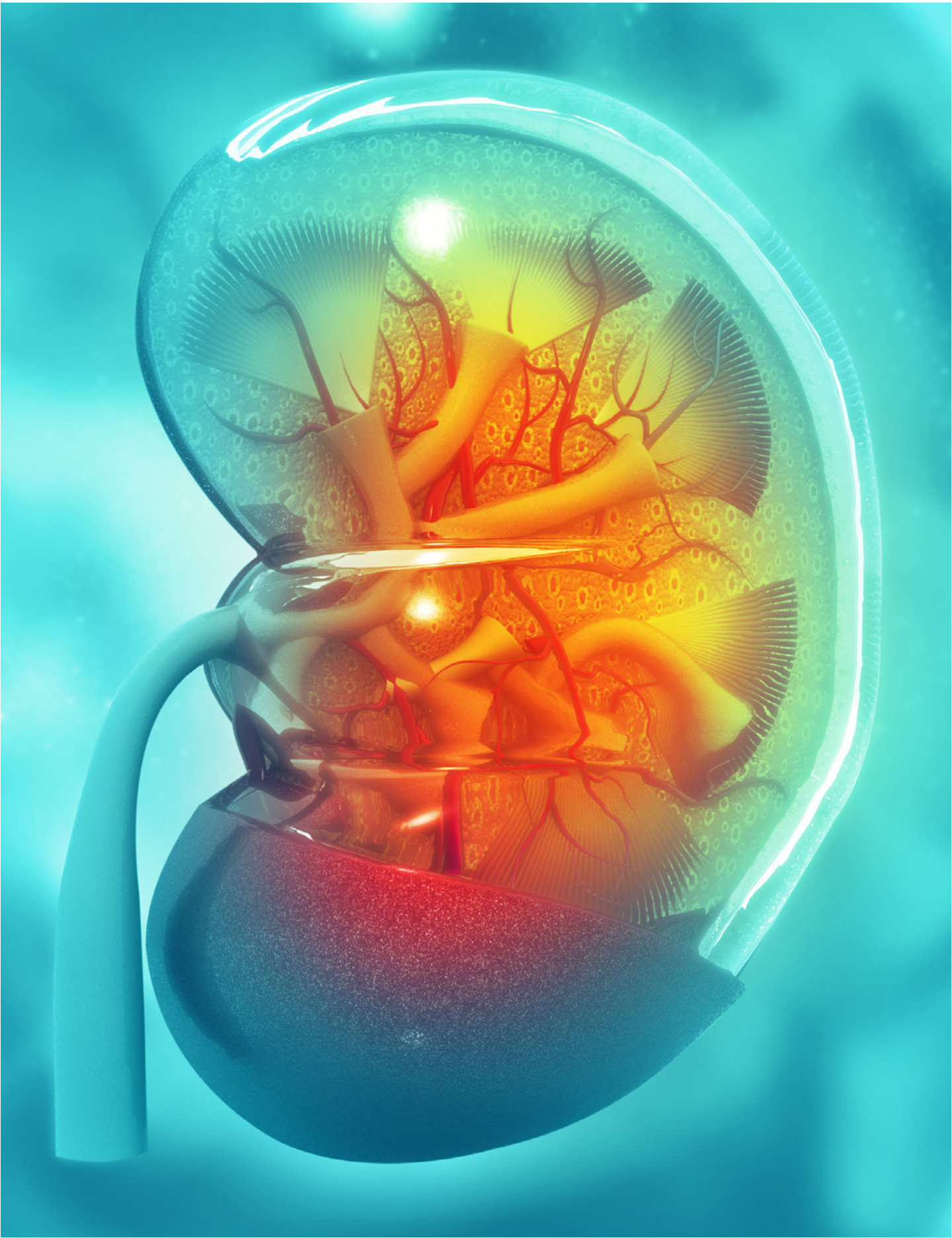

COMMITTEE 10

Active Surveillance for Renal Cell Carcinoma

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Background: The Rationale for Active Surveillance

The history and evolution of active surveillance for small renal masses

Historically, most patients with kidney cancer presented with advanced disease or larger, symptomatic tumours. For decades, surgery was and remains the mainstay of treatment for resectable masses, but this approach unintentionally limited and delayed our understanding of the natural history of renal cell carcinoma (RCC), the most common form of kidney cancer. Small renal masses (SRMs) are renal cortical tumours less than 4 cm in size that are suspicious for RCC.[1] SRMs represent a unique cohort of patients with kidney tumours, as a significant proportion of SRMs are benign tumours, and most RCCs at this size harbour no metastatic potential. While SRMs can refer to solid or cystic renal masses, this chapter will focus predominantly on solid renal masses suspicious for RCC.

With greater access to and use of cross-sectional abdominal imaging, there has been a significant stage migration toward incidentally detected SRMs.[2,3] Conversely, RCC mortality remained stable over the same time period, establishing concern for the overtreatment of SRMs and generating a rationale for active surveillance (AS) of SRMs. Prevalent malignancies such as prostate cancer are common at autopsy, but the frequency of occult kidney cancer in this setting is 0.65% to 0.72%.[4,5] With the increase in clinically detected kidney tumours, this rate has decreased further over the past 40 years.[4–7] This suggests that the apparent increase in SRM incidence is simply reflecting the detection of tumours that would have otherwise not been diagnosed. Indirectly, this further supports the belief that many SRMs possess an indolent biology and pose minimal risk for death due to kidney cancer, particularly to patients with competing health risks.

For decades, radical nephrectomy was the gold standard for treatment of RCC.[8] In recent years, the increasing proportion of patients presenting with small, localized renal tumours shifted the management of kidney cancer toward less-aggressive and less-invasive approaches. The adoption of partial nephrectomy (PN) followed by focal, thermal ablation (TA) for smaller tumours resulted from a growing appreciation of the low metastatic potential of clinical T1 RCC and the importance of renal preservation.[9] These events, combined with large surgical series demonstrating a >20% rate of benign tumour removal for cT1a renal masses suspicious for RCC[10–13] and low recurrence rates after removal of renal tumors <4 cm, set the stage for more conservative management of SRMs. Lastly, the momentum behind active surveillance for low-risk prostate cancer indirectly influenced the management of SRMs. Thus was born the concept of monitoring a patient with an SRM by active surveillance,[14–17] and active surveillance protocols were established as a means to avoid unnecessary treatment, preserve renal function, remove the risk for surgical complications, and maintain quality of life without detriment in oncologic outcomes.

Heterogeneous and indolent biology

SRMs represent a heterogeneous group of tumours ranging from benign to malignant, and the malignant tumours vary from indolent to potentially fatal cancers. Benign tumours represent 20% to 40% of SRMs and are most commonly renal cysts, angiomyolipomas, or oncocytomas.[13,18–20] RCCs are most commonly low-grade, low-stage, clear cell although high-grade and pT3 tumours are reported in up to 10% to 25% of surgical series.[13,19] Regardless of histology, few patients with SRMs will develop metastatic disease or die of kidney cancer. In fact, death from competing causes of mortality outweighs the risk for death due to RCC in almost all categories of patient age, comorbidity, and tumour size among patients with cT1 tumours.[21]

Analysis of tumour genetics from The Cancer Genome Atlas (TCGA) and, more recently, the TRAcking Non-small Cell Lung Cancer Evolution Through Therapy (Rx) (TRACERx) initiative indicates that clinical stage 1a RCCs are typically associated with low-genetic diversity and chromosomal complexity—providing a genomic explanation for the observed indolent behaviour.[22–24] This observation is termed the VHL mono driver subtype and is characterized by limiting genetic branching without additional driver mutations, tumour size <45 mm, and excellent long-term survival, as these tumours may require decades to acquire mutations conducive to metastatic potential.[23,24]

Expectant management: active surveillance and watchful waiting

Up to 66% of kidney cancers are now incidentally detected, many of which are SRMs.[25] Many patients who are diagnosed with an SRM are older and have competing health risks. Some patients are deemed poor surgical candidates and have been observed, further informing the natural history of untreated SRMs.[26] Furthermore, with the potential for overtreatment with surgery or ablation for these patients, the concept of active surveillance to closely monitor patients with SRMs has been incorporated into practice guidelines.[14,15,27] **Expectant management** of SRMs includes both watchful waiting (a.k.a., observation) and active surveillance—distinctly different entities. Active surveillance specifically refers to a management strategy that includes close follow-up with intention to treat when and if treatment for cure becomes necessary, whereas watchful waiting implies only palliative treatment would be offered if progression occurred. The American Urological Association (AUA) Guidelines released in 2017 and updated in 2021 explicitly endorse this distinction.[15] This book chapter will not discuss expectant management, rather choosing to focus, as best able given limitations of the scientific literature, on patients undergoing active surveillance for SRMs.

Guideline Support for Active Surveillance

The most widely used guidelines for the management of SRMs include those from the AUA, European Association of Urology (EAU), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and European Society of Medical Oncology (ESMO). Other national urologic societies, including those from Canada, Japan, Argentina, and Saudi Arabia, have produced guidelines on the management of renal cancers but these have not been updated in the 5 years since the time of writing so are not considered further in this text.

American Urological Association (AUA) Guidelines

The AUA Guidelines were modified to formally include active surveillance in 2017 and updated in 2021.[15,28,29] The AUA Guidelines make a conditional recommendation (**level of evidence [LOE]: C**) for clinicians to consider active surveillance in patients with a solid renal mass <2 cm with potential for delayed intervention for initial management. Similar to EAU below, as a clinical principle, they recommend surveillance as a preferred treatment when the "anticipated risk of intervention or the competing risk of death outweigh the oncological benefits of active treatment." Expert opinion from the AUA suggests the first interval scan should be performed within 3 to 6 months to assess for interval growth, and that renal tumour biopsy can be considered for additional risk stratification. The subsequent intensity of follow-up should be individualized to the patient and their inherent preferences and tolerance of uncertainty.

The guidelines go further to recommend that in patients where "the anticipated oncologic benefits of intervention outweigh the risks of treatment and competing risks of death, physicians should recommend active treatment. In this setting, active surveillance with potential for delayed intervention may be pursued only if the patient understands and is willing to accept the associated oncologic risk." Factors favoring active surveillance and expectant management, as well as a clinical algorithm for following patients are provided with the guideline (**Table 1**).

TABLE1 Patient and Tumour-Related Factors Favouring Active Surveillance Versus Intervention According to the AUA Guidelines.

	Patient-related factors	Tumour factors
Favour active surveillance/ expectant management	• Elderly • Life expectancy <5 years • High comorbidities • Excessive perioperative risk • Poor functional status • Marginal renal function • Patient preference to avoid treatment risks	• Tumour size <3 cm • Tumour growth <5 mm per year • Non-infiltrative on imaging • Low complexity • Favourable histology (if RMB performed)
Favour intervention	• Young • Life expectancy >5 years • Low comorbidity • Acceptable perioperative risk • Good functional status • Anticipate adequate renal function following intervention • Patient preference for treatment	• Tumour size >3 cm • Tumour growth >5 mm per year • Infiltrative on imaging • High complexity • Unfavourable histology (if RMB performed)

Abbreviations: AUA, American Urological Association; RMB, renal mass biopsy.

European Association of Urology (EAU) Guidelines

The EAU Guidelines (2021, updated annually) on active surveillance acknowledge that in population-based studies, there is a significantly lower cancer-specific mortality in patients treated with surgery compared to those treated nonsurgically.[30] The EAU Guidelines specifically cite analyses of patients over 75 years old that fail to show oncologic benefit to surgery, and many studies showing slow growth and low (1–2%) metastasis rates in patients with SRMs during surveillance. The EAU Guidelines discuss the importance of biopsy in active surveillance to establish histologic subtype, which can be used to guide whether surveillance is appropriate and the frequency of scans in the surveillance schedule. Histology-based protocols versus histology-agnostic active surveillance protocols are discussed later in the chapter.

The EAU Guidelines, based on limitations of the literature, make weak recommendations to offer active surveillance to frail or comorbid patients with SRMs. However, they do make a strong recommendation to discuss the risks and benefits regarding oncological outcomes and complications, when offering active surveillance as a treatment option.

National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO) Guidelines

In addition to patients with comorbidities and those with masses <2 cm, the NCCN mentions that active surveillance is an option for the initial management of patients with cT1a tumours that have a predominantly cystic component.[31] According to the NCCN, surveillance imaging protocols should include periodic metastatic staging including blood tests and chest imaging annually—specifically recommending abdominal cross-sectional imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) for the first 2 years and if no significant progression, to move to annual imaging with any modality (CT, MR, or ultrasound [US]) thereafter for 5 years.

Both ASCO and ESMO have produced guidelines that relate to the use of active surveillance. Common with all other guidelines, they highlight the use of active surveillance of cT1a tumours in patients with significant comorbidities. Renal tumour biopsy in select cases is recommended in both these guidelines, although only the ASCO guideline offers a suggestion that biopsy should be performed on patients embarking on active surveillance to assess risk for metastasis and inform patient counselling.

Collectively, there is agreement in the guidelines that active surveillance is an option in patients with comorbidities or limited life expectancy. Given a paucity of high-quality evidence on which to base recommendations, the role of biopsy, the intensity and best modality of imaging, or the triggers to active intervention lack strong guidelines. These all represent areas of research that should be prioritized to improve current guidelines.

Current utilization and barriers to implementation

Use of active surveillance for the management of SRMs has remained relatively static over the past 20 years. This has been demonstrated by analyses of both the Surveillance, Epidemiology, and End Results (SEER) and the National Cancer Data Base (NCDB) registries in the United States, where utilization of active surveillance for cT1 tumours has remained below 10%.[32,33] The use of both PN and TA has increased over this period of time, even in older patients.[34] This is likely due to the improved risk profile associated with these interventions compared to open RN, enabling access to them in patients with more comorbidities. Importantly, this is reflective of practice in the United States, with an advanced healthcare system where new technologies are widely available. There are currently no population-based studies of active surveillance use in other countries.

Barriers to implementation are based on patient factors, clinician factors, tumour characteristics, and healthcare settings. Ultimately, the decision to proceed with active surveillance needs to be shared between the clinician and patient based on individual preference using the diagnostic information available in the appropriate healthcare

setting. The remainder of this chapter will endeavor to provide practical, clinical guidance for the management of patients with SRMs considering active surveillance based on the best available literature and clinical expertise of world leaders in active surveillance.

Existing Data Supporting Active Surveillance for Small Renal Masses and Renal Cell Carcinoma

Current active surveillance literature: perspectives and limitations

Historically, active surveillance was supported by retrospective series and subject to a number of biases inherent to reports of this nature. In early studies, the definition and protocols regarding active surveillance were not well established, leading to a mixture of watchful waiting and active surveillance patients. To date, comparative effective evaluations using observational data are limited by the inability to differentiate active surveillance from watchful waiting (or no treatment) using claims data[35] and the level of evidence supporting the efficacy of active surveillance compared to definitive treatment with surgical excision or ablation is limited.[36,37] In addition to the heterogeneity of patients, a number of series include patients with benign, malignant, and undiagnosed masses; treated and untreated patients; and patients who developed metastatic disease and died may be lost to follow-up (e.g., recall bias). Lastly, while metastatic progression and disease-free survival are clear oncologic outcomes—very few patients with cT1a RCC die of disease, making superiority comparisons to surgical treatment challenging. As such, the *a priori* definitions and endpoints used in protocols quickly became outdated as the understanding of clinical progression evolved with long-term outcomes for these patients. Growth rate, tumour size, new symptoms (i.e., hematuria), and metastatic disease are accepted as clinical progression; however, their biological underpinnings and clinical implications remain unclear (more on clinical progression later in the chapter). For instance, and as expounded upon elsewhere in this chapter, the expected growth rate for clear cell RCC (ccRCC) is greater than for papillary RCC (pRCC).[38] However, the observed rates may vary dramatically in individuals and not necessarily reflect tumour biology (i.e., grade) or metastatic potential. While the development of metastatic disease certainly represents an adverse outcome and clinical progression, a number of patients in the early series developed metastatic disease early (within 6–12 months) likely indicating the presence of metastatic disease at diagnosis.[17,33] Finally, the follow-up for most active surveillance studies is relatively short, on the order of 24 to 36 months, leaving uncertainty regarding the long-term sustainability of an active surveillance practice. Coupled with the high historic cancer-specific survival rates (great than 95% at 5 years), the burden of proof to establish active surveillance as a priority management strategy remains high.

Summation of original research and systematic reviews

While representing heterogeneous populations, **the summation of published literature on active surveillance for SRMs indicates that active surveillance is a safe initial management strategy for many patients with SRMs**. A systematic review of the literature in 2018 demonstrated relatively slow linear growth rates (0.37 cm/year median, interquartile range, 0.15–0.7), low metastatic progression rates (0–6%), and highly variable cancer-specific (0–18%) and other cause mortality (0–45%) likely due to varying inclusion criteria among studies.[39] A number of subsequent reports from large, institutional, and/or prospective cohorts support the conclusions of the systematic review and are discussed below.

A prospective Renal Cell Cancer Consortium of Canada was recently updated and uniquely highlighted growth based on histology, and showed an average growth rate of 2–3 mm per year over a median follow-up of 5.8 years.[17,38] The initial report included patients with a cT1a renal mass deemed to be unfit for surgery due to advanced age, comorbidity, or refusal of interventional treatment. Patients were excluded if they had less than a 2-year life expectancy, had a diagnosed SRM for greater than 12 months prior to enrollment, were on systemic therapy for other malignancies, or had a known hereditary RCC syndrome. Their surveillance strategy recommends cross-sectional imaging (CT, MRI, or US] every 3 months for the first 6 months, then every 6 months until year 3, and then annually. The demonstrated growth rate is consistent with other reports.[36,40] Importantly, this program strongly encourages renal tumour biopsy at enrollment, and the rates of growth and progression varied significantly by the histology of the SRM, with papillary type 1 renal cell carcinomas (RCC) demonstrating a very indolent course and clear cell RCCs showing higher growth rates and increased risk for progression.[38] Of the 136 biopsy-proven RCC patients, 49 (36%) remained on active surveillance at 5 years. The 5-year progression-free survival (PFS) was 54%, mainly because of an elevated growth rate (82% of patients). Growth rates are extremely variable over the first year on surveillance, and of 21 fast-growing lesions, 8 stopped growing after the first year. Only 6 patients developed metastatic disease and 29 died (3 cancer-related deaths). A total of 53 (38%) patients transitioned to delayed intervention, and no adverse pathological features were encountered in these patients.

One of the largest registries is an American prospective cohort study comparing the outcomes of patients undergoing active surveillance versus primary intervention for newly diagnosed SRM, the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry. Began in 2009, DISSRM, at last report, includes 495 active surveillance patients with median follow-up of 3.3 years and a third of patients followed for at least 5 years.[41] The 5- and 7-year cancer-specific survival (CSS) for patients initially managed by active surveillance in DISSRM was 100% and was not significantly different from other management strategies (98.8% in the partial nephrectomy group at 7 years).[37,40] The 5-year progression-free survival in the active surveillance group was 67%, similar to retrospective sources and the prospective Canadian series. Progression in this cohort was driven largely by elevated growth rates and patient preference. Long-term overall survival was better for patients choosing primary intervention, but attributable to worse comorbidity profiles in the active surveillance group (CCI score 1–3, 48%), and cancer-specific survival at 7 years was similar among primary intervention and active surveillance (99%). These types of observational studies support the oncologic safety of active surveillance for carefully selected patients with an SRM, even those patients who were 60 years old or younger.[42] The DISSRM Registry

also provides data regarding growth rate variability over time, the minimal utility of routine chest imaging, and comparative outcomes among management strategies for a newly diagnosed SRM including patient-reported quality of life.[37,43–45]

The Fox Chase Cancer Center has a long history of investigating and reporting on patients undergoing active surveillance for SRMs. In the most recent retrospective update, 544 lesions in 457 patients over a median 67 months indicated that 80% of SRMs will grow slowly or not at all, approximately 40% will undergo intervention at 5 years, and the cancer-specific mortality is 1%.[46] Data from this cohort supports the safety of delayed intervention in the SRM cohort and indicates that elevated growth rate is associated with the highest rates of intervention.

In a recent cohort series of "universal" active surveillance from Roswell Park, all non-dialysis–dependent patients with newly diagnosed, nonmetastatic, nonhereditary SRMs seen by one urologist over a 4-year period were initially managed with active surveillance unless the patient already met a criterion for delayed intervention (<5% of presenting patients).[47] Delayed intervention was recommended for patients with symptomatic progression, unfavourable histology, cT3a stage, tumour diameter >4 cm, growth rate >5 mm/year for the longest tumour diameter >3 cm, or >3 mm/year for the longest tumour diameter >3 cm. Cross-sectional imaging (CT or MRI) and chest X-ray (CXR) were obtained after 6 months for tumours <3 cm and after 3 months for tumours >3 cm. Serial imaging was then obtained every 6 months until criteria for tumour stability was met (<3 mm/year over a 2- to 3-year period). Patients with low oncologic risk (tumour stability or benign histology on biopsy) or high treatment risk were switched to annual US monitoring after >3 years of cross-sectional imaging. Patients who met >1 progression criteria were offered treatment if life expectancy was >15 years or observation if life expectancy was <5 years. Of 128 patients, 75% remained intervention-free at 3 years based on predetermined intervention criteria, and no patients developed metastatic disease or died of RCC.

The prospective registries discussed above provide strong evidence to support the role of active surveillance for SRMs without hesitation, as oncologic outcomes remain similar to primary intervention and the likelihood of metastatic disease is minimal. The upcoming years will reveal a significant number of publications regarding active surveillance for SRMs including prospective series from the United States and Europe.

Selecting Patients for Active Surveillance: Balancing Life Expectancy with Cancer-Specific Mortality

When considering active surveillance for patients with SRMs, careful deliberation of patient and tumour factors is required to select the optimal management strategy for any given patient. While national and international guidelines (above) provide recommendations regarding utilization of active surveillance based on tumour size, life expectancy, and comorbidities including chronic kidney disease, very few strict tumour or age cutoffs exist

(**Table 1**).[15,29–31] Clinical parameters to help clinicians best select patients for active surveillance are discussed below. Remembering the low malignant potential of the vast majority of SRMs should provide confidence to both patients and providers that active surveillance is a safe, initial management option for many patients with SRMs.

Tumour size

The literature clearly and consistently demonstrates greatest tumour dimension to be the strongest predictor of malignant and metastatic potential for an SRM. The rate of benign, surgically removed tumours ranges from 20% to 40% and is highest for the smallest tumours—approaching 50% in some historical series.[18,20,48] In the most contemporary reports (with presumptive improved selection for malignant tumours), rates of benign histology are 32–40%, 19–25%, 11–21%, and 11–26% for tumours <1, <2, <3 and <4 cm, respectively.[13,18,19] Rates of low-grade, low-stage, "indolent" RCC vary from 94%, 86–89%, 76–85%, and 70–77% in the same respective categories, leaving only 6% to 30% of cT1a SRM as potentially aggressive based on pathology. Rates of metastatic disease remain exceedingly rare, approaching 0% for tumours <2 cm, approximately 1% for <3 cm, and 2–3% for <4 cm based on institutional data, population-based outcomes, and the von Hippel-Lindau hereditary kidney cancer literature.[21,49–55]

Rates of malignant tumours and metastatic rates do increase precipitously after 4 cm. Rates of malignant pathology range from 88–95% for tumours >4 cm, with aggressive pathology in 30–34% and 37–50% for tumours 4–6 cm and >6 cm, respectively.[13,19] Metastatic rates exponentially increase with increasing tumour size and stage.

Sex

Male sex is consistently associated with higher rates of malignant tumours and aggressive pathology at any given tumour size.[13,48] In a large systematic review, men were associated with nearly a 3-fold increased risk for cancer (effect size, 2.71; 95% confidence interval [CI], 2.39–3.02) when controlling for tumour size.[48] While challenging to quantify size and sex cutoffs, women with tumours less than 2 cm clearly have the highest rates of benign pathology and lowest rates of aggressive RCC pathology in a number of studies.

Age and life expectancy

While RCC represents only approximately 4% to 5% of all cancers worldwide,[56] the increasing incidence of incidental diagnoses[57,58] is particularly frequent in elderly patients who are more likely to undergo radiological investigations for other health-related problems.[59] Indeed, approximately 75% of newly diagnosed RCC are reported in patients over the age of 60. The age-standardized incidence rate in this patient population is as high as 35 cases per 100,000 persons/year, and the highest rate is recorded in patients aged ≥75 years.[56] Moreover, the incidence of SRMs is 30-fold higher in ≥75 years old than in younger patients.[60] Finally, studies exploring the benefits of surgery in patients older than 75 years with clinically localized cT1 renal masses demonstrated no

superiority of definitive treatment (either partial or radical approach) compared to active surveillance in terms of cancer-specific survival, due to decreased life expectancy in that specific patient population. In other words, most of these patients would not live long enough to benefit from surgery.[59]

While data and guidelines support active surveillance in the elderly and frail population, life expectation estimation is far to be established in this specific setting and no accurate biomarkers of either cancer aggressiveness or life expectancy are currently available—perhaps explaining the observed rates of overtreatment.[61] Daskivich and colleagues reported the patterns of treatment of patients with SRMs in a nationally representative sample of 9,825 patients over 65 years of age with life expectancy less than 10 years and less than 5 years.[62] Interestingly, among patients with SRMs and a life expectancy less than 5 years, the multivariate probability of aggressive treatment was 41% and more often surgery than ablation (68% vs. 32% of patients), suggesting that life expectancy should be better incorporated in the future into treatment decision-making for early-stage kidney cancer.[62] Similarly, Patel *et al.* indicate that other-cause mortality outweighs the risk for cancer-specific mortality for most patients with SRMs regardless of tumour size, age, comorbidity, or initial management strategy elected.[21,63] Psutka and colleagues recently created a risk calculator for patients with 5,300 patients with cT1 renal tumours from a variety of sources including the DISSRM Registry.[55] While this is the most comprehensive calculator to date (including a number of variables like tumour size, sex, body mass index, renal function, performance status, and Charlson comorbidity index), age remains among the strongest predictors of other-cause mortality.

One of the criticisms to active surveillance is that it is not suitable for younger patients or those with a long life expectancy given that most tumours will grow and require intervention. Recent data from DISSRM indicates that 70% of patients under the age of 60 and 80% of patients with SRM <2 cm will remain on active surveillance at 5 years, indicating a significant proportion of patients will have SRMs with low or no growth over a durable period of time.[42] While strict age cutoffs remain elusive, DISSRM and other registries indicate that patients greater than 70 years old, those with competing risks for mortality (specifically cardiovascular disease),[64] and those who report poor physical health are most likely to benefit from and remain on an active surveillance program.[55,65,66]

Renal function, chronic kidney disease, and end-stage renal disease

Any intervention on a renal unit will affect renal function with functional nephrons removed affecting the expected post-procedural estimated glomerular filtration rate (eGFR), with radical nephrectomy having the highest impact on eGFR and the highest rates of chronic kidney disease (CKD) progression compared to nephron-sparing surgical approaches like partial nephrectomy or thermal ablation.[34] Active surveillance is the only routinely offered management that may not affect the natural history of CKD progression.[34,37,67] Given the well-established risks for CKD and other-cause mortality,[68] patients at risk of developing end-stage renal disease are ideal candidates for active surveillance.[55] Patients with end-stage renal disease on dialysis may also be suitable for active surveillance pending suitability for renal transplant and centre-specific requirements for transplant.[69]

Illness uncertainty

One of the strongest predictors of delayed intervention is illness uncertainty or anxiety expressed by patients. This is clearly demonstrated in the DISSRM Registry where approximately 50% of patients who cross over to delayed intervention do so without an appreciable, biological "trigger" for intervention like tumour growth or growth rate.[70] Illness uncertainty predicts general quality of life, cancer-specific quality of life, and distress, which can all impact the success of active surveillance.[71] Interestingly, mental health scores improve over time in patients in a structured active surveillance program.[44] Therefore, enrollment in a structured surveillance program, consultation with an expert in RCC, and renal tumour biopsy may all influence illness uncertainty and therefore enrollment and durability in an active surveillance program.

In conclusion, patients' selection for active surveillance is currently based on the balance between risk for clinical progression and patients' life expectancy. While the former is currently adequately established, there is a clear need for accurate, easy-to-use life expectancy calculators to appropriately target patients who may benefit from active surveillance. Further insights in the future will be necessary to better estimate life estimation relying not only on age but also on individual patients' characteristics (comorbidities, frailty, and—ideally—genetics).

Role of Renal Tumour Biopsy in Active Surveillance

Renal tumour biopsy (RTB) usage experienced an almost about turn over the past decade. From previously being considered of limited value by all the major clinical guidelines such as the AUA and EAU, the utility of RTB is more acceptable in the urology community. Much of this change in practice has resulted from large-scale studies, systematic reviews, and recently a meta-analysis that show a high median diagnostic rate of 92% and an excellent safety profile for RTB.[72,73] Current AUA and EAU Guidelines recommend a biopsy in select patients who are considering active surveillance.[29,30] In practice, there seems to be general consensus that RTB can be useful as a risk-stratifying tool but should not be considered a requisite before embarking on active surveillance. This change in practice is evident from a recent update on the DISSRM study showing an increase from 5% to 20% of patients having an RTB.[43]

The majority of published active surveillance (AS) cohorts have been heterogeneous populations comprising histology-confirmed and histology-agnostic patients.[17,43] This has naturally limited extrapolation and interpretation of findings, given that up to 30% of SRMs can be non-RCC (benign or otherwise), the wide spectrum of recognized RCC histology, and observed median growth kinetics of 0.09 cm (±1.51 cm)/year in prospective series[17,74] and 0.37 cm/year median (interquartile range [IQR], 0.15–0.7) in systematic review.[39] However, with the uptake of RTB, more studies are now reporting on outcomes from histology-proven RCC on active surveillance, adding significantly to and improving the evidence base. The largest cohort of sporadic SRMs

with biopsy-proven RCC on active surveillance reported on 134 patients with 136 lesions, with a median duration of follow-up of 5.8 years (IQR, 3.4–7.5).[74] This showed that small renal RCCs generally exhibit a slow growth rate of 0.19 cm/year (maximal diameter), with notable inter- and intra-variability in histological subtypes. Clear cell RCCs seemed to grow most rapidly; however, there was significant heterogeneity within the 93 lesions included in this series. Most small clear cell RCCs demonstrated stable or little growth, while a subset of 15% exhibited growth of ≥0.5 cm/year. In contrast, the next most-frequent histology in the series, papillary RCC type 1 lesions (n=23) demonstrated near zero growth. The growth trajectories of chromophobe RCC (n=6) and papillary RCC type 2 (n=6) seemed to be similar and intermediate between clear cell RCC and papillary RCC type 1, respectively, though interpretation should be tempered given small number of cases.

Based on the current literature, RTB may assist in risk stratification by: 1) identifying benign neoplastic histology, namely oncocytoma or fat-poor angiomyolipoma; and 2) revealing unfavourable RCC histology based on grade, subtype, or genetics. The former of these goals is the predominant driver of RTB usage during active surveillance.[14,17,47,75] Historically, RTB differentiation of oncocytoma from RCC (particularly the eosinophilic chromophobe RCC variant) was challenged by significant histologic overlap necessitating instead diagnostic extirpation. More reliable RTB diagnostic performance has since evolved with the aid of immunohistochemistry biomarker panels for oncocytic tumour diagnostic differentiation that include the renal oncocytoma (RO) and chromophobe renal cell carcinoma (ChRCC)-specific biomarker CD117/c-KIT and RCC markers lacking in RO (e.g., CK7, CAIX, AMACR, vimentin), in addition to radiologic approaches that can further corroborate oncocytoma diagnosis, such as Sestamibi scan and CT-based PEER score.[76,77] Unfavourable/adverse RCC histology includes nuclear grade ≥3, papillary type 2 RCC, translocation RCC, and unclassified or otherwise unspecifiable RCC subtype.[28] RTB diagnostic sensitivity for unfavourable histology is low; however, specificity is high.[72,73] Data from the National Cancer Institute indicates that growth rate is associated with pathologic germline alterations, particularly with *BAP1*, and as diagnostics improves, RTB may further inform suitability for AS and triggers for delayed intervention.[78]

While it is clear that histology from RTB may inform expected growth rates, growth kinetics cannot reliably predict the presence of malignancy in SRM. Several studies now indicate that RCC tends to grow faster, particularly those of high grade.[17,47,79] There are currently no prospective clinical trials assessing whether having an RTB affects clinical management and active surveillance protocols. From a clinical practice standpoint, RTB can be useful in providing reassurance and alleviating anxiety for patients with benign tumours. Furthermore, some patients may benefit from the increased clarity that tumour histology may bring to guide their treatment preferences, and clinicians may find the knowledge of histology useful in their counselling of patients. However, the potential usefulness of the histological diagnosis has to be balanced with the risks of bleeding, pain, and the uncertain clinical significance of biopsy tract seeding.[28,73,80] The recent systematic review supporting the AUA Guidelines found a negligible rate of tumour seeding in percutaneous RTB series using contemporary techniques.[73] In the absence of reliable diagnostic and prognostic alternatives, RTB can be considered a useful adjunct in the era of personalized medicine and individualized management regimes for the growing problem of SRMs.

Understanding Active Surveillance Protocols

The current evidence evaluating imaging surveillance protocols while on AS is largely relegated to retrospective institutional cohort studies. Surveillance protocols include renal mass imaging, monitoring of renal function, RTB (discussed above), and periodic assessments for metastatic progression.[81] Review and comparison of existing institutional and prospective AS cohorts demonstrate that differences between imaging modality and surveillance intensity do not correlate with cancer-specific mortality in patients with SRM.[34] Other than tumour size at diagnosis and linear growth rate, imaging features to predict malignant potential are limited, and there is currently no consensus regarding triggers for delayed intervention.[35] Prospective cohort studies, like those discussed in this chapter, may represent the best source of data for future comparative effectiveness assessment of competing local treatment strategies. In the absence of level 1 evidence, rigorously defined eligibility criteria, strict surveillance schedules, and rigorous patient adherence are critical to documenting oncologic outcomes and identifying optimal candidates for delayed intervention in patients under consideration of AS for the SRM.

Renal mass Imaging: timing, frequency, and modality

In all protocols, cross-sectional imaging is performed at variable intervals to assess for changes in maximal tumour diameter as a surrogate for SRM growth. All studies include short-term surveillance, typically within 3–6 months, to rule out explosive growth rates and subsequently follow patients with intervals extending from 6–12 months.[17,40,46,47] In one of the largest existing cohort series at the Fox Chase Cancer Center, patients were stratified by absolute, relative, and elective indications for AS.[26] Patients were imaged at 3–6 month intervals (CT, MRI, or US) following their initial diagnosis with restaging intervals increased to every 6–12 months once stable growth kinetics were established. Similarly, patients in the Canadian cohort were imaged at 3, 6, and 12 months, and annually thereafter.[74] The prospective protocol from Roswell Park included imaging every 6 months for 3 years.[47] At its inception, the DISSRM Registry mandated imaging every 3–4 months within the first year and subsequently relaxed the recommendations to every 6 months based on data demonstrating very little change over a 3-month time interval and overestimation of linear growth rate based on short-term time intervals and variability in measurement.[43] The practice of establishing an early growth rate is based on the 15–20% of patients who will have tumours that grow faster than 5 mm per year[17,43,46] and the historical, retrospective data demonstrating “explosive” growth rates in patients developing metastatic disease.[33,36] It should be noted that explosive growth rates have yet to be reported in prospective series. The next iteration of nuanced imaging will likely involve intervals based on initial tumour size. For instance, the Roswell protocol recommends 3- versus 6-month imaging initially for tumours greater than and less than 3 cm, respectively.[47]

The majority of prospective protocols require multiphasic axial imaging at diagnosis or shortly thereafter. Once the greatest dimension is established, many protocols allow for CT, MRI, or ultrasound imaging. The Roswell protocol uses CT with contrast (when possible) at every interval in the initial 3-year period prior to long-term annual ultrasound for stable or slow-growing lesions; the Canadian program follows most patients

with ultrasound while DISSRM will alternate ultrasound with axial imaging in most patients.[40,47,74] It should be noted that the error of each modality is approximately ±3 mm and rationalizes small differences in measurement accounted for by changing modality.

Renal function assessment and metastatic evaluation

There is no consensus among protocols about the frequency of laboratory evaluations or chest imaging for continued assessment of renal function or metastatic survey. As the AUA and EAU Guidelines incorporate renal functional assessment into management decisions, renal functional tests including serum creatinine and evaluation for proteinuria should occur on at least an annual basis.[28,30] Patients with chronic kidney disease may require more frequent laboratory evaluation or referral to nephrology for management and risk stratification of any renal intervention.

Per the AUA Guidelines, annual blood work and chest imaging are recommended as standard practice in any patient undergoing active or post-treatment surveillance for metastatic disease.[29] However, as the short-term (3–5 year) risk for metastatic progression in AS patients is <2% in meta-analytic studies,[33] the utility of such rigorous surveillance comes into question. In addition, there is significant risk in the diagnosis of incidental diagnoses (including pulmonary and thyroid nodules) that are unrelated to kidney cancer and may result in unnecessary, costly, and potentially harmful workups. A recent examination of the DISSRM series revealed that of the 268 patients with available chest imaging reports, 51 (19%) were found to have abnormal baseline chest imaging, of which 57% were non-actionable.[45] Of the 217 patients with normal baseline imaging, 23 (11%) developed abnormal findings, of which only 43% were actionable. The authors concluded that patients managed with AS do not require annual chest imaging given the low rate of metastatic progression of stable SRMs coupled with the risks for morbidity and cost considerations involved with the diagnostic workups for incidentally diagnosed chest lesions. Baseline chest imaging is an important component to any active surveillance program, as a small but significant proportion of patients with cT1a RCC have pulmonary metastases.[49] However, annual chest imaging can likely be omitted unless (1) there is an abnormality on baseline imaging that requires follow-up, (2) the SRM demonstrates significant growth requiring restaging, or (3) there is any delayed intervention for accurate staging prior to intervention.[81]

Triggers for Intervention

Guiding principle for delayed intervention: oncologic risk > treatment risk

Delayed intervention occurs in 7% to 44% of patients in active surveillance studies at a median of 12–27 months.[82] Delayed intervention should be triggered during active surveillance whenever the oncologic risk

becomes higher than the treatment risk while accounting for comorbidities, anesthetic risk, functional status, and life expectancy.[14,15,30,31] This fundamental principle mirrors that for initial active surveillance versus treatment selection, and exploits the ability of an active surveillance interval to clarify the oncologic-to-treatment risk balance based on growth kinetics and/or biopsy histology.[47] Any change in tumour or patient status that definitively favours intervention should be considered an absolute trigger for delayed intervention, while a change to an equivocal risk balance may be considered a relative trigger that warrants shared decision-making.

Historically, "triggers" for intervention include increasing tumour size/stage (>4 cm, cT1b), elevated growth rate (>5 mm/year), development of symptoms, or metastatic disease. In many retrospective and older studies of active surveillance, many patients experiencing a "trigger" were not converted to delayed intervention,[17,36,70] reflecting common contamination of earlier AS cohorts with unhealthy observation patients, which is increasingly not the case.

Categories of triggers for delayed intervention

Delayed intervention triggers are divided into two categories: **1**) **Tumour Factors** related to progression; and **2**) **Patient Factors** unrelated to tumour progression. Tumour factors include: growth rate, tumour size, adverse biopsy histology, tumour stage, and symptoms/signs. Patient factors include: life expectancy, preference or anxiety, improved health, end-stage renal disease, noncompliance, and window for nephron-sparing.[82] The more precise term of progression criteria for intervention (PCI) distinguishes this event from classic clinical progression (i.e., stage, grade, death), as the former may not include the latter.[47] Historically, patient preference has been the most common delayed intervention trigger. Over time, maturation of oncologic safety data has increased patient and physician comfort with AS, and delayed intervention cases are now triggered less by subjective patient anxiety and more by objective tumour PCI. However, patient preference remains impactful in contemporary AS management and contributes to highly variable reported delayed intervention rates (range, 11–50%).[17,38,46,47,70,83–90]

Tumour factors

Standardization of delayed intervention triggers has been challenged by inconsistent descriptions of predefined objective PCI thresholds used prospectively during active surveillance.[17,38,47,70,83–89] Tumour-related PCI generally fall within 1 of 5 categories under the acronym "GLASS": 1) Growth rate; 2) Longest tumour diameter (LTD); 3) Adverse/unfavourable biopsy histology; 4) Stage (infiltration); and 5) Symptoms/signs. Based on incidence alone, growth rate and LTD can be considered major PCI, whereas the other GLASS PCI categories are minor.

In the Roswell Park cohort prospectively managed using all GLASS PCI categories, <3% of AS patients progressed based on biopsy/stage/symptoms (compared to 30% based on growth rate or LTD), and in each case there was simultaneous progression based on growth rate and/or LTD.[47] Objective thresholds used for each PCI category vary greatly among contemporary active surveillance series.[17,38,47,70,83,86,87] Furthermore, nonspecific subjective PCI

thresholds such as “fast” or “significant” growth, “radiological progression,” or “change in SRM’s features” are also still commonly used.[84,85,89,91] As a result, reported rates of PCI development vary widely (9–30%), reflecting heterogeneity in PCI definitions used.[17,47,89] Supporting data and other considerations for each PCI category including specific thresholds are discussed below.

Growth rate

Rapid primary tumour growth rate is the most common predefined PCI in contemporary active surveillance series,[38,47,70,83,87,89–91] and the most common tumour factor triggering delayed intervention in series that also include other PCI.[38,47] A number of contemporary studies support growth rate association with nuclear grade.[47,79,83,92–94] However, some of these series are subject to biases of retrospective data, and prospective studies demonstrate consistent association of growth rate to intervention but not metastases or cancer-specific survival.[46,70] An association between rapid growth rate and clear cell RCC histology is also reported, albeit not consistently.[47,74,87] Abundant and consistent observational evidence supports that rapid growth rate increases metastatic risk, particularly for growth rate >5 mm/year.[33,79,85–87,89,90] A systematic review of more than 800 patients from early active surveillance series identified a median growth rate of 6.5 mm/year among metastatic patients compared to 2.5 mm/year in nonmetastatic patients.[33] Among the >30 cases of AS metastasis now reported for which primary tumour growth rate is also provided, the vast majority had a primary tumour growth rate >5 mm/year.[33,79,85–87,89,90] However, most circumstances of metastases in the literature involve tumours at the larger spectrum of cT1a (approaching or surpassing 4 cm) that were not consistently followed in a prospective program, and doubled in size at the diagnosis of metastatic disease.

Given the limitations of the data, growth rate is believed to be the strongest indicator of biological behaviour. Therefore, current ASCO and AUA consensus guidelines recommend a linear growth rate of >5 mm/year as a PCI threshold, while other major committee consensus guidelines provide no growth rate details.[14,15,30,31] Few studies prospectively used growth rate >5 mm/year as a predefined PCI threshold during active surveillance.[47,70,74,83] These studies and a separate retrospective analysis report a 13–18% rate of meeting the growth rate >5 mm/year threshold with at least intermediate follow-up.[5,6,9,10] A high rate of adverse pathology (68% high grade and/or pT3a) was observed among delayed intervention resections performed due to growth rate >5 mm/year in the Roswell Park cohort.[47] However, data from DISSRM demonstrates no difference in diagnosis of cancer, rates of high-grade or pT3 disease in patients undergoing delayed intervention with growth rate >5 mm/year, those who undergo delayed intervention with growth rate <5 mm/year, and patients who undergo primary intervention.[70] In the study by McIntosh *et al.*, increasing growth rate was associated with higher rates of delayed intervention, but there was no attributable difference in cancer recurrence or mortality based on growth rate.[46] It is clear that elevated growth rate is associated with higher rates of delayed intervention and given the effectiveness of surgical therapy, meaningful conclusions about growth rate and oncologic outcomes remain elusive.

To address this knowledge gap, tumour size–stratified growth rate thresholds were proposed recently by investigators at Roswell Park Cancer Center, who described AS patient outcomes using predefined PCI that included growth rate >5 mm/year for SRMs with LTD <3 cm, and >3 mm/year for SRMs with LTD >3 cm.[47]

Rationale for the slower growth rate threshold with LTD >3 cm included: 1) multiple prior reports to date of active surveillance metastasis with growth rate <5 mm/year but not <3 mm/year; and 2) high likelihood that a patient with LTD >3 cm and growth rate >3 mm/year will meet size-based PCI thresholds (LTD >4 cm) within 1–3 years regardless, making long-term PCI avoidance unlikely in healthy individuals. The authors condoned some degree of overtreatment for these larger-growing SRMs given their higher metastatic risk (>2%), until other PCI thresholds with durable oncologic safety are better established for this group. Additional study is needed to define the role of size stratification in growth rate PCI thresholds.

An alternative to linear growth rate is volumetric growth or doubling rate, reported in a number of studies and used by clinicians from the Canadian RCC Consortium and University of Texas Southwestern Medical Center.[17,74,87] Approximately 90% of new PCI developments reported by these groups were due to rapid volumetric doubling, compared to only a minority due to LTD >4 cm. Caution must be exercised when using this threshold to avoid overtreatment among smaller tumours, as small changes in linear measurements, which can be an artifact or related to both intra- and inter-observer variability, can be correlated with large differences in volumetric assessments (e.g., growth of 0.3 cm in 1 year for a 1.0 cm spherical tumour will qualify as progression). Annual volumetric doubling also permits patients with relatively fast growth (~6–8 mm/year) to remain on surveillance when LTD is >3 cm. This growth rate threshold should be accompanied by an LTD >4 cm size threshold,[17,74,87] as large tumours (e.g., >6 cm) will typically not undergo annual volumetric doubling even when the linear growth rate is quite rapid.

Longest tumour diameter (LTD)

The association between LTD and metachronous metastasis is well described in observational studies, extirpative surgical series, population-based data, and the Von Hippel-Lindau literature.[10,13,19,49,52] In summation, the metastatic potential of tumours less than 2 cm approaches 0% and is less than 1% for tumours <3 cm. For tumours between 3–4 cm, rates of metastatic disease vary from 2% to 3%, and the risk continues to increase for masses greater than 4 cm. These predictions are consistent with metastasis rates observed in systematic reviews of early AS series, in which all metastatic patients had LTD >3 cm at metastasis, including all but 2 patients with LTD >4 cm.[33] More contemporary AS series are also consistent with a negligible metastatic rate when the primary tumour LTD remains <3 cm, and very low metastatic rate for LTD of 3–4 cm, with most metastases occurring with LTD >4 cm.[41,74,85–87,89,90] Accordingly, there is general consensus for use of LTD as a PCI.[14,15,27,30]

Most series use a combination of growth rate and LTD as a trigger for intervention.[17,47,70,74,87] Four centimeters is the most commonly reported cutoff given the inflection point for metastatic disease (described above) and that it represents a change in tumour stage (cT1b). In the Roswell Park cohort, 9% of patients developed a tumour >4 cm encompassing 30% of PCI cases and 50% of delayed interventions.[47] Only 25% of delayed interventions were triggered by LTD >4 cm in the Canadian Cohort.[74] A cutoff >3 cm LTD is endorsed by current AUA Guidelines and for patients with non-high–risk hereditary RCC syndromes.[15] However, prospective use of LTD >3 cm as a predefined PCI in sporadic SRM patients is rarely reported.[41,85] One rationale for this lower-size threshold among healthy patients is that those with LTD surpassing 3 cm will progress to LTD >4 cm shortly thereafter, as

Menon *et al.* observed that only half of patients surpassing 3 cm LTD remained PCI-free 3 years later[47] and the rates of delayed intervention are consistently higher for patients enrolled at 3 cm or greater.[41,42] Nevertheless, a 3-cm LTD threshold will likely overtreat a considerable portion of patients, particularly those with slow growth (<3 mm/year) for which metastasis rates appear to be negligible. In the DISSRM Registry, two-thirds of patients under 60 years old with SRMs >2 cm remained intervention-free at 5 years.[42]

Biopsy histology

The role of RTB for risk stratification during active surveillance remains controversial and is discussed at length previously in the chapter. Some active surveillance centres endorse routine RTB usage (56–67% of patients) and base surveillance strategy on histologic findings;[47,74] however, most contemporary active surveillance series elect a histology-agnostic approach and do not include routine RMB (8–24% of patients).[41,46,83,89]

In addition to providing information regarding cancer, histology, and expected growth rate, formal incorporation of pre-enrollment biopsy can reduce rates of surgery for benign tumours and allow for a risk-stratified approach to active surveillance.[47] The Roswell Park cohort demonstrated no benign tumours in the delayed intervention cohort while active surveillance series without routine RTB report benign tumours in 11–22% of patients undergoing delayed intervention.[17,46,70,83,91] Risk stratification based on RCC histology is more controversial. The PCI defined by the Roswell Park group lists adverse histology as a contraindication to active surveillance; however, the prevalence of adverse histology in SRMs is rare and the ability of RTB to reliably detect these tumours is doubtful. Although it is not yet standardized, there is growing consensus to reserve RTB for SRM with LTD >2 cm, given that smaller sizes have negligible oncologic risk and lower technical success rates.[15,19,47] Studies by Schiavina *et al.* and Menon *et al.* endorse RTB for a rapid growth rate if LTD <2 cm, which may rule out benign neoplastic histology prior to delayed intervention conversion.[47,91] The DISSRM Registry, which does not routinely biopsy patients at enrollment, recommends biopsy for growing renal masses either by growth rate >0.5 cm/year or when they exceed LTD size thresholds (i.e., 2, 3, or 4 cm based on patient characteristics).[41]

Stage/Infiltration

Clinical upstaging from cT1a to cT3a based on radiologic evidence of infiltration into the renal vein, sinus fat, or collecting system is an independent prognostic variable for metastasis. Pathological T3 invasion is rare in cT1a renal masses, typically occurring in 5% or less of patients in surgical series.[13,19] Given the low incidence and a low sensitivity of radiographic detection, clinical upstaging is a rare occurrence in most AS series including the large, prospective active surveillance series. One patient (1%) in the Roswell cohort developed cT3 disease but also demonstrated increasing growth rate and LTD.[47] Whelan *et al.* reported one (of 17) tumour thrombus in a retrospective cohort.[89] Regardless of its rarity, suspicion of cT3a upstaging should trigger delayed intervention consideration due to the increase in metastatic risk.

Symptoms/Signs

Tumour-related symptoms or signs such as gross hematuria, retroperitoneal bleeding, or paraneoplastic effects are well described for RCC but are exceedingly rare in the SRM population. Accordingly, the vast majority of SRMs remain asymptomatic during AS.[47,89] In more than 500 patients and a decade of enrollment, the DISSRM Registry has yet to encounter a patient who developed gross hematuria attributable to a renal mass.[41] One (1%) patient in the Roswell Park cohort and three (18%) patients in the study by Whelan *et al.* reported gross hematuria although it is unclear if attributable to the tumour.[47,89] Paraneoplastic syndromes are also exceedingly rare for clinically localized RCC and are unlikely to be present in patients with SRMs.

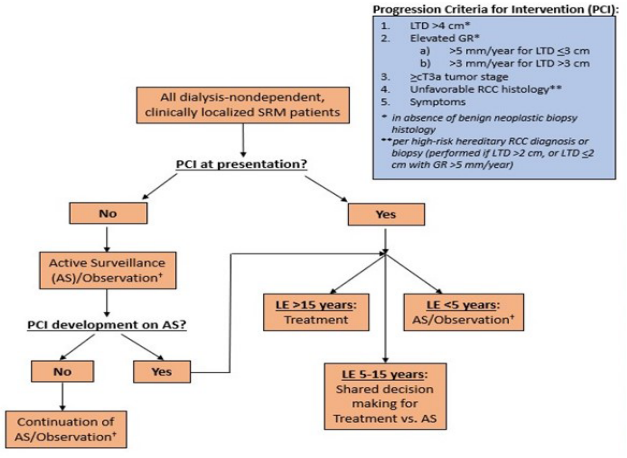
Patient factors

With the exception of a few recent active surveillance series in which delayed intervention conversions were almost entirely driven by PCI,[47,74,91] half or more of delayed intervention cases in contemporary active surveillance reports were performed due to patient factors without PCI.[17,19,26,83,84,90] Given the low rates of death due to RCC, this indicates that current definitions of PCI may not reflect biological behaviour of tumours and underscores the continued impact of patient preference and anxiety in contemporary active surveillance management.

Life expectancy

Life expectancy must be carefully considered prior to delayed intervention conversion, as increased metastasis risk may not increase mortality risk when life expectancy is limited (e.g., <5 years).[95] Age- and gender-adjusted life expectancy calculators are readily available (e.g., https://www.ssa.gov/OACT/population/longevity.html), but they must be further adjusted based on overall health.[96,97] Similarly, a renal mass–specific calculator was recently published by Psutka *et al.* (https://small-renal-mass-risk-calculator.fredhutch.org).[55] In young healthy individuals these triggers should serve as absolute indications for intervention, whereas the oncologic-treatment risk balance may or may not favour AS continuation or observation conversion in elderly/comorbid patients. More recent cohorts, like that reported at Roswell Park, integrate triggers with life expectancy calculations to guide decision-making regarding delayed intervention (**Figure 1**).[47] With extremely high compliance (98%) with protocol-based recommendations, delayed intervention was recommended for individuals with life expectancy >15 years; shared decision-making for individuals with life expectancy of 5–15 years; and observation for individuals with life expectancy <5 years.

FIGURE 1 Integration of PCI and LE in Determining Intervention



*Observation rather than AS was considered for all patients with LE <5 years.

Abbreviations: AS, active surveillance; GR, growth rate; LE, life expectancy; LTD, longest tumour diameter; PCI, progression criteria for intervention; RCC, renal cell carcinoma; SRM, small renal mass.

Source: Reproduced with permission Wolters Kluwer Health, Inc., from: Menon AR, Hussein AA, Attwood KM, et al. *Active surveillance for risk stratification of all small renal masses lacking predefined clinical criteria for intervention.* J Urol. *2021;206(2):229–239. doi:10.1097/JU.0000000000001714.*[47]

Patient preference/Anxiety

Patient preference, typically due to anxiety or disease uncertainty, is by far the most common patient factor triggering delayed intervention. Approximately half or more of delayed intervention cases in the DISSRM consortium, RCC Consortium of Canada, and several single-institute active surveillance cohorts were performed due to patient preference.[26,70,84,90] The acceptance of active surveillance among healthy patients is increasing likely secondary to the maturation of active surveillance practices in other cancers like prostate cancer. Patient anxiety may, in some cases, reflect physician uncertainty regarding the expected clinical course. When the physician is confident regarding an oncologic-treatment risk balance that favours AS, an anxious patient who still requests delayed intervention often may have correctable misconceptions regarding their diagnosis or expected clinical course. Thorough patient counselling and re-education are required in such scenarios, and psychologic supportive care may also be warranted.[98] Given that illness uncertainty can compromise quality of life among renal mass patients who defer intervention,[71] upfront discussion of management details such as specific PCI being monitored may mitigate anxiety by empowering the patient with information while reinforcing the negligible metastatic risk associated with PCI freedom. The DISSRM Registry demonstrates improving mental health domains while in a structured active surveillance program, indicating reductions in anxiety and illness uncertainty.[44] Only one (1%)

patient in the Roswell Park cohort and three (4%) patients in the study by Schiavina *et al.* converted to delayed intervention due to anxiety without PCI development.[47,91] Familial pressure is a less common source of patient preference for delayed intervention for which a medical case manager's involvement may be helpful.[26,75]

Improved patient health

Improved patient health or resolution of an acute health issue during active surveillance may change the risk-benefit ratio toward active treatment. For instance, passage of time beyond requirements for anticoagulation (e.g., deep venous thrombosis) or antiplatelet therapy (e.g., cardiac stent) reduces the risk of bleeding associated with intervention. In other cases, medical clearance may be obtained for an intervention that was previously felt to be risk-prohibitive. Mason *et al.* reported that 25% of delayed interventions could be attributed to this cause, although most contemporary series have not reported delayed intervention cases triggered for this reason.[90]

End-stage renal disease

Patients who have end-stage renal disease with or without dialysis dependence may need SRM resection to qualify for renal transplantation eligibility.[69] Biopsy confirmation of benign histology may or may not be adequate to avoid the need for resection. Some transplant centres are allowing transplant with delayed treatment of the SRM given the growing data supporting the safety of active surveillance, particularly in masses less than 2 cm. Delayed intervention due to end-stage renal disease is rare in contemporary active surveillance reports.[70]

Concern for patient noncompliance

Concern regarding patient noncompliance is a controversial trigger for delayed intervention. It is rarely reported as a reason for delayed intervention conversion, yet many reports of active surveillance metastasis have been attributed to patient noncompliance.[33,86] Careful recognition of potential noncompliance is important to avoid preventable progression to metastatic disease.

Additional unrelated surgery

The need for additional unrelated surgery has been reported as a delayed intervention trigger.[82] Other than renal transplantation, this reason is not generally endorsed, as many morbidities of partial or radical nephrectomy (e.g., renal dysfunction, hemorrhage, urinary fistula, etc.) persist and additional perioperative risks are introduced due to increased total operative time.

Loss of nephron-sparing window

Concern for losing a window to perform nephron-sparing treatment due to the treatment delay may also raise consideration for early delayed intervention. However, the vast majority of delayed intervention cases in contemporary active surveillance reports are amenable to nephron sparing, suggesting no compromise in renal preservation.[26,47,70,74,83–87,91]

Lessons from Delayed Intervention

The ability to safely salvage and cure a tumour with delayed intervention is critical to counselling patients who would initially embark on active surveillance. Based on prior discussions in this chapter, overall and cancer-specific survival are unaffected by active surveillance and delayed intervention. However, given the relatively short follow-up of most studies, adverse pathologic outcomes in delayed intervention cohorts may represent a surrogate for adverse oncologic outcomes. For instance, most tumours treated with delayed intervention would be expected to be inherently larger than found at diagnosis due to interval growth, but whether these individuals have a higher incidence of malignancy or worse cancer disease characteristics (including grade and stage) compared to those with similar-sized tumours removed at time of diagnosis is important to understand. Differences in disease characteristics could be indicative of selecting for treatment of tumours with a more aggressive biology, but there also is the potential for accumulation for additional genetic drivers over time that may arise and change the baseline disease biology.[23,24] Similarly, additional time can also allow aggressive disease the ability to move into adjacent tissue (perinephric fat, the collecting system, or a segmental vein), which leads to pathologic upstaging (pT3). Initial work on active surveillance focused on the ability to surgically salvage patients with more recent series, attempting to characterize the pathologic outcomes at time of resection with delayed intervention.

Rates of benign and malignant tumours at delayed intervention

With surveillance imaging monitoring growth kinetics, both biopsy-proven malignant and benign SRMs can grow with overlapping growth rates, so this may not be indicative of more aggressive biology.[17,99,100] In regard to the rate of malignancy found at surgery, many of the early series demonstrate a similar rate of malignancy from classic series involving SRMs. In 2007, Kouba and colleagues from the University of North Carolina reported 43 patients undergoing surveillance; those with delayed intervention had an 87% rate of RCC.[101] In 2008, Crispen and colleagues from Fox Chase Cancer Center demonstrated that most small renal tumours treated with delayed intervention had a similar expected rate of RCC (84%).[102] One outlier comes from a series in 2016 where Hawken and colleagues at the University of Michigan reported the outcomes of patients with tumours ≤4 cm treated with immediate or delayed treatment over a 7-year period.[106] Unlike prior series that showed similar rates of malignancy, the rate of benign disease was actually greater in those patients who underwent delayed intervention (18% vs. 10%; p=0.04). As there was an increased rate of biopsy and confirming malignancy in the immediate treatment group, this likely accounts for this imbalance and highlights the potential for biopsy to limit treatment even with lesions that could have interval growth or progression. In contrast to these studies, Menon *et al.* at Roswell Park reported a 100% malignant rate among delayed resections, aided by routine RTB to nonsurgically identify and avoid treatment for benign renal tumours.[47]

Upstaging to pT3 RCC

Upstaging to pT3 disease may have important implications on prognosis but is something that is seen infrequently in most series involving SRMs.[103,104] Series have attempted to evaluate whether SRMs not only grow but also exhibit locoregional invasion/upstaging. The Crispen series found a very low rate of upstaging to pT3 disease (1/82 tumours).[102] In 2009, Rais-Bahrami and colleagues from Johns Hopkins matched tumours with similar initial size and clinical demographics that underwent immediate treatment versus delayed intervention.[105] In this series there was no evidence of upstaging, with one found to be pT3 in each group. Despite matching, the series contained only 24 malignant tumours, therefore it was unlikely to discern small differences. A 2012 series from Li and colleagues at Peking University evaluated 32 patients with delayed intervention and while there was size upstaging to T1b or T2 disease due to tumour growth, no patients had progression to pT3 disease at time of surgery.[108] The Michigan cohort is the largest in the literature with 401 and 94 patients undergoing immediate and delayed intervention, respectively.[106] Both groups similarly had a low rate of upstaging to pT3 disease (6% vs. 8%, immediate vs. delayed). Similarly, the rate of pT3 RCC in 46 patients undergoing delayed intervention in the DISSRM Registry was 5.4%.[70] A 2021 series from Menon and colleagues from Roswell Park evaluated specific growth and size triggers for delayed intervention.[47] The rate of upstaging to pT3a was much higher than in other series 8/29 (27.6%), which could be related to the ability to keep most patients (99%) on surveillance until predefined progression. The ability to keep a large number of patients from crossing over to "elective" delayed intervention could have allowed for enrichment of those in greatest need of treatment.[107]

High-grade renal cell carcinoma

The identification of high-grade disease could also have long-term implications on prognosis. Most series involving tumours ≤4 cm have rates of high-grade disease ranging from 10% to 20%.[19,70,107] The Crispen series reported an expected rate of low-grade disease (82%) with an SRM series and the matched cohort from Hopkins with a similar rate between groups.[102,105] The Michigan cohort also had a similar rate of high-grade disease between those with immediate and delayed intervention, but perhaps due to differences in institutional reporting practices, both had greater rates of high-grade disease 49% versus 53% (p=0.6) than the Crispen series.[106] This series also did a composite analysis of the rates of adverse pathology but the groups were identical (44%). This study found that a rapid tumour growth rate predicts an increased likelihood of adverse pathology (20% increased risk for each 1 mm/year growth). This is also similar to the Peking series, which showed higher-grade tumours (at resection) had a more rapid growth rate.[108] In the Roswell Park series, those with a rapid growth rate of ≥5 mm appeared to have a very high rate (11/19; 57.9%) of high-grade disease, which is far greater than in other series.[47] This was also greater than the 5/15 (33%) for those with other triggers for intervention that could be due to the reasons above.

Special Circumstances

Hereditary renal cell carcinoma

Hereditary kidney cancer caused by a known germline alteration accounts for 5% to 8% of kidney cancer cases,[109] though the proportion of cases with a hereditary component may be upwards of 40%.[110] At least 17 genes have been implicated in the development of familial RCC syndromes, each of which is associated with a different histology, biologic potential, clinical natural history, and implication for treatment.[111] Active surveillance is used as an initial strategy for several syndromes, including von Hippel-Lindau (VHL), Birt-Hogg- Dubé (BHD), and hereditary papillary renal cancer (HPRC).

The most common and best studied of these syndromes is VHL. Patients with VHL have germline alterations in the *VHL* gene and are at risk for bilateral, multifocal, and recurrent clear cell RCC. Before cross-sectional imaging was widely available, management was typically bilateral radical nephrectomy, necessitating renal replacement therapy, or, conversely, watchful waiting.[112] Because of the high rate of RCC metastasis, watchful waiting was generally reserved for patients deemed not fit for surgery. With the advent of cross-sectional imaging and the increased use of partial nephrectomy, subsequent studies demonstrated that the metastatic potential of VHL-related RCC was related to tumour size. A threshold of 3 cm was initially adopted as a trigger for intervention and patients with small tumours underwent active surveillance.[54] Patients with VHL-related kidney tumours now routinely undergo AS until the largest tumour reaches 3 cm, at which time all tumours are resected. Using this strategy, there have been no reports of metastatic RCC in patients with VHL when the largest tumour is 3 cm or less. This mirrors sporadic clear cell RCC, where the risk for metastasis for a tumour <3 cm is <1%.[49] A study of 286 VHL-deficient tumours on AS demonstrated a median tumour growth of 0.37 cm/year, which was statistically distinct from other hereditary syndromes.[78] AS intervals can be individualized based on tumour size and growth rate, and generally consist of cross-sectional imaging between 6 and 36 months.

The 3-cm threshold was subsequently adopted for BHD and HPRC. Patients with BHD have a germline alteration in the *FLCN* gene and are at risk of developing chromophobe RCC, hybrid oncocytic tumours, and oncocytomas.[113] Tumours in BHD tend to be slow growing, with a median growth rate of 0.1 cm/year while on AS.[78] Using the same treatment strategy as outlined for VHL, patients with BHD were found to have no reported metastasis when the largest tumours were treated at the 3-cm threshold.[52,114] Because of their slow growth kinetics, patients with BHD may be eligible for extended intervals between cross-sectional imaging, up to every 3 years for appropriately selected, small tumours and larger-size cutoffs for intervention may be appropriate.[78]

Patients with HPRC have germline alterations in the *MET* gene and develop bilateral, multifocal papillary type 1 RCC.[115] Like BHD, HPRC tumours tend to be slow growing, with a median growth rate of 0.15 cm/year.[78] These tumours also demonstrate size-related metastatic potential, with no reported metastases when treated at or below 3 cm.[52] Like BHD, HPRC may also be eligible for extended interval AS.

BAP1-tumour predisposition syndrome is a more recently described hereditary syndrome caused by germline alterations in *BAP1* and is associated with the development of clear cell RCC, along with mesothelioma and melanoma.[116] Somatic *BAP1* alterations have been associated with high-grade, high-stage, low-survival clear cell RCC in the Cancer Genome Atlas.[22] Germline *BAP1* tumours are associated with accelerated growth on AS, with a median growth of 0.6 cm/year,[78] which is higher than the proposed cutoff of 0.5 cm/year for AS candidates. While long-term data for BAP1 AS is limited, more frequent surveillance intervals may be appropriate if AS is used in these patients.[78,111]

While AS is an initial strategy for the VHL, BHD, and HPRC, it should be noted that it is not recommended for all hereditary syndromes. For instance, patients with hereditary leiomyomatosis and renal cell carcinoma (HLRCC) as well as patients with succinate-dehydrogenase (SDH)-deficient RCC are at risk for development of metastatic disease even when tumours are small, and therefore AS is not recommended.[111]

Benign lesions (oncocytoma, angiomyolipoma)

Renal masses have traditionally been treated with extirpative surgery, leading to upwards of 40% of SRMs having benign pathology at the time of surgery.[20] The two most-common benign renal masses are renal oncocytoma and angiomyolipoma (AML), accounting for 75% and 11% of benign nephrectomy specimens, respectively.[49]

Most AMLs have a characteristic appearance on imaging related to presence of macroscopic fat in the tumours—including negative attenuation on CT, increased echogenicity on ultrasound, and signal drop on MRI.[117] Approximately 5% of AMLs known as fat-poor AMLs lack these findings and are diagnosed with surgery or renal tumour biopsy. Renal oncocytomas have a similar appearance to RCC on cross-sectional imaging, including early enhancement on CT scan.[118] Recent developments in imaging including the use of technetium-99m sestamibi single-photon emission computed tomography (SPECT)/CT[77] and artificial intelligence algorithms[119] have aided in the preoperative detection of renal oncocytoma. Together, with the rise in use of renal tumour biopsy, more benign lesions are being diagnosed before surgery, enabling the intentional use of active surveillance in these populations. Histologically, oncocytoma diagnosis by biopsy is challenged by considerable morphologic and immunohistochemical overlap with chromophobe RCC, both expressing the CD117/c-KIT protein biomarker. Amin *et al.* retrospectively identified and prospectively validated CT contrast enhancement level (tumour:cortex peak early enhancement ratio, or PEER score) to reliably distinguish CD117+ oncocytoma from CD117+ chromophobe RCC, including with 100% accuracy and 100% interobserver reproducibility in their series.[76] More recently, PEER scoring has been used by these investigators to achieve a 0% benign resection rate among more than 250 consecutive renal tumour resections, but it awaits external validation.[133]

The indications for treatment of a benign renal mass include reducing the risk of bleeding, mitigating uncertain oncologic risk or theoretical risk of renal compromise from mass effect. In the case of AML, larger size has historically been associated with an increased risk for spontaneous hemorrhage. A cuffoff of 4 cm was proposed as a threshold over which intervention,[121] usually in the form of angioembolization, was considered to mitigate the risk of bleeding. However, more contemporary series have demonstrated the safety of AS for AML above

4 cm, with >90% of AML demonstrated limited growth over 43 months of follow-up.[122] As a result, growth of >0.25 cm/year was proposed as a criteria for intervention. Other data suggest that pseudoaneurysms within an AML are more predictive of bleeding risk.[123] Taken together, an initial period of AS to determine growth rates, development of symptoms, and monitor pseudoaneurysm size can be considered in patients with AML.

Data on the treatment of oncocytoma is limited. While oncocytomas are benign tumours, there are rare case reports of patients with large oncocytomas that have metastasized to liver, although without lethality, and the malignant nature of these synchronous liver lesions remains unclear.[124] Moreover, in several cases, histologic images accompanying the report of oncocytoma metastasis have suggested instead misdiagnosis of RCC. A recent report of 89 patients with biopsy-proven oncocytoma demonstrated no metastatic progression or disease-specific death. Median tumour growth was 0.24 cm/year, and 27% of patients converted to active treatment.[125] The active surveillance program at Roswell Park excludes patients with benign oncocytoma histology on biopsy from meeting progression criteria for delayed intervention.[47]

There has been a theoretical concern that mass effect from oncocytomas can impact renal function. A single study demonstrated that patients with oncocytoma treated with surgery had better GFR preservation compared to those on AS.[126] However, Roswell Park investigators more recently used volumetry software to measure ipsilateral renal parenchyma volume during oncocytoma growth and found that loss of either renal parenchymal volume or renal function was uncommon and unrelated to tumour growth when present, supporting the functional safety of active surveillance for oncocytoma patients.[120] Similar stability in renal function in a cohort of patients with oncocytic tumour patients comprising predominantly oncocytomas was reported by Miller *et al.*[127] While active surveillance is an oncologically safe and potentially functionally safe strategy, data on triggers for intervention in this population requires further study.

Renal cysts

Renal cysts are commonly diagnosed on imaging. Upwards of 50% of the population will develop at least one renal cyst by the time they reach 50 years of age.[128] Increasing complexity within a cyst (e.g., septations, enhancement, or mural nodules) is associated with increasing oncologic potential. The Bosniak system was developed based on the CT characteristics of cystic lesions and the risk of harbouring malignancy.[129] Because of the high proportion of malignancies associated with Bosniak III and IV lesions, surgery has traditionally been recommended. The incidence of RCC in Bosniak IIF, III, and IV cysts is 6–18%, 51–55%, and 89–91%, respectively.[130] Compared to solid tumours, cystic tumours are associated with a better prognosis.[131] More recently, active surveillance has been used for complex cystic lesions, given their typical absence of metastatic potential. A recent series of 336 patients with Bosniak IIF and greater lesions followed for a median of 63 months demonstrated only one cancer-related death, and 88% of resected tumours demonstrated low-grade disease on pathology.[132] The authors conclude that active surveillance may be considered as an initial treatment strategy for Bosniak III lesions and select patients with Bosniak IV lesions. Future research is needed to determine ideal surveillance protocols for cystic lesions and triggers for intervention.

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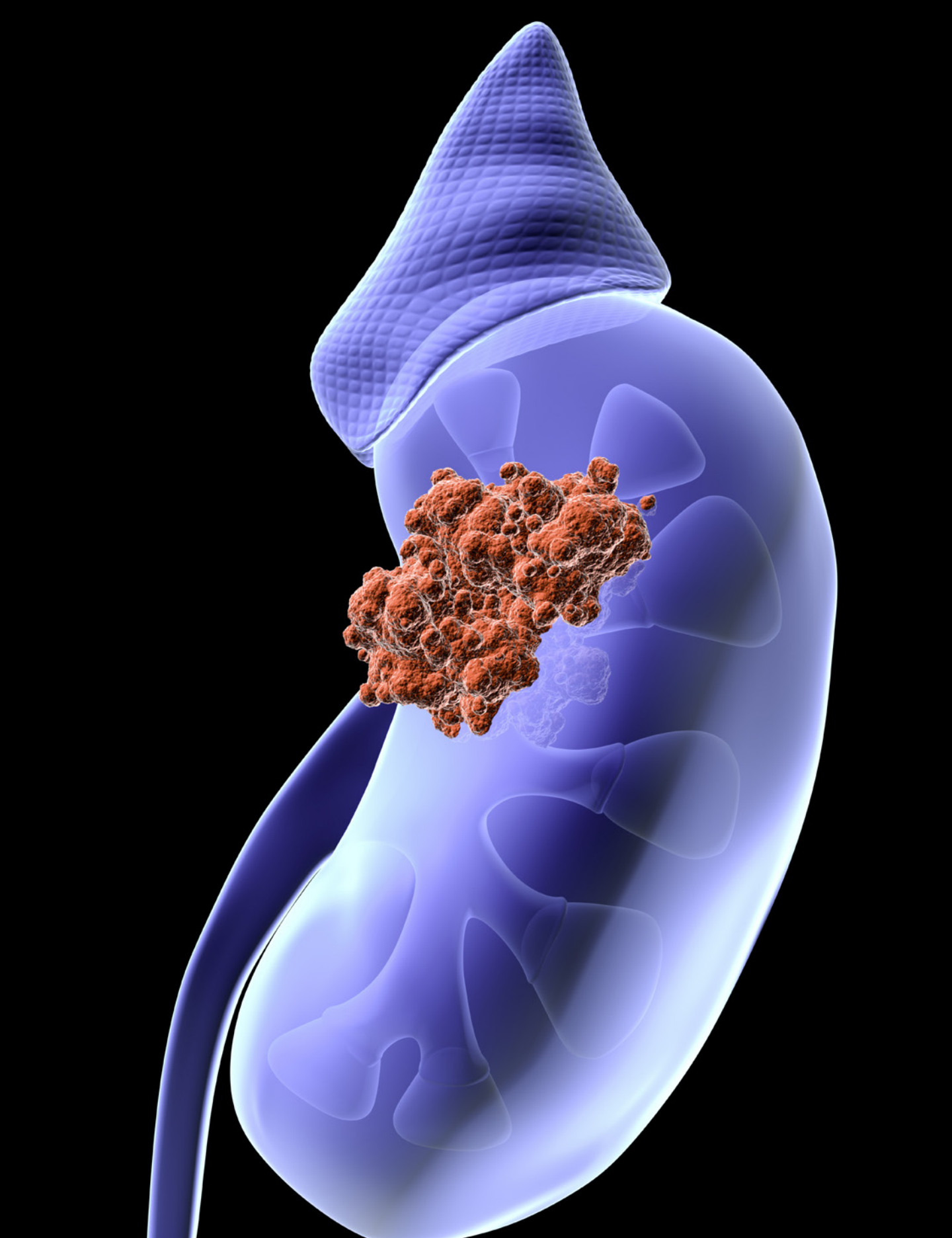

COMMITTEE 11

Management of Locally Advanced Disease (Including Caval Thrombi)

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Introduction

Locally advanced renal cell carcinoma (RCC) comprises stage III and nonmetastatic stage IV disease. This includes RCC extending beyond the kidney, specifically into the intrarenal and perirenal adipose tissue and pelvicalyceal system, into the major veins, or invading beyond Gerota's fascia, including contiguous extension into the ipsilateral adrenal gland or surrounding organs. Tumours with regional lymph node involvement, including invasion of the regional or hilar/retroperitoneal lymph nodes, such as the paraaortic, paracaval, and interaortocaval lymph nodes, are also generally included in this category. According to the American Joint Committee on Cancer (AJCC) tumour-node-metastasis staging system (TNM), these tumours are designated cT3a-c or T4 N0-1 M0.[1]

The incidence by stage of RCC at diagnosis is observed to be 5–19% for stage III RCC and up to 30% for stage IV RCC (including patients with metastatic RCC).[2,3] Over the past quarter century, the prevalence of localized RCC has increased, while the prevalence of regional and metastatic RCC has declined to less than 15%.[3] Venous tumour thrombus (VTT) involvement is identified in up to 10% of patients with RCC.[4] In the most recent iteration of the AJCC staging system for RCC, node-positive (cT1-3N1M0) malignancies were recategorized as stage III.[1] Current pN1 rates in localized, low-risk populations (cTxN0N0) range from 1% to 5% and increase to 5.2–13.2% in pT1-2 disease and 23.4–36.1% in pT3-4.[5]

Survival with RCC varies broadly across stages, with 5-year relative survival in patients with localized (cT1-2), regional (cN+), and distant (cM+) RCC being 93%, 70%, and 12%, respectively.[6] The 5-year survival estimates vary according to the criteria by which a patient meets criteria for locally advanced disease (**Table 1**). Of note, while the tumours are classified according to the TNM staging by the most advanced feature the tumour demonstrates, the number of advanced features has also been associated with survival outcomes, with worsening prognosis observed in patients with tumours meeting multiple high-risk criteria.[7–12]

TABLE 1 5-Year Survival Estimates for Patients with Locally Advanced RCC, Specific to Locally Advanced Criteria[1,13–20]

Stage-defining criteria	TNM stage (8th edition)	5-year survival estimate (%)
Invasion of the pelvicalyceal system	T3aN0M0	50-70
Invasion of the perinephric or renal sinus fat	T3aN0M0	50-70
Extension into the renal vein or its branches	T3aN0M0	40-60
Extension into the IVC below the diaphragm	T3bN0M0	30-50
Extension into the IVC above the diaphragm or invasion into the IVC wall	T3cN0M0	20-40
Extension into the ipsilateral adrenal gland	T4N0M0	0-30
Invasion beyond Gerota's fascia	T4N-M0	0-20
Regional lymph node involvement	T(any)N1M0	0-20

Abbreviations: IVC, inferior vena cava; TNM, tumour-node-metastasis staging system.

Currently, surgery remains the only curative approach for M0 RCC with inferior vena cava (IVC) invasion. While an open approach most commonly used, there is growing interest regarding the role for minimally invasive approaches (e.g., laparoscopic, robotic-assisted laparoscopic surgery) in appropriately selected patients; however, there is limited data regarding long-term outcomes regarding these approaches. The optimal surgical approach is determined on a case-by-case bases, considering tumour- and patient-specific characteristics, as well as surgeon experience. In many cases, the surgical management of locally advanced RCC with IVC tumour thrombus requires multidisciplinary collaboration between the urologic oncologists and colleagues in vascular, hepatobiliary, transplant, and/or cardiothoracic surgery, as well as medical oncology. In select patients presenting with IVC tumour thrombus and synchronous distant metastases, cytoreductive nephrectomy with IVC tumour thrombectomy may be considered with or without neoadjuvant systemic therapy. In this chapter, we will discuss the presentation and pathophysiology, management approaches, and clinical and oncologic outcomes for patients with locally advanced RCC with or without IVC tumour thrombus.

Classification of VTT in Renal Cell Carcinoma

An unusual hallmark of RCC is its predilection for vascular invasion, where the tumour grows directly into the venous drainage of the tumour. The VTT can then form a cast of the main renal vein (pT3a) and extend proximally into the inferior vena cava (IVC; pT3b), in some cases extending into the left atrium of the heart (pT3c) or invading directly from the venous lumen into the endothelium (pT3c). Early series suggested that the prevalence of VTT in RCC was as high as 36%, although more recent estimates in contemporary practice suggest that VTT is identified in approximately one in ten patients with newly diagnosed RCC.[21–30] Involvement of the right cardiac chambers is encountered in 1% of cases.[31]

TABLE 2 Classification of VTT Level in RCC: The Mayo Classification System

Level	Anatomic landmark
0	Thrombus limited to the segmental or main renal vein, detected clinically or during pathologic evaluation.
I	Thrombus extends into the infradiaphragmatic IVC, within 2 cm of the renal vein ostium.
II	Thrombus extends into the infradiaphragmatic IVC, > 2 cm above the renal vein ostium but below the confluence of the hepatic veins.
III	Thrombus extends into the infradiaphragmatic IVC, above confluence of the hepatic veins.
IV	Thrombus extends above the diaphragm, and may involve the right atrium.

Abbreviations: IVC, inferior vena cava; RCC, renal cell carcinoma; VTT, venous tumour thrombus.

Source: Originally described by Neves RJ, Zincke H. Surgical treatment of renal cancer with vena cava extension. Br J Urol. *1987;59(5):390–395. doi:10.1111/j.1464-410x.1987.tb04832.x.*[32]

VTT is classically categorized according to the height or extent of the VTT, according to the Mayo Classification system (**Table 2**). The level of tumour thrombus is relevant not only from the perspective of oncologic prognosis but also in terms of anticipating surgical complexity and surgical planning. Among 650 patients with VTT treated at the Mayo clinic between 1970 and 2004, interruption of the IVC was required in 160 of 650 patients (24.6%), including 15% of level II tumours, 28% of level III tumours, and 50% of level IV tumours.[30] Blute *et al.* proposed categorization of IVC tumour thrombi according to the degree of occlusion and distal or bland thrombus to predict optimal management of the IVC following thrombectomy (**Table 3**). It is notable that the placement of IVC filters prior to nephrectomy and IVC thrombectomy remains controversial due to the risk for incorporation of the filter into the thrombus, which can complicate thrombectomy.[30]

TABLE 3 Classification Scheme for IVC Interruption Based on Degree of Venous Occlusion and Bland Thrombus

Venous occlusion of the IVC?	Bland thrombus present/ Location?	Postthrombectomy IVC recommended management
No	No	Primary cavotomy closure, IVC in continuity
Partial	Distal (pelvic veins)	Greenfield Filter placement
Total/Partial with visible collateralization	Yes	Staple ligation of the IVC below the renal hila
Total occlusion	Yes	Segmental resection of the IVC below the renal hila

Abbreviations: IVC, inferior vena cava.

Source: Based on Blute ML, Boorjian SA, Leibovich BC, et al. *Results of inferior vena caval interruption by greenfield filter, ligation or resection during radical nephrectomy and tumor thrombectomy*. J Urol. *2007;178(2):440–445; discussion 444.*[30]

Beyond the extent of the tumour thrombus as classified above, other features of the VTT are associated with both surgical complexity as well as oncologic outcomes. Direct invasion of the tumour thrombus into the endothelium of the renal vein or IVC is associated with increased surgical complexity due to the need to both excise and potentially reconstruct IVC.[33,34] Recent reports have highlighted the prognostic relevance of associated bland thrombus in RCC, which has been demonstrated to be independently associated with inferior cancer-specific survival.[35–37] Bland thrombus may be associated with both occlusive and nonocclusive VTT and may propagate adjacent to or in a retrograde fashion distal to the tumour thrombus. In cases where bland thrombus is identified on preoperative imaging or there does not appear to be flow through the IVC, preoperative therapeutic anticoagulation is generally recommended.[38]

Macroscopically, venous tumour thrombi can also be categorized according to their consistency, and may be described as either solid or friable, where friability has been associated with worse prognosis. Friable VTT is described as an innate characteristic of the tumour thrombus, involving approximately one-third of tumour thrombus cases, and is independent of tumour handling.[39] Friable VTT has been associated with increased risk for synchronous nodal and distant metastases, high tumour grade, high pathologic stage, and perinephric invasion.[39,40] However, results from a large multiinstitutional cohort challenged these findings,[41] and a subsequent metanalysis of 19 articles suggested that tumour thrombus friability was associated with other adverse pathologic features but was not independently associated with poor cancer-specific or overall survival.[42]

At the molecular level, evaluation of VTT specimens demonstrated a high number of proliferating Ki-67–positive tumour cells, also demonstrating activation of PI3K-AKT-mTOR signalling pathways, which are associated with both cell survival and proliferation.[43] Recent efforts using multiregion whole-exome sequencing of RCCs with VTT suggests that preexisting subclones of the primary tumour are responsible for driving the formation of VTT.[43] Furthermore, clear cell RCC (ccRCC) demonstrates a high degree of mutation heterogeneity,[44] with approximately 9% of all altered genes in viable tumour thrombus cells not identified in the corresponding primary tumour.[43] Clonal phylogeny analyses of RCC with VTT demonstrated phylogenetic separation between the primary tumour and tumour thrombus, with higher replication rates in the venous thrombi cells compared to the primary tumour samples. Finally, mutational signature analysis demonstrates that a subset of RCCs with VTT show signs of "BRCAness," reflecting mutations in DNA repair genes such as *BRCA1* or *BRCA2*. Among sequenced RCC with VTT, no mutations were detected in *BRCA1* or *BRCA2* specifically; however, mutations were identified in *BAP1, CKD12, RTCC1,* and *PTEN*, which are implicated in "BRCAness".[45] This work has been interpreted to suggest that, despite mutational heterogeneity in RCC, no additional specific mutations are required for the RCC to form VTT, such that this process can be driven by preexisting subclones of the primary tumour.

Pathophysiology of Tumour Venous Thrombosis

The affinity of RCC for invasion into the venous drainage of the kidney is a key hallmark of the disease and is associated with poor clinical and oncologic outcomes. In a population-based analysis, untreated VTT is associated with a median survival of 5 months and a 1-year overall survival of 29%.[46]

Complete occlusion of the IVC by VTT or by propagation of proximal bland thrombus that develops due to venous stasis related to tumour-thrombus-related obstruction has multiple potential physiologic consequences. The temporal nature of IVC obstruction is highly relevant, as rapid progression and IVC obstruction without adequate time for development of collateralization and alternate routes for venous return to the heart may result in rapid lower extremity edema and pain, with decreases mobility. Men may report new scrotal swelling and development of varicoceles due to venous obstruction of the gonadal veins while women may report pelvic pain from ovarian vein obstruction. In men, new presentation with a right-sided varicocele should prompt evaluation of the IVC venous drainage, as this is an uncommon presentation in the absence of IVC tumour thrombus and IVC obstruction.

Rapid progression of IVC tumour thrombus may result in IVC occlusion, reduced venous return to the right atrium (reduction in preload), and consequent reduction in cardiac output. To compensate, the heart rate may increase to preserve adequate perfusion to end organs. However, with prolonged insufficient venous return and cardiac output, patients may develop hemodynamic instability, and altered mental status, end-organ failure, and death. Other commonly reported symptoms may include fatigue, dizziness, weight loss, abdominal pain, night sweats, anorexia, palpitations, diaphoresis, dizziness, and shortness of breath on exertion.[47]

Venous outflow obstruction of IVC due to tumour thrombus can impact the viscera with veins that drain into the abdominal IVC. For example, failure for the ipsilateral or contralateral kidney to have adequate venous drainage can result in progression of renal insufficiency, elevated creatinine/reduction in estimated glomerular filtration rate, and the sequelae of renal failure. Similarly, obstruction of the hepatic veins by level III or IV IVC tumour thrombus can lead to hepatic congestion, which presents with transaminitis, hepatic insufficiency or failure, ascites, and Budd-Chiari syndrome, characterized by hepatomegaly, splenomegaly, jaundice, peritoneal ascites, portal hypertension, with or without impaired liver function, resulting from obstruction of the hepatic venous system by a bulky IVC thrombus.[48–51] Notably, end-stage organ failure is associated with substantial increase in the risk for perioperative morbidity and mortality and can preclude a patient from undergoing nephrectomy and IVC thrombectomy.

Up to 5% of patients with RCC and IVC tumour thrombus may present with pulmonary embolism.[20,52,53] Massive pulmonary embolism can result in hypoxia and rapid hemodynamic compromise and death, while patients with subsegmental pulmonary embolism of VTT may have limited physiologic impact. It is of note that pulmonary tumour emboli contain viable neoplastic cells, which has prompted some authors to advocate for pulmonary embolectomy at the time of surgery to optimize cancer control.[54] Finally, either embolization

or locally advanced level IV IVC tumour thrombus that grows into the right atrium can cause atrioventricular blockage with acute heart failure and death.

While many of the above pathophysiological processes are related to relatively rapid IVC obstruction, in the setting of slower tumour progression to complete IVC obstruction, venous collateralization can develop to provide alternate routes of venous return to the heart. Collateral venous return in the setting of IVC obstruction may include drainage via the azygos-hemiazygos circulation, vertebral pathways via prominent lumbar veins, collateralization of the portal-venous system, as well as via aberrant parasitic vessels emanating from the tumour itself or superficial/subcutaneous veins, as is observed in patients presenting with a "Caput medusa".[55,56] The degree of collateralization depends on the duration and extent of the IVC obstruction and is important to consider when determining optimal management of the IVC itself as well as anticipating potential blood loss and surgical risk.

Clinical Manifestations of RCC with IVC Tumour Thrombus

RCC with associated VTT may demonstrate several salient and unique clinical findings that are generally associated with reduction in venous return through the IVC and resultant venous collateralization as described in the previous section. As is the case for RCC without VTT, many of these tumours do not cause clinical symptoms initially due to their protected location within the retroperitoneum. However, rapid local growth or VTT propagation, hemorrhage, paraneoplastic syndromes, or synchronous metastatic disease may be associated with systemic symptoms. In current practice, the ubiquity of cross-sectional imaging has been associated with a stage migration in the diagnosis of RCC, with a higher proportion of tumours being diagnosed incidentally at lower stages.[57–59] The classic triad associated with RCC including a palpable renal mass, flank pain, and hematuria is an unusual presentation in contemporary practice. Systemic symptoms including generalized fatigue, malaise, night sweats, unintentional weight loss with cancer cachexia, and declines in performance status are nonspecific, but are associated with poor outcomes in patients with RCC with or without VTT.[20,60]

Classic signs and symptoms that are unique to RCC with associated VTT of the IVC resulting in venous obstruction include lower extremity edema, acute varicocele, especially on the right side, and ascites. With longstanding bulky IVC thrombus causing complete obstruction of the IVC, patients may present with painless dilation of the subcutaneous veins of the abdomen, generally branching out from around the umbilicus, termed "Caput medusae". Additionally, patients may present with Budd Chiari syndrome, as described above, other signs of IVC Syndrome, as described in the previous section, or complications related embolization of the thrombus including pulmonary embolism and right heart failure. It is important to note the preoperative pulmonary embolism in the context of RCC with VTT does not necessitate deferral of surgical management with nephrectomy and IVC thrombectomy. Of note, preoperative pulmonary embolism in this setting is not associated with increased 90-day mortality, RCC recurrence, or cancer-specific mortality.[20,61]

Diagnostic Imaging and Staging

The evaluation of a patient presenting with concern for a locally advanced RCC begins with a detailed history-taking, with the goal of establishing a patient's symptom profile. A comprehensive physical examination including evaluation for symptoms that may be associated with tumour vein thrombus involving the IVC should be undertaken. Basic laboratory evaluation includes a comprehensive metabolic panel, complete blood count with differential, assessment of coagulation profile, serum calcium, and urinalysis to assess for the presence of microscopic hematuria and proteinuria.[62]

Staging evaluation consists of cross-sectional imaging of the chest, abdomen, and pelvis to characterize the size of the primary tumour and assess for potential involvement of adjacent structures or distant metastases, to assess for the presence of a VTT. In the case where a VTT is identified, cross-sectional imaging provides critical details regarding the level of the thrombus, the presence or absence of IVC occlusions, the degree of associated parasitic blood vessels and of venous collateralization, and the volume and location of association bland thrombus.[47,63,64] Multiphase computed tomography (CT) and magnetic resonance imaging (MRI) are acceptable staging imaging modalities for the staging and characterization of locally advanced RCC; however, there are advantages specific to each modality. In general, the metastatic evaluation should be performed within 30 days of definitive surgery. In patients with lower extremity edema, a Doppler ultrasound is indicated to assess the venous patency of the lower extremities. Also, in patients with neurological symptoms, head imaging (CT or MRI) should be obtained to rule out brain metastases.

The arterial phase on CT imaging is helpful to establish understanding of the arterial supply to the kidney and primary tumour, while the portal venous phase on CT imaging is used to evaluate the endoluminal tumour thrombus level and permit classification according to the Mayo system as detailed above. This phase may also permit distinction of bland thrombus from VTT, and detect local invasion of the VTT into adjacent structures.[38,65] It is notable that recent studies suggest that, while CT and MRI form the cornerstone of RCC diagnosis, they have relative limited sensitivity for the diagnosis and accurate characterization of stage III RCC, and specifically for T3a tumours, the sensitivities are limited for the diagnosis of perirenal fat invasion and renal vein involvement (15.4% and 11.3%, respectively).[66]

Regarding characterization of VTT, given the propensity for rapid progression, most authors advocate for abdominal MRI to be performed within 1-2 weeks of definitive surgery.[27,28,47,56,64] Gadolinium administration at the time of MRI is dosed according to renal function and is recommended for patients with estimated glomerular filtration rates (eGFR) greater than 60 mL/min/1.73 m^2 with dose reduction for eGFR between 30 and 60 mL/min/1.73 m^2 to avoid the risk for nephrogenic systemic fibrosis. MRI is generally favoured over CT for the detection of VTT because the sensitivity in this setting approaches 100% while the sensitivity of conventional CT scans is 65% compared to 93–96% with multidetector CT scans.[67,68] Thus, multidetector CT imaging provides an acceptable alternative for patients in whom MRI is contraindicated due to non-MRI-compatible implants such as pacemakers, morbid obesity, or in those patients who are unable to tolerate an MRI due to claustrophobia.

Characterization of the IVC tumour thrombus, beyond assessment of the extent and distribution of bland thrombus, as detailed above and discussed by Blute *et al.*,[30] has also been proposed as important for surgical planning and risk prognostication in the setting of IVC tumour thrombus. Poor prognostic indicators include maximal IVC thrombus diameter > 40 mm,[33] complete occlusion of the IVC,[69,70] anterior-posterior diameters of the IVC and renal vein at the level of the renal vein ostium > 19 and 14 mm, respectively, which was found to be 90% sensitivity for IVC wall invasion.[70] Other features characteristic of wall invasion include tumour signal on both the intraluminal and extraluminal IVC wall on MRI.[71] A recent contemporary series of 172 patients with IVC venous tumour thrombi demonstrated that the presence of a right-sided primary tumour, AP diameter of the IVC at the renal vein ostium of at least 24 mm, and radiographic evidence of complete occlusion of the IVC at the level of the renal vein ostium were independently association with risk of need for extensive vascular resection and/or reconstruction beyond a primary cavorraphy at the time of IVC tumour thrombectomy.[34]

Historically, venography was used to evaluate for VTT; however, this modality has fallen out of favour due to its invasiveness and moderate risk for associated complications.[65] In current practice, venography may be useful to establish the extent of collateralization in cases of bulky IVC tumour thrombus with chronic IVC occlusion where IVC resection is anticipated.

Comprehensive radiographic characterization of IVC tumour thrombus is critical to inform anticipation of the extent of vascular resection and/or reconstruction as well as additional surgical expertise (e.g., vascular surgery) that could be needed at the time of nephrectomy and IVC tumour thrombectomy. At the time of surgery, transesophageal echocardiography can provide real-time, additional information regarding the tumour thrombus, with respect to the upper extent of the thrombus and involvement of the intra- and supra-hepatic IVC, hepatic veins, and left atrium. It can also provide helpful information regarding the consistency and mobility of the thrombus. Transesophageal echocardiography (TEE) is helpful to evaluate for involvement of the intra- and supra-hepatic IVC, hepatic veins, and left atrium. It may also be used throughout the case to evaluate for embolization and cardiac function in real time.[72] Contrast-enhanced ultrasound has also been proposed as a useful intraoperative adjunctive imaging study to differentiate bland from VTT and for the identification of IVC wall invasion, with a sensitivity and specificity of 100 and 96%, and 93 and 94%, respectively.[73]

Neoadjuvant Therapy Before Radical Nephrectomy and Thrombectomy

Currently, neoadjuvant treatment is not recommended prior to surgical resection of kidney cancer off clinical trial. However, neoadjuvant treatment has been identified as a high-priority area for contemporary RCC research.[74,75]

There are a number of hypothetical advantages to neoadjuvant therapy for locally advanced RCC. Firstly, there is the potential to downstage the tumour, be that the primary lesion or a VTT, the rationale being to enable less-invasive surgery as more extensive approaches are associated with greater morbidity and mortality.[52] Secondly, it is possible that neoadjuvant therapy can prevent subsequent cancer recurrences after surgery, enabling a more successful multimodal approach. Thirdly, treatment prior to surgery allows systemic therapy to be delivered to a patient at the earliest point in the disease process. Given than patients may be more physiologically robust at the presurgical timepoint, they may be able to tolerate treatment more successfully than they would be following surgery. The corollary to this is that some patients might have their fitness for surgery compromised by time on toxic systemic therapy, and as the neoadjuvant treatment duration supersedes the usual waiting time for cancer surgery, the delay to surgery might compromise the outcome in patients with disease progression despite systemic therapy. Fourthly, for neoadjuvant immunotherapy regimens, there is growing evidence that neoadjuvant T-cell checkpoint inhibitor treatment can activate antigen-specific T cells in the primary tumour. This process may have an antitumour effect on any remaining cancer cells following resection, which might prevent recurrence but also might prime the immune system for subsequent adjuvant therapy.[76] Data from other cancer types has shown that neoadjuvant therapy can be more oncologically effective that adjuvant therapies.[77] Finally, neoadjuvant trials allow the study of changes that occur with novel systemic therapies by enabling the collection of tumour biopsies before, during, and after treatment (e.g., from the nephrectomy). These precious sample sets allow study of the mechanisms of action and resistance of novel therapies in RCC.

As mentioned above, there are no current guideline-based recommendations for neoadjuvant treatments for use in RCC. However, there have been several clinical trials designed to evaluate the use of neoadjuvant systemic therapy that have been completed, are actively recruiting at the time of this writing, or which are anticipated. Notably, Karam *et al.*[78] performed a phase 2 trial evaluating 12 weeks neoadjuvant axitinib in patients with cT3a ccRCC. The authors were able to titrate all patients up to 10 mg axitinib with no grade 4/5 toxicities and with good RECISTv1.1 responses (46% partial response [PR] and 54% stable disease [SD]). They reported a median reduction in primary tumour diameter of 28% (median change from 10 cm to 6.9 cm) by week 12.

There is no level I or II evidence of presurgical systemic therapy in either nonmetastatic or metastatic RCC VTT. Retrospective studies have been undertaken and these focused on mixed groups of targeted therapies:[79–82] sunitinib[83,84], axitinib,[85] and pazopanib.[86] The median number of treatment cycles administered was 2. VTT level decreased in a median of 22.6% patients (range, 14.9–32.9%), remained stable in 73.6% (64.1–81.4%), and increased in 7.2% (3.4–14.3%). Results were most favourable for preoperative sunitinib and axitinib.[79,81,85] There are also several prospective studies on vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) in the pre-nephrectomy setting,[78,87,88] but none had a primary or secondary endpoint of addressing whether these agents downstaged VTT-based local extension of kidney cancer. As part of a larger study of neoadjuvant pazopanib, Wood *et al* reported on four patients with IVC VTT but reported no change in the subsequent surgical management, and did not report changes in the extent of venous involvement.[87] The results of these various small studies in non-metastatic RCC patients suggest that neoadjuvant VEGFR

TKI treatment of RCC patients is safe and reduces tumour size. However, the effect of these drugs on the extent of the VTT and effect on surgical approach has not been confirmed. As such the NAXIVA clinical trial (NCT03494816) was undertaken to determine safety, efficacy, and effect of neoadjuvant axitinib on VTT.[89]

NAXIVA was a single-arm, single-agent, multicentre, phase 2 feasibility study enrolling 20 patients with resectable ccRCC and VTT who received up to 8 weeks of presurgical axitinib. The primary endpoint was percentage of evaluable patients with an improvement in VTT by Mayo level as previously described.[52] Secondary endpoints included percentage change in surgical approach and VTT length and surgical morbidity (Clavien-Dindo grade). The study found that 35.3% (7 of 20) patients with VTT had a reduction in Mayo level with axitinib therapy: 37.5% (6 of 16) with IVC VTT and 25% (1 of 4) with renal vein RV-only VTT. No patients had an increase in Mayo level. Of the patients, 75% (15 of 20) had a reduction in VTT length (median, 27.2%; range, -20% to 51%). And 41.2% (7 of 17) of patients who underwent surgery had a less-invasive surgical approach. Drug and surgery-related adverse events were as expected with Clavien-Dindo grade ≥3 complications observed in 11.8% (2 of 17) of patients. As such, this trial provided initial evidence that VEGFR TKIs can successfully downstage VTT in a significant proportion of patients, leading to a reduction in the extent of surgery. However, before this strategy can be considered for routine clinical practice, future randomized studies evaluating contemporary standard-of-care treatment combinations (immuno-oncology [IO/IO] or IO/TKI) are needed, together with consideration of survival-based endpoints.

As the evidence for adjuvant T-cell checkpoint inhibitor use in RCC gathers pace,[90] there is considerable interest in RCC as to the role of a neoadjuvant strategy in high-risk localized RCC, either as an adjunct to subsequent adjuvant treatment or as a standalone therapy, with the potential advantages of this latter strategy as detailed above. The PROSPER trial is evaluating the combined neoadjuvant-adjuvant strategy.[91] In PROSPER, the investigational arm will receive two doses of nivolumab prior to surgery followed by adjuvant nivolumab for 9 months. The control arm will undergo standard nephrectomy followed by observation.

Surgical Technique of Radical Nephrectomy with IVC Thrombectomy

The main difference between standard radical nephrectomy and nephrectomy in patients with IVC thrombosis is the necessity for vascular control of the involved portion of IVC for safe and complete removal of intracaval tumour. Key principles of radical nephrectomy with thrombectomy include: 1) prevention of tumour embolization; 2) complete removal of all tumour fragments from the IVC; 3) prevention of acute massive blood loss; 4) restoration of venous blood return from the contralateral kidney and liver to the IVC; and 5) maintenance of venous return to the right atrium.

The optimal methodology of nephrectomy and thrombectomy is determined by the thrombus level, primary tumour characteristics, and lymph node status. These factors influence the selection of the surgical approach, and the eventual necessity of cardiopulmonary bypass (CPB) or venovenous bypass (VVB).[92–95]

The surgical approach for performing radical nephrectomy and thrombectomy must provide adequate exposure of IVC, aorta, renal veins, and in the case of level III and IV thrombi provide access to the main hepatic veins and right atrium. In select cases of level I-II thrombi, minimally invasive techniques (laparoscopic) may be an option,[96,97] and a growing body of case series demonstrates the feasibility of robotically assisted nephrectomy and thrombectomy in patients with type III thrombus in carefully selected patients, when performed by experienced robotic surgeons.[96,98]

However, the safety and oncological equivalence of minimally invasive approaches has yet to be demonstrated, therefore open surgery remains the method of choice in most cases. Further clinical experience is necessary to determine the role of robotic surgery in managing patients with IVC involvement.

Several open approaches for radical nephrectomy and thrombectomy have been described. An extraperitoneal lumbar approach is inadequate for good visualization of major vessels and should not be considered in this patient cohort. A unilateral subcostal incision extended vertically in the midline to the xiphoid process can be used in patients with level I-II thrombi but may not provide sufficient exposure in the setting of infrarenal IVC involvement or with a large primary renal tumour. Surgery in patients with level III and IV tumour thrombi is therefore generally performed through midline, chevron, or thoracoabdominal incision.

The bilateral subcostal (chevron) incision is favoured by many surgeons, as it provides optimal access to the major vessels, both kidneys, liver, diaphragm and can be used for removal of type III-IV thrombi. The incision can be extended vertically if necessary to the lower abdomen or chest.[95,99] Alternatively, a right thoracoabdominal approach is a standard incision in many centers for type III and IV thrombi, providing a safe access to the retrohepatic IVC, the pericardium, and the right atrium.[92,100] Skinner *et al.* (1989) and Langenburg *et al.* (1994) reported the technique with the thoracoabdominal approach without any form of bypass, but with the need for vascular control over the intrapericardial IVC.[92,101] This approach, however, may be inconvinient with a left-sided renal tumour. However, thoracotomy is associated with major surgical morbidity and postoperative pain. Recently, Ciancio *et al.*(2006) described a strictly transabdominal approach to level II-IV tumour thrombi that decreases morbidity and mortality as compared to CPB and thoracotomy.[95] To minimize the morbidity associated with a thoracoabdominal approach, many high-volume VTT surgeons prefer to perform radical nephrectomy and thrombectomy via midline abdominal approach, which provides an exposure similar to the thoracoabdominal incision and can be used for all levels of VTT. The midline can be easily extended to median sternotomy for the management of level IV VTT in settings where CBP is indicated. In all other cases, the supradiaphragmatic IVC and right atrium are easily reached via a transdiaphragmatic approach without use of sternotomy.

Regardless of the primary tumour laterality, the access to the retroperitoneum and great vessels is achieved by incising the posterior peritoneum lateral to the ascending colon, around the cecum to the ileocecal junction. The right colon is reflected medially and the duodenum is kocherized to expose the anterior surface of the IVC and aorta. Early ligation of the renal artery significantly decreases the bleeding from venous collaterals and may permit retraction of the cephalad most extent of the VTT. The right renal artery is exposed and ligated in the aortocaval space following mobilization of the left renal vein and regional lymph node dissection (if performed).

For left-sided primary tumours, the left renal artery is exposed with or without limited lymph node dissection on the left side of the aorta. The mobilization of the kidney should be deferred until after complete vascular control is achieved. To provide a bloodless operative field, the involved portion of IVC must be isolated with vascular tourniquets or clamps and most of collateral veins must be ligated and divided (**Figure 1A**). Methods of IVC control vary depending on the level of tumour thrombus.

Thrombectomy in patients with perirenal (level I) tumour thrombus

After ligation of the renal artery, the vena cava is completely dissected from the surrounding structures above and below the renal vein. The perirenal portion of IVC is mobilized with ligation of the lumbar veins and the right gonadal vein. The opposite renal vein is also mobilized. A Satinsky clamp is positioned around the ostium of the renal vein and the edge of the thrombus. For larger level I VTT that cannot be successfully isolated within a Satinsky clamp, Rummel tourniquets or vascular clamps are placed around the infrarenal IVC, contralateral renal vein, and suprarenal IVC cephalad to the superior extent of the VTT. The ostium of the renal vein is circumferentially excised, and the thrombus is removed via the cavotomy. After evaluating for remnant thrombus fragments adhering to the IVC intima, the defect of the IVC is closed with 3-0 or 4-0 running vascular suture, the cavorraphy is backbled to avoid an air embolism, and the clamps are removed in the following order: 1) suprarenal IVC, 2) contralateral renal vein, 3) infrarenal IVC.

Thrombectomy in patients with subhepatic (level II) tumour thrombus

In patients with a subhepatic thrombus, a more extensive mobilization of the IVC is required. All collateral veins are meticulously ligated and divided. The infrahepatic IVC is isolated with a Rummel tourniquet or Satinsky clamp, and 2 tourniquets are placed around the infrarenal IVC and contralateral renal vein. (**Figure 1C**).

To facilitate the placement of the upper clamp, several (2-4) accessory hepatic veins from the caudate lobe of the liver may be ligated and divided (**Figure 1B**). As a result of this maneuver, 3–5 cm of additional IVC is exposed, which allows a safe positioning of a vascular clamp above the upper extent of the thrombus without

mobilization of the liver. A tourniquet on the left renal vein must be positioned distal to its tributaries to minimize blood loss due to unoccluded inflow at the time of clamping (left adrenal, left gonadal, and lumbar veins).

In the case of the right-sided primary, the right kidney is then completely mobilized with the adrenal gland and perinephric fat outside Gerota's fascia, leaving the kidney attached only by the renal vein. Care is taken to avoid unnecessary manipulation of the renal vein and IVC to prevent tumour fragmentation and embolism.

Following complete mobilization of the IVC, the tourniquets on infrarenal IVC, contralateral renal vein, and IVC above the upper extent of the thrombus are sequentially closed (**Figure 2A**). In patients with a left-sided primary tumour, the right renal artery may be temporarily controlled with a bulldog clamp between aorta and IVC in addition to or instead of closure of right renal vein, however, this is not universally performed. Contrary to the left renal vein, which has several venous collaterals, venous collaterals draining into the right renal vein are rare. Right arterial clamping can prevent development of intrarenal venous hypertension, which has a deleterious effect on nephrons and can lead to significant deterioration of renal function postoperatively. However, there is no consensus as to whether the right renal vein or the right renal artery should be clamped in patients with a left-sided primary tumour and associated IVC VTT. After sequential closure of all tourniquets or application of vascular clamps according to surgeon preference (1) infrarenal IVC, 2) contralateral renal vein, and 3) suprarenal IVC), the antero-lateral wall of vena cava above the thrombus is longitudinally incised, the incision is continued cephalad, and the thrombus is extracted with blunt and sharp dissection from the vessel wall followed by a circumferential excision of the ostium of the renal vein (**Figure 2B**). In most cases, there are no attachments of the thrombus to the wall of the vena cava or these attachments are easily divided. Ideally the thrombus is removed *en bloc* with the kidney unless it has fragile structure and fragments during mobilization. In this case, the fragments of the thrombus and kidney are removed separately. The lumen of the IVC is flushed with heparinized solution and carefully inspected for residual fragments of the thrombus, which may be left unnoticed. The most frequent site of fixation of the thrombus to the intima of IVC is at the renal vein ostium. Direct caval invasion of the tumour may necessitate resection of a portion of the IVC wall to obtain negative margins. Narrowing of the caval lumen by up to 50% can be performed safely without adverse impact on venous hemodynamics. Following tumour thrombectomy, the cavotomy is repaired with a continuous 3-0 or 4.0 polypropylene suture. Before the last sutures are placed, the infrarenal tourniquet may be released temporarily with the patient being placed in Trendelenburg position to flush remaining fragments of tumour thrombus and air from the vena cava. The tourniquets are sequentially removed from the 1) suprarenal IVC, 2) renal vein, and 3) infrarenal IVC.

In the case of a left-sided tumour, the kidney is mobilized only after completion of thrombectomy. The thrombus is always managed first. The left renal vein is mobilized completely by ligating and dividing the gonadal, adrenal, and lumbar veins. After extracting the vena cava portion of the VTT and excising the ostium of the left renal vein, the thrombus is wrapped in small gauze or surgical glove to minimize the risk for tumour spillage while nephrectomy is completed (**Figure 2C**). Following cavorraphy, the left kidney mobilization is completed. The wrapped thrombus is then carefully passed through the window between the mesocolon and aorta to the left retroperitoneum and removed *en bloc* with the primary tumour (**Figure 2D**). Alternatively,

in the rare case with a small left renal mass, the mobilized kidney is brought through the window between the mesocolon and aorta to the paraaortic retroperitoneal space and removed *en bloc* with the thrombus. Alternatively, especially in patients with fixed wide thrombus, the left renal vein can be transected with a TA stapler similar to patients with level III thrombus, and the VTT/renal vein and left kidney are passed off as separate specimens.

Note: All images of courtesy of Vsevolod B. Matveev, Deputy Director on Science and Head of the Department of Urology, N. N. Blokhin Cancer Research Center, Correspondent member of Russian Academy of Science, President of Russian Association of Oncological Urology, Moscow, Russia.

FIGURE 1 Radical nephrectomy with thrombectomy in cT3bN0M0 RCC of the right kidney with level II tumour thrombus.

A. Schema of tourniquet placement.
B. Short hepatic veins to the caudate lobe are divided.
C. Tourniquets on infrarenal IVC, LRV, and subhepatic IVC cranial to the thrombus.

Abbreviations: IVC, inferior vena cava; LRV, left renal vein; RCC, renal cell carcinoma.

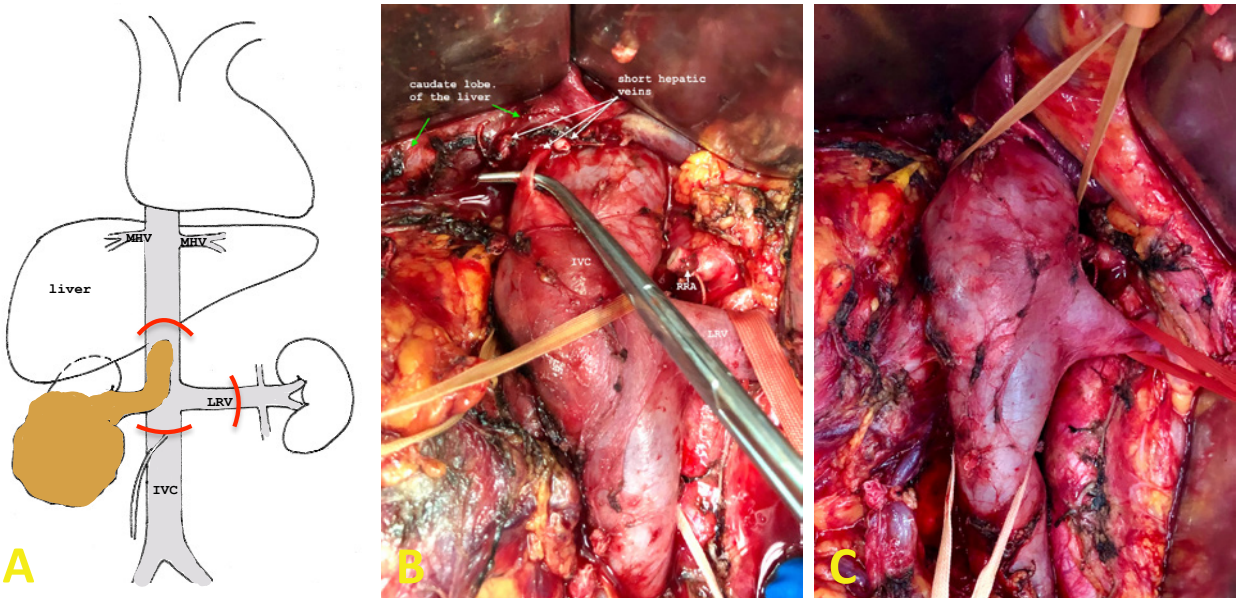
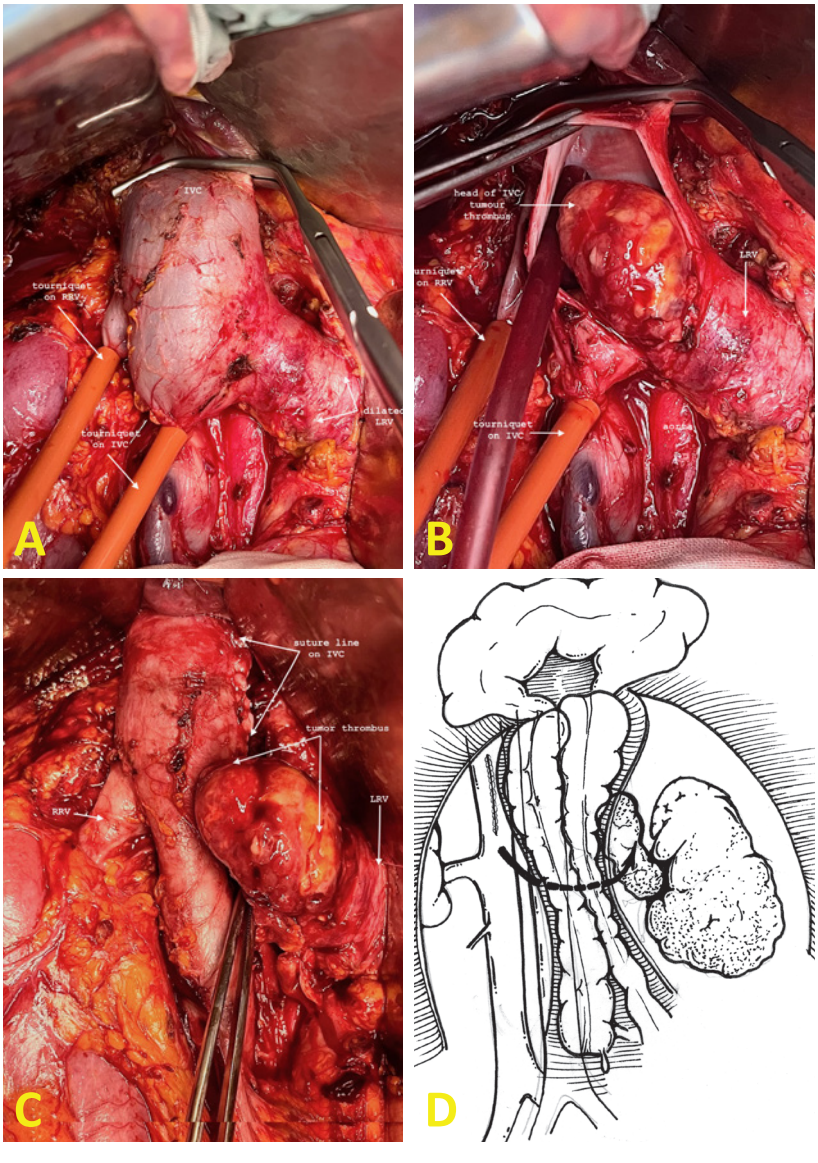


FIGURE 2 Radical nephrectomy with thrombectomy in cT3bN0M0 RCC of the left kidney with level II tumour thrombus.

A. Tourniquets are closed on infrarenal IVC and RRV; Satinsky clamp positioned above the thrombus.
B. IVC is incised, and tumour thrombus is visualized in the IVC lumen.
C. Cavotomy incision is closed, and tourniquets are removed. Tumour thrombus is left attached to the left renal vein.
D. Schema: the tumour thrombus with a stump of left renal vein is brought through the window between the mesocolon and aorta to the left retroperitoneum.

Abbreviations: IVC, inferior vena cava; RCC, renal cell carcinoma; RRV, right renal vein.



Thrombectomy in patients with retrohepatic (level III) tumour thrombus

Radical nephrectomy with thrombectomy is a challenging procedure in the case of intrahepatic (level III) thrombus, which reaches the confluence of the main hepatic veins. Complete vascular control of the entire intraabdominal IVC is required in this situation. The methods of IVC control vary depending on the level and mobility of the thrombus, involvement of the main hepatic veins, and intraoperative signs of IVC wall invasion. Some surgeons use CPB in patients with retrohepatic (level III)[93,102] tumour thrombosis, which significantly increases the complexity of the procedure, requiring sternotomy and systemic heparinization. However, resection of a level III VTT can be safely performed with a procedure without circulatory support[92,95] by mobilizing the liver and retrohepatic IVC. Intrapericardial control of IVC enables safe thrombectomy with retrohepatic and supradiaphragmatic thrombi, eliminating the risk and morbidity of bypass.

Due to the longstanding occlusion of the IVC, patients with level III thrombus often have massive venous collaterals. Disruption of this collaterals can lead to increased blood loss and significantly complicate the thrombectomy. At the N.N. Blokhin Cancer Research Center, surgeons routinely use a cell saver in patients with level III and IV thrombi to decrease the allogenic blood transfusion rate. Long-term results of the surgical management support the oncologic safety of this approach, without demonstrating increased risk for recurrence or metastasis.[103]

Thrombectomy in patients with right-sided tumours and level III VTT

After ligation of the right renal artery in the interaortocaval space, the tourniquets are placed on the infrarenal IVC and the left renal vein. Mobilization of the liver allows exposure of the intrahepatic and subdiaphragmatic segments of IVC (**Figure 3C**). Some authors suggest using the piggyback technique for IVC control during thrombectomy in patients with levels III and IV thrombi. The classic piggyback liver transplantation technique includes ligation and division of all small hepatic veins passing from the right and caudate lobe of the liver. As a result, the liver is left attached to the IVC only by the major hepatic veins. We never use the classic "piggyback" liver transplantation technique,[99] as it is time consuming, requires meticulous ligation of all short hepatic veins, and increases the risk for venous hemorrhage due to avulsion. Instead, we perform partial mobilization of the liver of the IVC to the extent required in every specific case. The medial surface of the IVC remains nonmobilized from the liver (**Figure 3C**).

Vascular control of the retrohepatic IVC can be provided by placing a clamp below the diaphragm, cephalad to the upper limit of the thrombus ether below or above major hepatic veins depending on the upper limit of the thrombus. However, circular mobilization of the subdiaphragmatic IVC is a delicate procedure often associated with possible damage of the main and minor hepatic veins as well as the phrenic veins that can lead to serious haemorrhage. Absence of tributaries makes circular mobilization of intrapericardial part of the IVC significantly easier to perform compared with subdiaphragmatic circular mobilization. For this reason, some

advocate that a transdiaphragmatic approach to the intrapericardial portion of IVC is the simplest, safest, and most reliable method of IVC control above the upper extent of the level III thrombus.[104]

To accomplish a transdiaphragmatic IVC clamp, the diaphragm and underlying pericardium are incised above the IVC, and the pericardium cavity is entered. Incision of the pericardium on both sides of the intrapericardial IVC is performed, which allows passing a tourniquet around the intrapericardial IVC adjacent to the heart[104] (**Figure 3 A, B**). Alternatively, the pericardium can be separated from the diaphragm by blunt and sharp dissection and left intact. The intrapericardial portion of IVC is controlled with a tourniquet between the incised diaphragm and pericardium. The advantages of approaching the intrapericardial IVC through a diaphragmatic incision include simplicity, decreased surgical trauma, and ability to perform the procedure by one surgical team using a strictly abdominal approach. This same technique was described in 2007 by Ciancio *et al.*[95]

The entire kidney and right adrenal gland are mobilized, leaving the kidney attached only by the renal vein. The hepatoduodenal ligament is isolated to control the hepatic circulation with a Pringle maneuver. The duration of liver ischemia should not exceed 20–30 minutes, which is considered safe for postoperative liver function.[95,104] After tightening the tourniquets on 1) the infrarenal IVC and 2) the left renal vein, and 3) performing the Pringle manoeuvre, the last tourniquet on the intrapericardial IVC (4) is closed. Care must be taken not to tighten the upper tourniquet over the tumour thrombus to avoid avulsing a portion of the thrombus and resulting in embolization. Gentle palpation of the IVC or intraoperative use of TEE helps to determine the level of the upper extent of the thrombus. If needed, the superior extent of the thrombus can be gently milked down before the tourniquet closure; however, this should be performed judiciously, given that any pressure on the thrombus is associated with potential risk of its fragmentation and an embolic event.

After closure of all tourniquets, the IVC is longitudinally incised at the retrohepatic level. Provided that all major venous tributaries are well controlled, bleeding from the IVC is minimal. The incision of the IVC is continued toward the upper level of the thrombus and can be extended up to the diaphragm if the thrombus is adherent to the IVC wall. The cavotomy can be limited to the retrohepatic IVC below the main hepatic veins provided that the apex of the thrombus is mobile. In this case, the cranial part of the thrombus can be evacuated from the lumen of IVC by gentle traction on the thrombus. The vessel lumen is continually flushed with heparinized saline for better visualization and prevention of blood clot formation and inspected for residual tumour fragments. The ostia of main hepatic veins are the frequent sites of thrombus fixation and propagation. Widely opening the IVC at this level allows the surgeon to perform visual inspection of the ostium of the major and minor hepatic veins. Any thrombus seen invading the veins is excised. In most cases the thrombus is attached to the vessel wall without direct invasion. Rarely, in a case of a dense adherence of the thrombus to the vessel wall, resection of the IVC may be required with patch grafting.

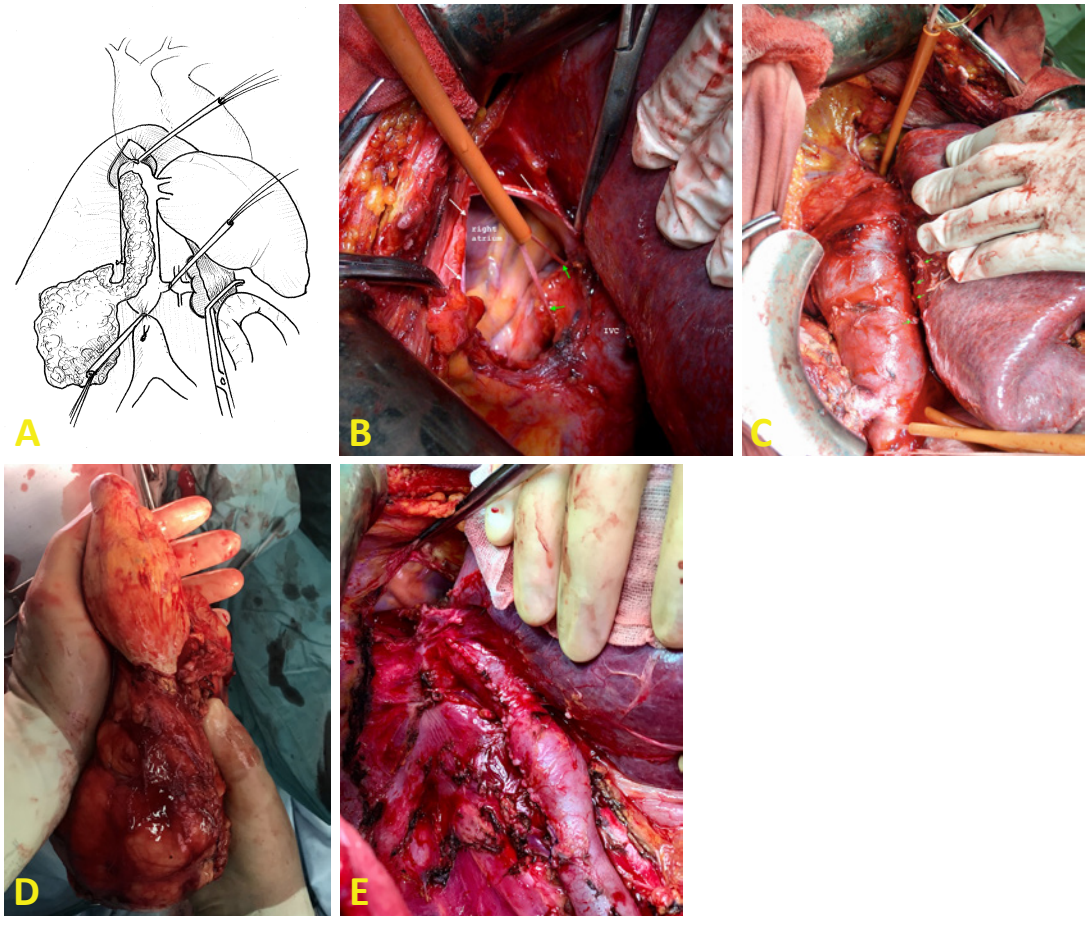
Following thrombectomy, the upper part of the cavotomy is closed with a running polypropylene suture 3-0 or 4-0. Closure of the retrohepatic IVC must be performed as fast as possible to restore the hepatic circulation with minimal ischemia time, and the venous blood return to the right atrium from the IVC. As soon as the suture line reaches the subhepatic portion of the IVC, a Satinsky clamp is placed on the subhepatic IVC above the last stitch, the tourniquet from intrapericardial IVC and the Satinsky clamp from the hepatoduodenal ligament

are released, thereby restoring hepatic circulation. At this point, the thrombectomy and caval reconstruction are completed as previously described. The cavotomy incision is continued toward the ostium of the right renal vein, which is circumferentially excised, and the thrombus is removed *en bloc* with the right kidney (**Figure 3D**).

FIGURE 3 Radical nephrectomy with thrombectomy in cT3bN0M0 RCC of the right kidney with level III tumour thrombus.

A. Schema of tourniquet placement.
B. Diaphragm and pericardium are incised (white arrows) and tourniquet is placed on intrapericardial IVC (green arrows).
C. Mobilization of the liver. Several short hepatic veins have been divided (green arrows). Tourniquets applied to the infrarenal IVC, left renal vein, and intrapericardial IVC.
D. Surgical specimen: kidney with the tumour thrombus *en bloc*.
E. IVC closed with a running suture (primary cavotomy).

Abbreviations: IVC, inferior vena cava; RCC, renal cell carcinoma.



In cases where a level III thrombus is free floating, the thrombus can be extracted via an infrahepatic-only cavotomy, and rapid clamp placement on the infrahepatic IVC and release of the suprahepatic clamp and Pringle to minimize the hepatic ischemic time given that hepatic caval reconstruction is not required.

If the IVC was significantly dilated before the thrombectomy or contained adherent tumour fragments resection of its wall is performed prior to closure with a running suture (**Figure 3E**). Enough of the IVC should be preserved without narrowing of its lumen for more than 50% for restoring laminar venous circulation. If an extended IVC wall resection was performed a patch graft can be considered with the goal of reducing the risk of postoperative bland thrombus formation.

Thrombectomy in patients with left-sided tumours and level III VTT

After ligation of the left renal artery, the tourniquets are placed on the right renal vein (or right renal artery), while the left renal vein is sutured and divided with a TA stapler prior to thrombectomy. The fragments of the thrombus are removed from the stumps of the dissected renal vein. Contraindication for this approach include partial left renal vein and IVC occlusion with a thin floating tumour thrombus, which is not fixed to the vessel wall and may be a cause of pulmonary embolization and death. As an option, left renal vein can be ligated with a 1.0 silk ligature and divided. Transection of the left renal vein in patients with fixed IVC thrombi allows for greater IVC mobility, provides good access to the left renal artery and aorta, and facilitates *en bloc* removal of the thrombus with the ostium and VTT-containing stump of the left renal vein.

The venous collaterals are insufficient for venous blood return from the right kidney and therefore the right renal vein must be preserved in all cases in patients with left-sided tumours. Mobilization of the liver is performed identical to patients with right-sided tumours, and the hepatoduodenal ligament is isolated to control hepatic circulation (Pringle maneuver). The right adrenal vein is mobilized but should be left intact if it is not invaded by the tumour. The upper tourniquet is placed on the intrapericardial portion of the IVC. After closure of all tourniquets (infrahepatic, right renal vein or artery, hepatoduodenal ligament suprahepatic IVC), the IVC is diagonally incised at the retrohepatic level. The right adrenal vein and any nearby lumbar veins can be controlled with a small bulldog clamp. After evacuation of the upper part of the thrombus from the IVC lumen, incision of the IVC is continued diagonally in the direction of the stump of the left renal vein, which is circumferentially excised. Unlike cases of right-sided tumours when the surgeon has relatively unlimited time after restoration of the hepatic circulation to complete the cavotomy (particularly in cases where patients tolerate IVC clamping without hemodynamic compromise, related to extensive collateralization), in patients with left-sided tumours the clamp-time of the right renal vein (or artery) must be minimized to limit the time of renal venous congestion or ischemia. Only after completion of thrombectomy and restoration of vascular supply to the right kidney (either release of the right arterial or venous clamp) is the left radical nephrectomy performed.

Thrombectomy in patients with supradiaphragmatic (level IV) tumour thrombus

In cases of type IV tumour thrombi, the key to a successful surgery lies in the safe removal of the head of the thrombus and avoidance of a life-threatening VTT embolism. In general, the approaches used for supradiaphragmatic thrombectomy can be divided into those that use any type of circulatory support and those that avoid it. No significant differences in oncologic outcomes were observed between cardiopulmonary bypass with deep hypothermic circulatory arrest, or partial bypass under normothermia, or techniques without circulatory support.[105] The complications profiles and rates differ between these approaches, but no surgical method was shown to be superior for the excision of VTT. The surgical approach selected should depend on the level of the tumour thrombus, the degree of IVC occlusion, the size of intraatrial thrombus, the mobility of the thrombus apex, the presence of Budd-Chiari syndrome, the anticipated blood loss, and some individual characteristics of the patient. Most patients with nonadherent intraatrial thrombus can be managed without circulatory support.[92,95,104]

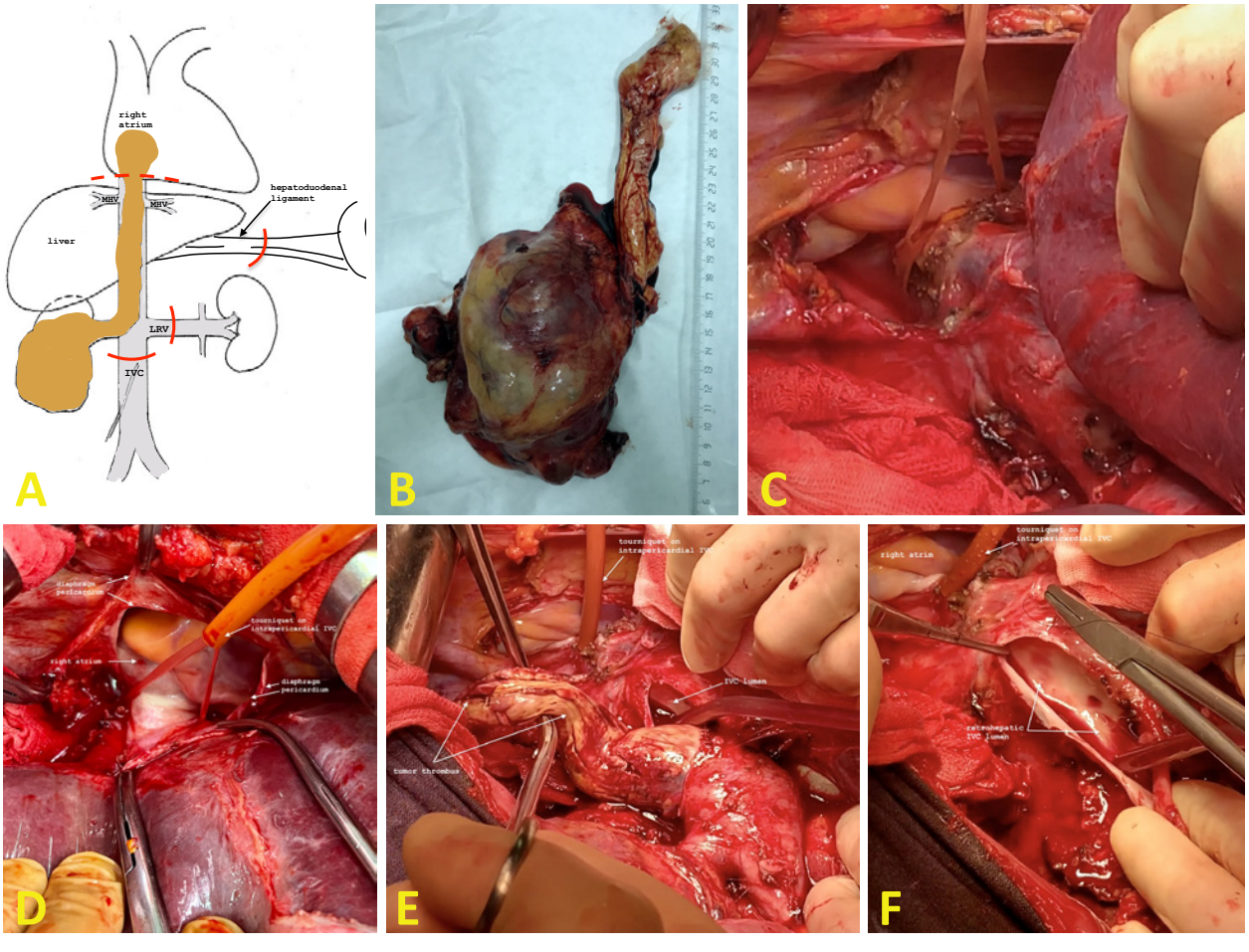
Thrombectomy in patients with level IV thrombus without circulatory support

From a practical point of view, level IV thrombi can be divided into intrapericardial and intraatrial VTT. The first steps of the procedures are the same for either case, and follow the techniques described above for patients with level III tumour thrombi. Mobilization of the contralateral renal vein and subhepatic portion of IVC is performed. The tourniquets are placed around the 1) infrarenal IVC, 2) the contralateral renal vein, and 3) the hepatoduodenal ligament (**Figure 4A**). The central tendon of the diaphragm with the underlying pericardium is widely incised above the IVC, and the intrapericardial part of IVC is exposed. In patients with intrapericardial thrombus only, there is no need for complete mobilization of the intrapericardial IVC. Instead, only incisions of pericardium on both sides of the intrapericardial IVC are performed for tourniquet placement. The IVC hiatus may be left intact.

FIGURE 4 Radical nephrectomy with thrombectomy in cT3cN0M0 RCC of the right kidney with level IV tumour thrombus.

A. Schema of tourniquet placement.
B. Surgical specimen: kidney with tumour thrombus *en bloc*.
C. Intrapericardial and retrohepatic IVC is completely mobilized.
D. Tourniquet on intrapericardial IVC.
E. The cephalad part of the thrombus is evacuated from IVC lumen.
F. IVC lumen after evacuation of the tumour thrombus, before closure.

Abbreviations: IVC, inferior vena cava; RCC, renal cell carcinoma.

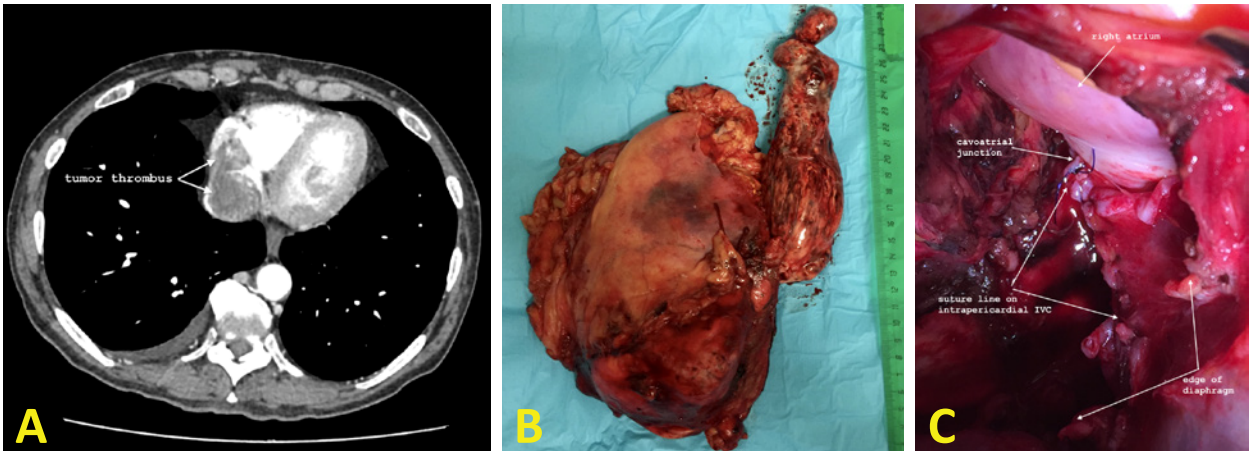


On the contrary, in the case of an intraatrial thrombus (**Figure 4B**), the intrapericardial IVC needs to be completely mobilized so that it can be encircled at the cavoatrial junction. The diaphragm at the IVC hiatus must be completely mobilized from the IVC to widen the natural narrowing for safer extraction of the thrombus from the right atrium. The upper tourniquet is placed around the mobilized intrapericardial IVC and is left unclamped until the apex of the thrombus is removed from the heart (**Figure 4 C, D**). After all tourniquets are sequentially clamped, the IVC is incised at the retrohepatic level. The incision is continued depending on the diameter of the head of the thrombus up to the cavoatrial junction. The thrombus is gently mobilized from the retrohepatic IVC (**Figure 4E**). If the head of the thrombus is mobile, the retrograde blood flow from the right atrium will evacuate the thrombus. If the thrombus is adherent to the vessel wall, the incision is extended on the intrapericardial IVC and the thrombus is resected from the intima of the intrapericardial IVC under direct visualization. In the case of a large head of the tumour thrombus, the incision may even be extended 5–10 mm on the right atrium wall for safer evacuation of the thrombus (**Figure 5**). To avoid excessive blood loss at this point, provisional sutures ("stay sutures") are placed on the atrium wall on either side of the planned incision. Alternatively, a Satinsky clamp can be placed at the atrium. TEE monitoring is important for precise localization of the thrombus apex. As soon as the thrombus is evacuated from the right atrium and intrapericardial IVC, the upper tourniquet is closed. The IVC and the ostia of the hepatic veins are evaluated for residual tumour. Then the IVC lumen is flushed with heparinized saline and the IVC closure is initiated from the cephalad-most extent of the incision (**Figure 4F**). Once the intrahepatic cavorraphy is closed, a vascular clamp is placed on the subhepatic IVC cephalad to the last suture, and the tourniquet from the intrapericardial IVC and the Satinsky clamp from the hepatoduodenal ligament are removed. The rest of the procedure progresses as described above for patients with level III thrombus.

FIGURE 5 Radical nephrectomy with thrombectomy in cT3cN0M0 RCC of the right kidney with large intraatrial level IV tumour thrombus.

A. CT scan shows large intraatrial thrombus.
B. Surgical Specimen: right kidney with tumour thrombus removed *en bloc*.
C. Suture line on the intrapericardial IVC ending at the cavoatrial junction.

Abbreviations: CT, computed tomography; IVC, inferior vena cava.



Indications for circulatory support during excision of level IV thrombus

The majority of cases with level IV thrombus can be managed without circulatory support unless the head of the thrombus is too bulky for removal without performing wide atriotomy. Patients with an intraatrial thrombus that occupies most of the atrium require CPB. The thrombi that are fragile carry the risk for fragmentation with possible development of pulmonary embolism. These are best managed with the use of CPB, but reliably defining the thrombus consistency preoperatively is not currently possible. The consistency of the thrombus is often appreciated only after performing cavotomy and directly inspecting the VTT. Thrombi that have a long history of surveillance and those in patients who received systemic therapy with TKIs may be adherent to the vessel wall or invade it. Removal of a level IV thrombus in these patients may require longer time and may be associated with excessive blood loss. Circulatory support may be beneficial in these circumstances. Specialized centers performing these cases should have a cardiosurgical team on a standby for all level III/IV VTT. This is crucial in the life-threatening event of a VTT embolism to the pulmonary vasculature.

Technique of thrombectomy with CPB

Cardiopulmonary bypass, with or without deep hypothermic circulatory arrest is generally indicated in patients with a bulky intraatrial thrombus. Circulatory support requires systemic heparinization (3–4 mg per kg) with regular (every 30 minutes) evaluation of the coagulation profile. In conjunction with hemorrhage, acidosis, and dilution, CPB activates fibrinolysis and impairs platelet function, which can contribute to substantial intraoperative coagulopathy. As such, in addition to conventional coagulation assays such as prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen levels, some authors advocate for routinely obtaining assays such as thromboelastographic (TEG) and rotational thromboeleastometry (ROTEM) to inform blood component transfusion requirements.[160] ROTEM and TEG assays return rapidly, with a time saving of 30–60 minutes in the detection coagulation abnormalities.[161]

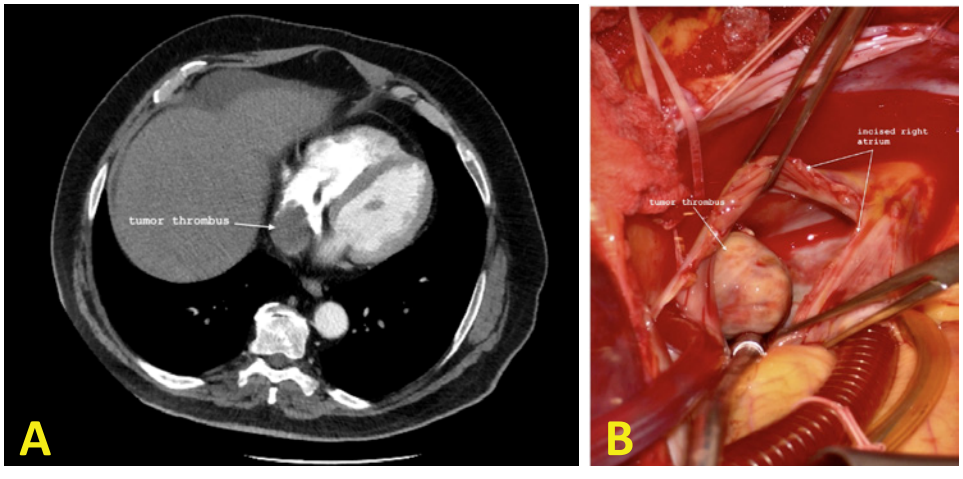
A second cardiosurgical team works simultaneously with the urological surgical team. After performing median sternotomy, the superior vena cava, ascending aorta, and infrarenal IVC below the tumour thrombus are cannulated. In patients with descending bland infrarenal thrombosis, the femoral vein is cannulated instead of the IVC. In patients with thrombosis of the IVC and both femoral veins and massive venous collaterals, canulation of major veins below the thrombus may be omitted. The venous blood from the venous cannulas enters the CPB machine by gravity where it is filtered, oxygenated, and cooled (or warmed) before returning to the body through the arterial cannula. Cardioplegia can be administered to stop the heart if CPB with deep hypothermia and cardiac arrest is planned. The cannula used to return oxygenated blood is usually inserted into the ascending aorta, but it may be inserted into the femoral, axillary, or brachiocephalic artery.

The subdiaphragmatic IVC is mobilized as it is described in patients with level IV thrombus. After cardioplegia is established and the heart stops beating, the right atrium is incised with scissors and the thrombus is dissected from the endocardium (**Figure 6**). If the size of the intraatrial tumour matches the size of IVC ostium, the thrombus can be pushed down into the IVC and removed through the subdiaphragmatic cavotomy. When the tumour burden is too large, the atrial component may be fractured and removed first by cardiosurgeons, while

the IVC part is removed through cavotomy. After visual inspection for residual tumour, the defect in the atrium and in the IVC is closed, cardioplegia and heparinization are reversed, bypass is terminated, and cannulas are removed.

The method of partial bypass for removal of an atrial thrombus is preferred by some cardiosurgeons. Partial CPB requires systemic heparinization but avoids deep hypothermia and cardioplegia, decreasing the rate of complications of CPB. The use of partial CPB on beating heart with immediate return of blood through the pump into the circulation helps to minimize blood loss, compensates for the decreased venous return, maintains the blood pressure, and decreases the risk for embolic events.[52,106] Following completion of the procedure, heparinization is reversed by administration of protamine sulfate.

FIGURE 6 Intratrial tumour thrombus.
A. CT scan shows tumour (arrow) in the right atrium.
B. Incised right atrium with a tumour in its lumen (arrow).

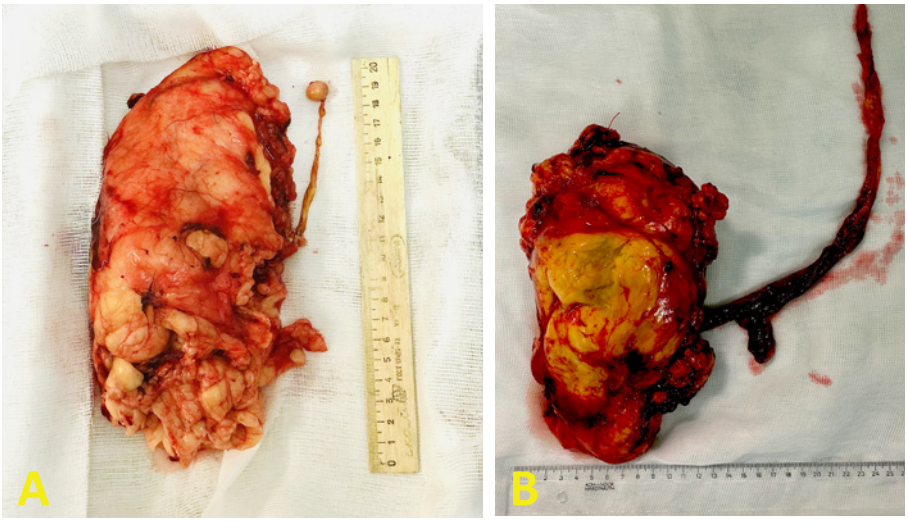


Technique of thrombectomy in patients with mobile level III and IV thrombus

In patients with completely mobile level III-IV thrombi, confirmed by radiological evaluation, mobilization of the liver can be selectively avoided, as can placement of a tourniquet at the level of intrapericardial IVC. The tourniquets are placed at the infrarenal IVC and the contralateral renal vein. The upper tourniquet is placed as in patients with level II thrombus at the subhepatic IVC but is left open until the thrombus is evacuated from the vessel lumen. After closure of the tourniquets on the infrarenal IVC and on the contralateral renal vein, a cavotomy is performed at the anterolateral aspect of subhepatic IVC. A Pringle maneuver may be used to reduce blood loss and facilitate retrograde blood flow to evacuate the thrombus from of the right atrium and

upper portions of the IVC. As soon as the upper part of the thrombus is evacuated from the IVC through the cavotomy, the infrahepatic tourniquet is closed and the Satinsky clamp is removed from the hepatoduodenal ligament to restore the hepatic circulation. The rest of the procedure like that in patients with level II tumour thrombus (**Figure 7**). Generally, the free-floating thrombus is easily flushed out from the right atrium and retrohepatic IVC and blood loss is limited to 500 cc. Thus, the technically difficult mobilization of the liver and diaphragmatic incisions are avoided.

FIGURE 7 Thin mobile level III (A) and level IV (B) thrombi *en bloc* with the kidney.



Comparison of Thrombectomy without CPB, with CPB, and Deep Hypothermic Circulatory Arrest (DHCA)

Although the majority of patients can tolerate the short hemodynamic consequences of reduced venous return with IVC cross clamping, CPB is indicated to maintain hemodynamic stability in some patients during thrombectomy. Removal of the thrombus with CPB provides excellent control over the thrombus apex regardless of its size and of eventual fixation to the endocardium or the ostium of the IVC. Cardioplegia allows ideal visualization and makes removal of the tumour more comfortable for the surgeon. One of the most important benefits of CPB is the reduction in the risk for pulmonary embolization. However, CPB is not benign, and there are numerous problems associated with it. CPB significantly increases the complexity of surgery and requires sternotomy, cannulation of major vessels, and systemic heparinization. Many reports show a high rate

of complications associated with the use of CPB such as bleeding due to platelet dysfunction and coagulopathy, neurologic deficit, pulmonary, liver, and renal failure, as well as infectious complications.[107,108]

Orihashi *et al.* (2008) found no significant difference in outcomes between CPB and DHCA or partial bypass under normothermia or single caval clamp without circulatory support.[76,102] Nguyen *et al.* (2014) retrospectively analyzed 362 patients with RCC and with level III or IV tumour thrombi who underwent radical nephrectomy and complete tumour thrombectomy from 1992 to 2012 in 22 US and European centres. This large multi-institutional analysis showed no significant impact of CPB use on cancer-specific survival or overall survival in patients undergoing nephrectomy and level III or IV tumour thrombectomy. Surgical complications (Clavien 1–4), intraoperative and 30-day mortality, and hospital length of stay were not independently associated with surgical approach.[105] In the study by Navia *et al.* (2014),[109] CPB was associated with significantly less bypass time and total operative time compared with DHCA for patients with thrombus extending to the right atrium. Fewer major complications were reported with CPB, although the differences were not statistically significant (p=0.17).

To minimize the morbidity of CPB, several minimal access (MA) techniques have been proposed for patients with level III and IV thrombus. Most of the studies demonstrated advantages of MA compared to standard sternotomy. Wotkowicz *et al.* (2006)[110] found statistically significant differences in favour of MA with respect to transfusion rates, length of hospital stay, and ventilator requirements. Faust *et al.*[111] also observed statistically significant differences in favour of MA for wound infection, sepsis, hospital stay, and ventilatory requirements.

Surgical approaches without circulatory support are less complex, resulting in decreased surgical morbidity, operative time, and cost. Considering similar long-term and process outcomes, implementation of these techniques may be beneficial from a cost-saving perspective as well. However, the ability to perform thrombectomy without circulatory support is determined by size of the thrombus apex and should be performed in centres where CPB is available on demand.

In summary, currently the surgical technique for excision of level IV thrombus should be selected on case-by-case basis, depending on institutional and surgeon experience and preferences.

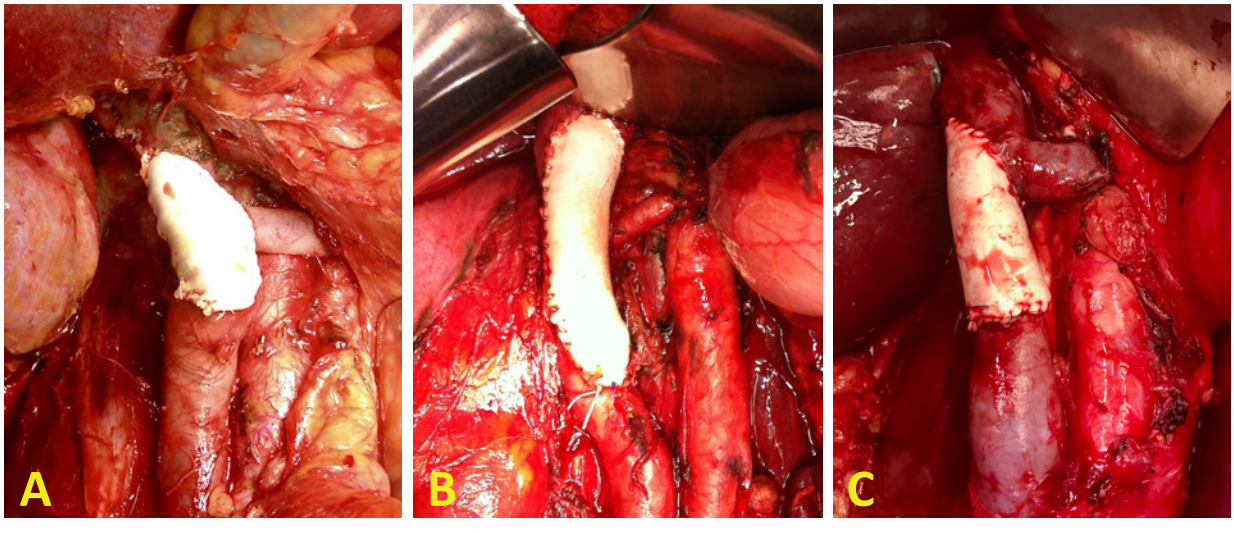
Thrombectomy in Patients with Tumour IVC Wall Invasion

One of the most important factors that determines the complexity of thrombectomy, apart from the length of the thrombus, is the adherence and invasion of the vessel wall by the thrombus. Adherence to the endothelium necessitates widely incising the IVC with sharp dissection of the thrombus under direct visualization, precluding the surgeon's ability to perform a limited cavotomy. Vena cava resection is required in cases where the wall of the IVC is directly invaded by tumour. Repairs of the IVC include primary repair by venorrhaphy,

prosthetic and autologous patch repair, and circumferential complete IVC replacement (**Figure 8**). In the majority of cases, resection of the dilated part of IVC does not result in clinically significant IVC narrowing, and primary repair (e.g., primary cavorraphy) with a continuous suture is preferred. Indications for patch repair or circumferential repair include narrowing of IVC >50%, which increases the risk for postoperative deep venous thrombosis with pulmonary embolism. However, prosthetic grafts and patches expose patients to an increased risk for infection and thrombosis. Therefore, the optimal management of the IVC after resection is controversial. The decision whether to ligate the IVC or perform reconstruction depends on the amount of IVC involved, the laterality of the primary tumour, the degree of IVC obstruction, and the presence of spared venous collaterals, associated descended bland thrombosis of the IVC and iliac veins, and edema of the lower extremities.[104]

FIGURE 8 Variants of IVC repairs.
A and B. Perirenal IVC patch repair.
C. Circumferential perirenal IVC replacement with PTFE graft.

Abbreviations: IVC, inferior vena cava; PTFE, polytetrafluoroethylene.



Resection of the infrarenal IVC

Descending thrombosis in patients with RCC and VTT is quite frequent and occurs according to our data in 9.8% of patients.[94] Descending thrombus in most of the cases is bland (84%) but in 16% of the specimens tumour cells can be found in the infrarenal thrombus. The margin between tumour and bland thrombus often cannot be reliably assessed intraoperatively. Therefore, we suggest the maximum evacuation of the thrombus below renal veins to ensure R0 resection. Bland infrarenal thrombus can be densely fixed to the intima of the IVC and its dissection of the IVC wall may be problematic, if at all possible. Even if the thrombus is removed

from the infrarenal IVC, residual bland thrombi in the iliac veins increase the risk for development of recurrent thrombosis and embolic events postoperatively. Primary closure of the infrarenal IVC after thrombus excision often leads to IVC narrowing given the smaller diameter of the blocked infrarenal IVC preoperatively. Taking into account all of the above and the presence of collateral pathways, we can see that the infrarenal IVC can be safely resected without reconstruction below the level of the proximal bland thrombus or just above the IVC bifurcation without any consequences.[94,95,112,113] Existing collaterals provide sufficient venous return to the heart and edema of the lower extremities is infrequent. Most authors indicate that lower extremity edema after ligation of the IVC occurs rarely, is well tolerated, and resolves spontaneously.[112,113] In patients with a patent infrarenal IVC and bland thrombosis of iliac veins, the ligation or suturing of the vessel proximal to the segment where patency is restored may minimize the risk for future embolization. In this case, care must be taken to preserve the lumbar veins entering the infrarenal IVC. If the lumbar veins are not spared, the infrarenal segment should be resected to prevent clot formation in the blind end of the vessel. In rare cases where the IVC is resected before robust collaterals have been established, or collateral pathways are resected for complete tumour removal, reconstruction with a polytetrafluoroethylene (PTFE) or polyethylene terephthalate graft may be an option to prevent lower limb venous complications and improve quality of life (**Figure 8**).[114] A ring-supported PTFE graft for complete replacement demonstrated its safety and good patency rates, reaching 88% and 79% at 6- and 12-month follow-up, respectively. The prothesis should have a diameter smaller than the IVC to promote faster blood flow velocities in the graft segment. The reported morbidity of IVC reconstruction with patch or tubular graft is low (10.6%).[114]

Resection of the suprarenal IVC

The suprarenal IVC can be safely resected with ligation of the left renal vein in patients with right-sided RCC with IVC tumour thrombosis. The collateral venous return from the left kidney through the adrenal, gonadal, and lumbar veins, together with newly formed venous collaterals, is sufficient to preserve normal renal function. The left renal vein can be safely ligated even in patients with partial IVC obstruction in the absence of multiple venous collaterals, although temporary renal failure has been described by some authors following suprarenal IVC resection.[112] Thus, resection of the IVC *en bloc* with right-sided RCC and tumour thrombus from the level of major hepatic veins to the level of IVC bifurcation can be performed without reconstruction.[94,39] In case of true tumour invasion into the IVC wall, *en bloc* tumour and IVC resection facilitates an R0 resection with complete removal of the thrombus (**Figure 9**).

In rare cases when the tumour involves the main hepatic veins, reconstruction of the hepatic veins can be performed using a bovine pericardium patch (**Figure 10**), which has been successfully used in cardiac and vascular surgery due to its biocompatibility and lack of antigenic response.[115]

In patients with left-sided RCC, the right renal vein must be spared to preserve adequate venous drainage from the right kidney. Possible options include reimplantation of the right renal vein into the stump of the IVC or vena portae by interposition of synthetic vascular graft or complete IVC replacement with a tubular ring-supported PTFE graft with reimplantation of the right renal vein.[114]

FIGURE 9 *En bloc* resection of the IVC with RCC and associated caval thrombus.

A. Schema.
B. Surgical specimen: resected IVC with tumour thrombus *en bloc* with kidney. Resected IVC: pink arrow. Tumour thrombus: blue arrow.
C. Surgical field after IVC transection. Arrows show IVC stump and head of the thrombus.
D. Closed IVC stump below hepatic veins and above the IVC bifurcation.

Abbreviations: IVC, inferior vena cava; RCC, renal cell carcinoma.

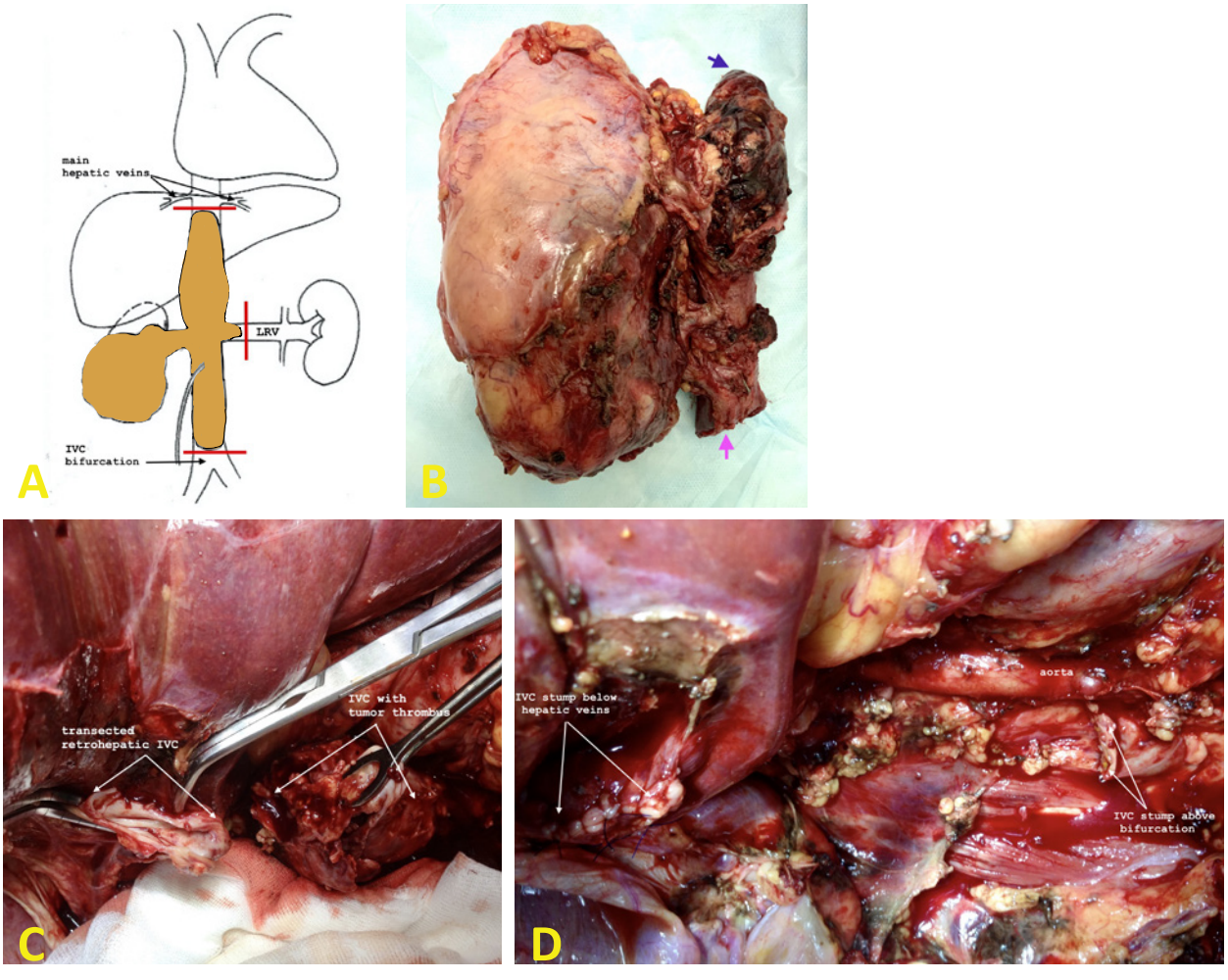
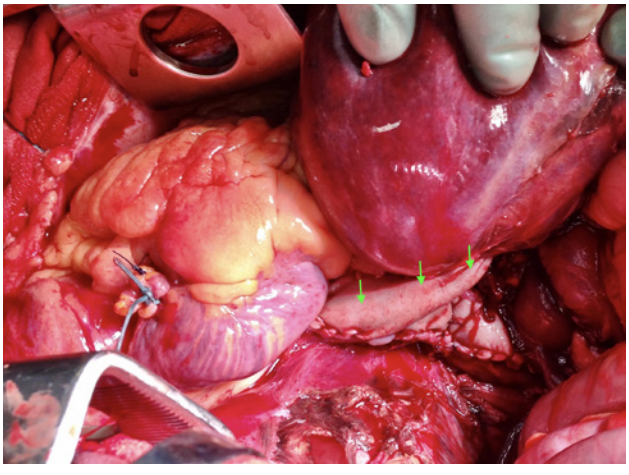


FIGURE 10 Major hepatic vein repair with bovine pericardium after thrombectomy and IVC resection. Arrows point to the graft.

Abbreviations: IVC, inferior vena cava.



Technique of resection of the IVC *en bloc* with right-sided RCC and tumour thrombus

After ligation of the right renal artery, the IVC is ligated and divided using a vascular stapler below the renal vessels and the inferior-most margin of the thrombus. Early transection of the IVC renders further piggyback-like liver mobilization easier to perform. Elevating the transected distal end of the IVC provides excellent exposure of the lumbar veins and short hepatic veins, which are sequentially ligated and divided. The left renal vein is ligated distal to the left adrenal vein and divided. After division of the coronal and right triangular ligament, ligation of several short hepatic veins is performed, and the right hepatic lobe is gently rolled medially exposing the retrohepatic IVC. All small hepatic veins are meticulously secured to the level of main hepatic veins. The hepatoduodenal ligament is mobilized to control hepatic circulation with a Pringle maneuver. The right kidney is completely mobilized extrafascially, together with the right adrenal gland, and is left connected to the IVC only by the renal vein. Depending on the level of the thrombus, a transdiaphragmatic approach to the intrapericardial IVC may be applied, as described earlier, with placement of a tourniquet on the intrapericardial IVC.

After placement of a Satinsky clamp on the hepatoduodenal ligament, the IVC is incised below the level of the main hepatic veins for evacuation of the head of the thrombus in case it is located above the major hepatic veins. In patients with level III thrombus, the head of the thrombus can be milked down to enable placement

of a Satinsky clamp just below the main hepatic veins, which allows to avoid cessation of liver blood flow. The IVC is transected below the clamp and the whole specimen of the IVC with thrombus and kidney is removed *en bloc*. The IVC stump below the Satinsky clamp is closed with a running suture.

Methods of Maintaining Hemodynamic Stability during Thrombectomy

In patients with level III and IV thrombus undergoing thrombectomy without CPB, a profound decrease of venous return to the right atrium after clamping of IVC with a Pringle maneuver may lead to a drop in blood pressure. Systemic blood pressure was found to fall to less than 80 mm Hg at cross-clamping in 44% of patients with a patent IVC.[116] Systemic blood pressure is more stable in patients in whom the IVC is completely occluded by a thrombus. The duration of the Pringle maneuver rarely exceeds 15 minutes, and short periods of hypotension are generally able to be tolerated by the patient. However, difficult cases that require extensive reconstruction of the IVC may require longer time. Methods of maintaining hemodynamic stability include the use of a venovenous bypass (VVB) and aortic cross-clamping.[29,116,117]

VVB is a technique that was developed in the 1980s to mitigate the hemodynamic effects of complete cross-clamping of the IVC during liver transplantation. Hemodynamic stability is restored by creating a VVB from the common femoral vein to the axillary vein, thereby maintaining venous return. Pump-driven VVB, modified by adding portal decompression by cannulating the IVC and the inferior mesenteric vein with return of blood to the right atrium, was shown to be a safe and useful procedure and avoids the important risks connected with deep hypothermic circulatory arrest.[117] In a study reported by Granberg *et al.* (2008) VVB was associated with significantly shorter bypass, operative, and anesthesia times, as well as trends toward decreased blood loss and hospital stay compared with CPB.[29] It would be wrong to compare different bypass methods, as each has different indications, advantages, and pitfalls. Therefore, the choice of bypass technique must be individualized and discussed between the surgical and anesthesiologic teams preoperatively.

Aortic cross-clamping during IVC occlusion is much simpler than the VVB method to prevent hypotension and maintain hemodynamic stability. In a study reported by Jibiki *et al.* (2004), hemodynamic stability was obtained with partial or total cross-clamping of the infrarenal or supraceliac segment of the abdominal aorta, with maintenance of systemic blood pressure above 100 mm Hg without any adjunctive procedure.[116] The authors suggested performing infrarenal cross-clamping of the aorta if the systemic blood pressure decreases to less than 80 mm Hg after IVC clamping. In the case the blood pressure is not maintained with this procedure, the supraceliac segment of the aorta can be cross-clamped. Supraceliac cross- clamping should not be continued for more than 30 minutes.[116] The relatively satisfactory postoperative results of aortic cross-clamping indicate that this method of maintaining hemodynamic stability should be considered in patients with RCC undergoing extensive IVC reconstruction.

Minimally Invasive Radical Nephrectomy and IVC Thrombectomy

Open surgery has traditionally been the primary approach for IVC thrombectomy in patients with RCC.[32,52,62,92,118] However, with improvement in surgical instrumentation, laparoscopic and robotic skills, minimally invasive IVC thrombectomy has now become quite common in some institutions throughout the world. Some of the main reasons for this transition are the well-known benefits of a shorter hospital stay, less postoperative pain, and decreased morbidity.

Since the first report of laparoscopic IVC thrombectomy in 2000, numerous studies have highlighted the feasibility of minimally invasive techniques.[98,119–129] While initially the reports focused on level I thrombectomy using a laparoscopic approach,[120,125,130] more publications have documented successful outcomes with level II and III IVC thrombi.[98,119,121–124,126,128,129,131–133] In this section we will focus on the surgical approach for a successful minimally invasive radical nephrectomy with IVC thrombectomy. It is important to recognize that the long-term oncologic outcomes of minimally invasive IVC thrombectomy have yet to be well studied, and that there is a paucity of randomized trials comparing minimally invasive IVC thrombectomy with open surgery. Therefore, we will focus primarily on the preoperative considerations and technical aspects required for successful execution of this complex surgery. These include following the key principles of surgical safety, proceeding with a minimally invasive IVC thrombectomy when equipped with the necessary skills, ensuring appropriate preparation, having the necessary support staff and team available, and equally important, performing an oncologically sound procedure.

Patient selection and preoperative considerations

Patient selection and timely preoperative imaging are crucial for successful radical nephrectomy with IVC thrombectomy. As described above, MRI remains the gold standard for visualization, especially for higher-level thrombi.[27,134] Multidetector CT, with improved resolution and anatomical detail, may also be used, especially in patients unable to undergo MRI.[27,63,134] Interestingly, some suggest that preoperative ultrasound may also have an adequate assessment of the level of the IVC thrombus.[134] Typically, most aim to have the imaging completed within 2 weeks of surgery.[136] Some also argue that those with extensive IVC wall invasion by the tumour may require greater IVC excision with grafting and thus may be better candidates for open surgery.[124] However, in experienced hands this can be accomplished using minimally invasive techniques, such as the description by Scott and colleagues of a robotic synthetic graft replacement of the IVC.[135] Nevertheless, regardless of the approach, preoperative imaging to assess for thrombus extent, thrombus volume, and possible IVC wall invasion is of critical importance.[63] Preoperative cardiovascular evaluation may also be beneficial.[133] Finally, the possibility of intraoperative conversion to an open approach should remain a consideration throughout the procedure.

Preoperative embolization

Most minimally invasive IVC thrombectomies have been performed on right-sided renal tumours.[119] Some have advocated that in individuals with left-sided renal tumours, preoperative arterial embolization may be beneficial due to limited access to the left renal artery while the patient is in flank position with the right side up.[124] These same authors have also suggested that bulky tumours may benefit from preoperative embolization as well.[124] However, this is not a routine practice in most institutions and remains controversial, as others have documented worse outcomes in patients undergoing preoperative embolization when compared to those who did not. Ultimately, it remains unclear whether these findings are the result of patient selection bias or are truly issues associated with embolization, as it is possible that most challenging patients are offered preoperative embolization more often.[20,136] Regardless of the tumour laterality and the decision regarding embolization, the "thrombus first" approach is necessary: the IVC thrombectomy should be completed prior to nephrectomy. This is done to avoid the potentially catastrophic event of tumour thrombus embolization, which can cause a deadly saddle tumour embolism.

Retroperitoneal approach

For minimally invasive surgery, a retroperitoneal approach may be used for right-sided renal masses with IVC thrombi or left-sided renal masses with the renal vein thrombi. Because of limited access to the IVC via the retroperitoneal approach from the left side, a left-sided RCC with extension into the IVC would necessitate a transperitoneal approach.[122]

In any retroperitoneal approach, the patient should be placed in a lateral decubitus position with the affected kidney up. Port placement for the retroperitoneal approach has been well described previously.[122,131] Development of the retroperitoneal space and maintenance of the orientation along the psoas muscle are most important technical considerations. The peritoneum is mobilized medially. This allows for the creation of a larger working space, maintains the orientation of the dissection along the psoas muscle, and provides early access to the renal hilum and thus early division of the renal artery.[122,131] Access to lower-level II caval thrombi should be adequate to allow for complete encircling of the cava for right-sided tumours, should cross clamping be needed. Despite the technical feasibility of the retroperitoneal approach, the small working space is a significant limitation. Additionally, challenges with obtaining adequate access of the cava for left-sided tumours is another drawback. For these reasons, most surgeons performing robotic IVC thrombectomies prefer a transperitoneal approach.

Transperitoneal approach

Applied in both pure laparoscopic and robot-assisted techniques, a transperitoneal approach may be used for thrombi associated with both right- and left-sided renal tumours.[124,129] Regardless of laterality of the renal mass, the patient is placed in a left lateral decubitus position with the right side up. After insufflation

of the intraperitoneal cavity, a 12-mm camera port is inserted with an additional three or four ports placed in a paramedian or mid-clavicular vertical line. Often the angle of the costal margin is used to determine port placement. Typically, one small port is placed at the sub-xiphoid region for liver retraction as well as an additional 12-mm assistant port[119,124,129,137] Positioning and port placement are highly dependent on body habitus, and ports may need to be shifted laterally in obese patients.[98] During the IVC thrombectomy, the patient remains in the left lateral decubitus position regardless of the tumour laterality.[129] The dissection is begun with an incision into the posterior peritoneum, followed by mobilization of the colon medially, duodenal kocherization, and exposure of the IVC and the renal vessels.[98,119,128,129, 133,137]

Minimally invasive level 0-I thrombectomy

Identification of the hilum or interaortocaval space and gentle dissection of the renal artery allows for early arterial ligation and may help to slightly reduce the size of the thrombus. Care must be taken to minimize any manipulation of the renal vein so as not to disrupt or dislodge the thrombus. Ligation of the renal artery (with either an endo-GIA stapler or Hem-o-lok clips) may be performed at the hilum or in the interaortocaval space. The interaortocaval space for right-sided tumours may be a safer place for dissection, as it can minimize manipulation of the right kidney, avoid manipulation of the occasionally bulky right renal vein, and be helpful in cases of prior arterial embolization. This allows for early arterial control and minimizes thrombus manipulation and risk for subsequent embolization.[98,119,128]

For thrombi limited to the renal vein, dissection of the IVC can be avoided. After the renal artery is ligated, the renal vein may become flattened and allow for the thrombus to be "milked" away from the IVC. An interoperative ultrasound is helpful to identify the extent of the thrombus and to assure adequate clearance for placement of the vascular stapler or clips across the origin of the renal vein. Intraoperative ultrasound can also help in assessing the contralateral renal vein to assure that it is patent.[117,125,130] Sometimes, the endo-GIA vascular stapler itself can be used to "milk" the specimen backwards prior to ligation of the renal vein instead of a laparoscopic or robotic instrument.[130] Completion of the radical nephrectomy and placement of the *en-bloc* specimen into an EndoCatch bag allows for a controlled extraction of the specimen. For left-sided level I tumour thrombi with recent imaging, one should consider doing the surgery in the right lateral decubitus (if the thrombus seems that it can be "milked" away from the IVC). Ligation of the left gonadal vein and occasionally the adrenal and lumbar branches are also often performed early in these cases.

Minimally invasive level I and II thrombectomy

For IVC thrombi projecting less than 2 cm into the IVC, dissection of the contralateral renal vein and pre-placement of a vessel loop with a secured Hem-o-lock clip (Rummel tourniquet) for later identification and cinching is often performed.[133] This is not necessary in all cases, as the simple use of laparoscopic bulldogs can be safely performed to cross-clamp the cava and contralateral vein.[135] Identification of the extent of the thrombus with an intraoperative ultrasound should be performed. Ligation of the right gonadal and lumbar veins allows for excellent hemostasis during the cavatomy. Leaving a 1–2 cm gonadal vein stump for later

assessment of hemostasis may be helpful prior to cavatomy to assess for bleeding and adequacy of cross-clamping. Occasionally, a small cavatomy may be performed to assess for bleeding prior to making a larger IVC incision.

Careful mobilization of the medial and superior aspects of the kidney may be performed, but is usually avoided, if possible, to decrease the possibility of thrombus dislodgement and vascular embolization.[124] Gentle lateral retraction of the kidney away from the IVC may return the thrombus to the renal vein. However, this should be attempted with great caution, as the "vascular surgery first" principle should be followed to prevent inadvertent dislodgement of the tumour thrombus.[121] Ureteral division may allow for additional traction if needed.[98] Using ultrasound guidance, the caudad and cephalad extent of the tumour is assessed prior to cross-clamping the IVC. Some have described tangential IVC clamping for smaller, less bulky level II thrombi. Like level 0 thrombi, VTT exclusion with excision of a small IVC cuff surrounding the renal vein ostium may be employed via the laparoscopic Satinsky clamp and vascular stapler.[119,132] Of note, there are flexible laparoscopic ports that allow for the introduction of the curved Satinsky.

For larger level I and level II thrombi, the IVC must be cross-clamped and the right adrenal vein may require ligation. For right-sided thrombi, Rummel tourniquets or the vascular bulldogs should be cinched in the following order: 1) infrarenal IVC, 2) left renal vein, and 3) suprarenal IVC. For left-sided thrombi, the right renal artery should also be controlled with a vascular bulldog to prevent right renal engorgement. The vessels should be clamped or cinched in the following order: infrarenal IVC, right renal artery, right renal vein, and suprarenal IVC.[129] Of note, the clamping of the right renal artery is debatable, as there is no consensus on whether this is absolutely indicated for left-sided IVC thrombi. In cases of right renal artery clamping, the renal warm ischemia time should be recorded and minimized.[129] Performing a cross-clamping IVC trial for hemodynamic stability is the first step prior to cavatomy, and this should be clearly communicated with the anesthesia team. As described earlier, if the patient tolerates clamping, assessment of hemostasis by a small venotomy at the gonadal vein stump or cava may be a helpful maneuver.[119,124,132]

After cross-clamping of the IVC, incision of the IVC is performed until the cephalad extent of the thrombus is delivered. The renal vein is eventually circumferentially excised at the level of the ostium of the IVC, leaving a sufficient cuff for closure to minimize luminal narrowing. Most commonly, blunt dissection of the thrombus allows for its separation from the wall of the IVC, but if invasion of the wall is suspected, then caval excision is performed so as not to compromise the oncologic outcome. Upon thrombus removal, irrigation of the IVC lumen with heparinized saline is performed.[119,122,128,132] Closure of the IVC with 4-0 prolene sutures in a single layer allows for excellent hemostasis. Should excision of the portion of the IVC wall be performed with significant narrowing (more than approximately 50%), patching can be performed. Several materials are available for this, including Gore-Tex and bovine pericardium. Bovine pericardium may allow for excellent volume expansion without the need for the long-term postoperative anticoagulation.

Several sequences of the clamp release have been described. For right-sided VTT, traditionally, Rummel tourniquets or vascular bulldogs are loosened and subsequently released in the following order: 1) suprarenal

IVC, 2) left renal vein, and 3) infrarenal IVC. For left-sided thrombi, bulldog clamp and Rummel tourniquets should be released in the following order: 1) suprarenal IVC, 2) right renal vein, and 3) infrarenal IVC. However, this approach has not been uniformly followed. Some have described leaving the superior caval clamp until the very end, allowing for back-bleeding at the cavatomy and evacuation of potential trapped air or small clots within the repaired lumen.[98,135] Such an approach is thought to minimize the risk for air or clot embolus at the expense of a short period of controlled bleeding, which is repaired as the cava is refilled with blood.

Level III thrombectomy

Initially performed by Bratslavsky and Cheng in March of 2013 for an 11-cm IVC thrombus, this surgery remains technically demanding and dangerous.[98] As with any IVC thrombectomy, avoiding IVC manipulation is of the utmost importance in level III thrombectomy. To minimize renal manipulation and potential thrombus disruption, initial dissections should focus on finding the ipsilateral renal artery. For the right renal mass, this is best accomplished in the interaortocaval space.[124] Intraoperative ultrasonography as well as transesophageal echocardiography can help with intraoperative planning and assessment of the cephalad extent of the tumour.[98,124]

Incision of the right triangular ligament and cephalad retraction of the liver will expose the retrohepatic IVC. Transection of the right triangular ligament and mobilization of the right hepatic lobe will provide excellent access to the caudate lobe and its drainage via short hepatic veins, which can be ligated using laparoscopic clips.[98,123] For right-sided thrombi, Rummel tourniquets are cinched in the same order as in cases of level II thrombi as follows: 1) infrarenal IVC, 2) left renal vein, and 3) retrohepatic IVC. Alternative sequences of cross-clamping have also been successfully employed.[98,123,124]

For left-sided thrombi extending to the level of hepatic veins, bulldog clamps and tourniquets may be cinched as follows: 1) infrarenal IVC, 2) right renal artery (not always employed), 3) right renal vein, and 4) retrohepatic IVC.[124] Upon cross-clamping, transecting the ipsilateral renal vein with an endo-GIA vascular stapler is often employed, as the rest of the left renal vein will be removed with the specimen. This also allows for greater IVC mobility to ensure all posterior feeder vessels are sufficiently ligated.[124] Additionally, it allows for immediate disposal of *en-bloc* thrombus with the renal vein stump to minimize potential local spillage.[124] Incision of the renal vein stump at the level of the IVC ostium is performed and extended proximally as needed for complete thrombus extraction. Upon *en-bloc* thrombus removal with the renal vein stump, irrigation of the IVC lumen with heparinized saline is performed, and closure of the cavatomy is performed with restoration of blood flow via the IVC. The patient is then repositioned and the left nephrectomy is completed. While this technique has been used by some, it has been questioned due to concerns of possibly violating oncologic principles if the tumour itself is divided using the stapler. The need for repositioning and potential need for preoperative arterial embolization on the left side may be a reason for most surgeons to adapt a minimally invasive approach preferentially for the management of right renal masses with IVC thrombi.

In summary, while no prospective studies comparing minimally invasive techniques for IVC thrombectomy exist, it is most important to recognize that such an approach requires meticulous preparation, experience and expertise with vascular surgery, requisite skills for vascular reconstruction, and an experienced team. Ultimately, safety and oncologic principles should always remain the primary goals of any oncologic surgery.

Results of Surgical Management of RCC with VTT

Invasion of the venous system by RCC has long been associated with poor prognosis.[138] However, the ability to provide a durable cure for some patients with RCC provided rationale for aggressive surgical management for almost a century.[139] Even prior to the development of modern anesthesia or critical care techniques, there were reports of successful surgery to remove renal tumours invading into the IVC.[140] Unfortunately, early series of nephrectomy with IVC thrombectomy also reported high complication rates and perioperative mortality.[141]

Surgery to remove renal tumours with venous invasion may be complex and has higher risks for perioperative adverse events compared to a radical nephrectomy without venous thrombus. Isolation of the IVC may require extensive dissection, mobilization of adjacent structures, or extension of the surgical field into the chest. RCC tumours with venous extension are often bulky and associated with parasitic neovascularity. As the IVC becomes occluded, increased pressure causes collateral vessels to form throughout the retroperitoneum to return blood from the lower extremities. These vessels are non-anatomic, prone to bleeding, and may need to be ligated to facilitate surgery. To completely remove the tumour from the IVC, it is often necessary to temporarily occlude venous flow from the lower extremities, contralateral kidney, or liver. In the most advanced cases, vascular or cardiac bypass techniques are used, which can also increase the risk for perioperative adverse events.

A systematic review of surgery for RCC with IVC thrombus cited major perioperative complication rates as high as 70% and perioperative mortality rates ranging from 3% to 16%.[142] Perioperative outcomes data for nephrectomy with IVC thrombectomy must be critically reviewed focusing on some important limitations. First, RCC with venous extension is relatively rare and reported outcomes vary significantly. To increase the numbers of patients available to evaluate, many series have long study periods. For example, Blute *et al.* provided an excellent report of perioperative outcomes for RCC with venous thrombus in patients from 1970–2000.[52] However, it is difficult to evaluate how advances in surgical technique, anesthesia, critical care, and tumour imaging contributed to different outcomes observed over a study period spanning three decades. Second, most published data are single-centre retrospective series from centres of excellence, which may not be applicable to different practice settings. Third, unmeasured baseline differences in patients' health, extent of tumour thrombus, presence of metastases, and surgical techniques may act as confounding variables when analyzing outcomes for patients with RCC who have venous thrombus overall. Fourth, most studies do not use standardized definitions to classify perioperative complications such as the Clavien-Dindo system,[143] which limits the ability to compare or measure the severity of events. Finally, there is significant variation for when complications are reported (e.g., intraoperative, in-hospital, 30-day, and 90-day).

Perioperative mortality

Given that most data for surgery for RCC with thrombus are retrospective, perioperative mortality is considered the most reliable endpoint to track outcomes. Variations in modern mortality rates may be attributed to differences in how long after surgery mortality was reported. The most common metric is 30-day mortality, which may underestimate delayed mortality attributed to complex procedures.[144]

A systematic review and meta-analysis of 226,372 kidney cancer patients treated with radical or partial nephrectomy demonstrated 1.6% perioperative (in-hospital or 30-day) mortality rate for radical nephrectomy overall,[144] which was increased for nephrectomy with venous thrombus. Wagner *et al.* evaluated 1,192 patients with either renal vein or IVC thrombus treated at 13 European institutions between 1982 and 2003 and noted an overall 30-day mortality rate of 5%.[26] The authors noted a 3% perioperative mortality for 933 patients with thrombus confined to the renal vein compared to 10% for 192 patients with IVC thrombus.[26] Similarly, a study of 433 patients from the Ontario Cancer Registry treated with nephrectomy and renal vein or IVC thrombectomy found 30- and 90-day mortality rates of 2% and 5%, respectively.[145] Population-level data demonstrated the in-hospital mortality rate of 7% for 816 patients treated with radical nephrectomy and IVC thrombectomy in Canada from 1998 to 2007.[146]

Although not universally observed, most data demonstrate increased mortality as thrombus height increases, with higher mortality observed in patients with IVC thrombus that extends above the diaphragm or above the hepatic confluence of veins (Neves/Mayo level III and IV).[32] Unfortunately, data for upper-level thrombus outcomes are especially sparse and vary significantly, so it is difficult to compare techniques with adequate statistical power to draw strong conclusions. In the largest study of 362 cases of level III/IV thrombus, data was collected from 22 centres over 21 years, which is less than one surgical case per institution per year, highlighting the rarity of this clinical situation.[105] Early mortality rates from notable studies range from 8% to 22%.[26,29,52,105,106,147,148] In a series of 162 consecutive patients with upper-level IVC thrombus treated at 4 centres from 2000–2012, mortality at 30 and 90 days was reported at 5.6% and 10.5%, respectively, including 4 deaths within 24 hours of surgery.[20] No difference in mortality was observed between centres or among patients treated with cardiopulmonary bypass, similar to later reports.[105]

Hospital volume and surgeon volumes are associated with early mortality for nephrectomy with thrombectomy similar to other complex surgical procedures. In a meta-analysis, Hsu *et al.* found that patients treated with radical nephrectomy and venous thrombectomy had a 52% reduction in short-term mortality when treated at higher volume hospitals.[144] Toren *et al.* found that surgeon experience was critically important, noting that 75% of all in-hospital deaths occurred during the first two cases of a surgeon's experience.[146] Similarly, Yap *et al.* found both surgeon and hospital experience to be associated with risk for early mortality following nephrectomy with thrombectomy.[145] Given these data and an emphasis on multidisciplinary surgical management at high-volume centres,[149,150] establishing centres of excellence for patients treated with nephrectomy and thrombectomy may improve overall outcomes.[144]

Approximately 30–50% of RCC patients with VTT have metastatic disease at presentation,[26,151] and most studies evaluate outcomes for nonmetastatic and metastatic patients in aggregate. However, patients with metastatic RCC have a significantly worse prognosis compared to patients with locally advanced RCC, which should be discussed in surgical planning. In a study of 427 patients treated at four centres with cytoreductive nephrectomy with VTT, the 30- and 90-day mortality rates were 3.6% and 10.3%, respectively, similar to aggregate studies that include nonmetastatic patients.[152] However, additional mortality rates during days 91–180 and days 181–270 postoperatively were 8% and 10%, creating a cumulative mortality of 32% in the 9 months following surgery for patients with metastatic disease. Although it is likely that many deaths occurring beyond 90 days are attributed to progression of metastatic disease, the risk for increased mortality should be discussed with patients with metastatic RCC who are considering surgery.

Perioperative complications

Data for perioperative adverse events following nephrectomy with thrombectomy are also limited by retrospective reporting, and the event rates vary significantly among studies. Few studies have used standardized reporting systems such as Clavien-Dindo[143] to classify complications according to severity.[20,153,154] Complication rates may be underreported when patients receive treatment for complications outside the institution where they received surgery or when complications are less severe. In population level data, Toren *et al.* estimated the overall complication rate to be 78% in 633 patients treated with nephrectomy and IVC thrombectomy, including a 37% rate of surgical complications.[146] Similar overall rates of complications have been reported at large centres,[142,154] with Blute *et al.* demonstrated that 30-day complication rates varied from 9% to 30% stratifying from thrombus level zero to four.[52] In addition, the authors noted late complications (31–365 days following surgery) in 22–35% of patients treated with nephrectomy and thrombectomy.

Commonly reported intraoperative complications include hemorrhage, injury of adjacent structures, and cardiac events.[52] Tumour thrombus embolization is a feared complication that occurs in 1.5% of patients and is associated with a reported 75% risk for mortality.[155] Early postoperative complications include hemorrhage requiring transfusion, venous thromboembolic events (deep venous thrombosis and pulmonary emboli), cardiac events, pulmonary events, renal failure, and infectious complications. Late complications may include lower extremity edema, chronic renal insufficiency, and incisional hernia.[52] For patients with level III or IV tumour thrombus, major complication rates (>Clavien-Dindo 3a) were identified in 34% of 162 patients following surgery at four centres. Independent predictors of major complications include preoperative systemic symptoms (weight loss or fatigue) and thrombus level.[20] Use of cardiac bypass or deep hypothermic cardiac arrest was not identified as a predictor of major complications in this study[20] or subsequent analyses,[105] but data is limited because of the study techniques as described earlier. Similar to data with perioperative mortality, complication rates following nephrectomy with thrombectomy are lower at higher-volume centres[144] and with more experienced surgeons.[146]

Oncologic outcomes

Managed expectantly, RCC with VTT is associated with a median survival of 5 months with increased risk for cancer-specific mortality observed with pT3b/c and metastatic disease.[46] In a population-based study of patients treated with nephrectomy and venous tumour thrombectomy, 1-year overall survival in patients with localized disease was 90%.[156] At 5 years, cancer-specific mortality in patients with RCC and associated VTT ranges from 40 to 60%.[52,60,62,157] Prognostic factors associated with cancer-specific mortality in patients with VTT include increasing level of VTT, nodal and systemic metastases, advanced Fuhrman grade, non-clear cell histology, and increasing tumour size.[19,28,60,154,156,158,159]

Conclusion

Renal cell carcinoma with venous thrombus provides a fascinating example of seemingly implausible tumour biology. Although these aggressive tumours have acquired the ability to invade and shed tumour cells into the largest blood vessel in the human body, some patients do not develop metastatic disease when treated with definitive, aggressive surgery, resulting in complete extirpation. In patients who do not develop metastases, circulating tumour cells may not have developed the ability to invade into host tissues and survive outside the primary tumour. It's also likely that immune cells destroy some or all micro-metastases before they become clinically apparent. Regardless of the mechanism, the observation that aggressive surgery as a monotherapy may be curative for some patients with large aggressive RCC with associated VTT is critical.

Surgery for RCC with venous thrombus is complex and may require advanced maneuvers to obtain vascular control that facilitate complete removal of all gross tumour. Experienced multidisciplinary surgical, anesthesia, and critical care teams provide the best environment to achieve ideal outcomes. Because the risk for progression to metastatic disease is increased significantly in patients with locally advanced disease, careful staging and patient selection are important. The use of presurgical and postsurgical systemic therapies is likely to increase with advances in systemic therapy in the future and represents a high-priority area for contemporary investigation.

Multiple techniques have been described for resection of tumour thrombus, which depend significantly on the extent of the thrombus and the institutional expertise. Minimally invasive procedures may be appropriate for some patients, especially with lower-level thrombus treated at experienced centres; however, long-term oncologic outcomes with these approaches remain to be defined. Perioperative complications and mortality are significantly higher for nephrectomy when thrombectomy is necessary. Patients should be counselled carefully preoperatively and complex surgeries should be undertaken by experienced surgeons at high-volume centres for the best outcomes.

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COMMITTEE 12

Neoadjuvant and Adjuvant Therapy for Renal Cell Carcinoma

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Table of Contents

Introduction

Patients undergoing definitive therapy for nonmetastatic kidney cancer, by surgery, ablative techniques (radiofrequency ablation, cryoablation, thermotherapy), radiotherapy (SBRT), have varying degrees of risk for recurrent disease post-procedure. The ultimate goal of "adjuvant therapy" is to reduce the incidence of recurrent disease, and to cure more patients.

This chapter summarizes the current state of perioperative therapy for kidney cancer and explores future directions to develop optimal adjuvant strategies. We define risk and risk for recurrence post-definitive therapy, and describe the adjuvant trials landscape of adjuvant vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKI) trials and immune checkpoint inhibitor (IO) trials. We review data on neoadjuvant therapy before advanced kidney cancer resection. Radiologic, ethnic, economic, and geographic considerations with regard to adjuvant therapy are highlighted. Also covered are adjuvant therapy issues especially pertinent to patients, future directions in adjuvant trial design specifically targeted to biomarkers and patient selection, and sequencing of treatment after adjuvant therapy in those patients with recurrence.

Defining Risk

Risk for disease recurrence post-nephrectomy for renal cell cancer depends largely on the characteristics of the primary tumour. This risk can mainly be stratified based on stage and grade of the cancer. Patients with larger tumours and higher grade are at increased risk for recurrence after nephrectomy. Risk for recurrence for high-risk patients is greatest early (0–3 years) post-nephrectomy and plateaus after 4–5 years.[1]

Some predictive models that have been used for survival outcomes post-nephrectomy for renal cell carcinoma are as follows:

1. UISS (University of California LA Integrated Staging System)[2]—based on TNM staging, nuclear grade, and Eastern Cooperative Oncology Group (ECOG) performance status (PS). For localized disease (N0, M0), low-risk 5-year disease-specific survival is 91.1%, intermediate risk is 80.4%, and high-risk 5-year disease-specific survival is 54.7%.
2. SSIGN (Stage, Size, Grade, Necrosis)[3]—based on TNM staging, nuclear grade, tumour size, and presence of tumour necrosis. If the SSIGN score is 0–2, it is classified as low risk, with 5-year metastases-free survival of 97.1%. With a score of 3–5, it is classified as intermediate risk, with 5-year metastases-free survival of 73.8%. If the SSIGN score is more than 6, it is considered high risk, with 5-year metastases-free survival of 31.2%.
3. Karakiewicz nomogram[4]—based on TNM staging, nuclear grade, presence of tumour necrosis, and S classification (asymptomatic, local symptoms, or systemic symptoms).
4. GRANT[5]—based on TNM staging, nuclear grade, tumour size, and risk group (favourable/unfavourable).
5. Leibovich[6,7]—based on TNM staging, nuclear grade, tumour size, and presence of tumour necrosis.

Based on these predictive models, in general, patients having had surgery for stage T3 or higher, and high-grade tumours, are at the highest risk for recurrent disease, and are most likely to benefit from an adjuvant agent that would decrease their risk for recurrence and improve overall survival (OS). Patients at lower risk (T1 and T2A disease) receiving adjuvant therapy for the most part may be overtreated, as the risk for recurrence is less than 20%, with implications that up to 80% of this patient group would receive adjuvant therapy, with its associated toxicity, cost, and inconvenience, unnecessarily. The patient population that would likely benefit the most from adjuvant therapy is those with resected metastases, as demonstrated in the KEYNOTE-564 adjuvant pembrolizumab trial.[8]

The ideal adjuvant agent should be for those patients at highest risk for recurrence, who are active on microscopic disease not visible by conventional imaging, have minimal symptomatic and acceptable financial toxicity, and provide a clinically meaningful outcome (improved OS).

In addition, patient comorbidities should be taken into account when considering an adjuvant agent, balancing them against the toxicity of the adjuvant therapy. Real-world evidence (RWE) may be valuable and may give data for a more heterogeneous population receiving adjuvant therapy and their outcomes.

Unanswered questions in adjuvant therapy trials include its role in non-clear cell histology, including papillary, chromophobe, and sarcomatoid histology. We know these pathologies can be more aggressive and have higher risk for recurrence, and are often excluded in adjuvant trials, including the recent landmark KEYNOTE-564 adjuvant pembrolizumab trial, which required a clear cell component post-nephrectomy (sarcomatoid differentiation allowed).[8] A consensus meeting of experts called for inclusion of patients post-nephrectomy with positive margins, high-risk disease, with negative postoperative imaging in future trials.[9] Such patient populations await more data in future research.

Adjuvant Therapy Trials in Renal Cell Carcinoma

Historical treatments

Some earlier adjuvant trials with cytokines or biologicals are reviewed in **Table 1**. Unfortunately, all these trials are concluded to be of no benefit.

Adjuvant trials with targeted agents

The rationale for testing agents targeting the vascular endothelial growth factor (VEGF) receptor pathway in the adjuvant setting is based on multiple observations showing that VEGF is involved in the pathogenesis of metastasis.[10]

Six placebo-controlled, adjuvant, phase 3 studies investigated the benefit of targeted therapy with VEGFR TKIs and a mammalian target of rapamycin (mTOR) inhibitor versus placebo. **Table 2** outlines randomized phase 3 trials conducted with targeted agents (tyrosine kinase inhibitors or mTOR inhibitors). The primary endpoint in all trials was disease-free survival (DFS); however, patient populations and study designs varied between the trials, and the trials encompassed a variety of questions such as duration of therapy (up to 3 years) in SORCE[11] and ATLAS[12] versus 1 year for ASSURE,[13] PROTECT,[14] S-TRAC,[15] and EVEREST.[16] Multiple agents were tested in this setting including sunitinib, sorafenib, axitinib, pazopanib, and everolimus.

Of these, only S-TRAC,[15] which enrolled the highest-risk group (pT3 and higher), demonstrated an improvement in DFS. Patients assigned to sunitinib had a significantly improved DFS (6.8 years; 95% confidence interval [CI], 5.8–not reached) when compared to patients in the placebo arm (5.6 years; 95% CI, 3.8–6.6). Based on these findings, sunitinib was approved as an adjuvant treatment for high-risk resected clear cell RCC by the US Food and Drug Administration (FDA). In contrast, the European Medicines Agency (EMA) did not recommend adjuvant treatment with sunitinib due to the lack of OS benefit.

TABLE 1 Ongoing or Completed Adjuvant Trials with Immune Checkpoint Inhibitors in RCC

Trial	*N*	Patient characteristics	Treatment arms /vs. placebo	Treatment duration	Primary endpoint
High-dose IL-2[126]	68	pT3b-T4 or N1-3 or M1 resected	High-dose IL-2 q 8 hr days 1–5 and 15–19 vs. observation	Up to 28 doses	2 yr-DFS improvement was 40–70%. Closed for futility.
Low-dose IL-2 in combination with IFN-α[127]		pT1, T2, T3 a-b-c; pN0-pN3, M0	4-week cycle subcutaneous IL-2 (5 days/week, on days 3, 4, and 5) + IFN days 3 and 5 of each week)	Every 4 months for the first 2 years and every 6 months for the remaining 3 years	RFS: HR, 0.84 (95% CI, 0.54–1.31; p=0.44); OS: HR, 1.07 (95% CI, 0.64–1.79; p=0.79)
Phase 3 trial of adjuvant IFN-α[128]		pT3-4a and/or node+ disease post-nephrectomy and lymphadenectomy	IFN-α daily for 5 days every 3 weeks for a total of 12 cycles	36 weeks	Coprimary endpoints. Median RFS rate was 3 years in the observation arm and 2.2 years in the treatment arm.
Phase 3 trial of adjuvant 5-fluorouracil in combination with IFN-α and IL-2[129]	309	pT3b-c, T4 or any pT with pN1 or pN2, or positive margins, or microscopic vascular invasion	Adjuvant 5-fluorouracil in combination with IFN-α and IL-2 versus observation		DFS rate was 50% with observation and 61% with adjuvant treatment (HR, 0.84; 95% CI, 0.63–1.12; p=0.233). OS rate was 63% with observation and 70% with treatment (HR, 0.87; 95% CI, 0.61–1.23; p=0.428).
Randomized phase 3 trial of adjuvant autologous tumour cell vaccine versus observation[130]	558 IIT for 379 pts. 179 pts lost to follow-up	pT2-3b, pN0-3, M0	Six intradermal applications of autologous renal tumour cell vaccine at 4-week intervals or observation		Tumour progression in the vaccine and observation groups HR, 1.58 (95% CI, 1.05–2.37) and 1.59 (95% CI, 1.07–2.36), respectively, (p=0.0204). The 5-year and 70 mo. PFS rates were 77.4% and 72%, respectively, in the vaccine group versus 67.8% and 59.3% in the observation group.
ARISER trial: adjuvant girentuximab, a carbonic anhydrase IX antibody, in patients with high-risk RCC[1]	864	pT3/pT4/Nx/N0/M0 or pT any/N+/M0 or pT1b/pT2/Nx/M0 with nuclear grade 3 or greater	A single loading dose of 50 mg followed by weekly infusions (20 mg) for 24 weeks or placebo		No statistically significant difference between groups in DFS and OS—DFS: HR, 0.97 (95% CI, 0.79–1.18); OS: HR, 0.99 (95% CI, 0.74–1.32); the median DFS was 71.4 months for girentuximab and the median OS had not been reached in either group.

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; IFN-α, interferon-alpha; IL-2, interleukin-2, OS, overall survival; RCC, renal cell carcinoma.

TABLE 2 Adjuvant Trials with Targeted Agents in RCC

Trial	*N*	Patient characteristics	Treatment arms /vs. placebo	Treatment duration	Primary endpoint
S-TRAC: Sunitinib	615	High-risk ccRCC patients according to UISS	Sunitinib	1 year	DFS
ASSURE: Sorafenib or Sunitinib	1,943	Nonmetastatic cc and non-ccRCC; disease stage II–IV selected by UISS	Sunitinib/ Sorafenib	1 year	DFS
SORCE: Sorafenib	1,656	Patients with Leibovich high- and intermediate-risk resected clear cell RCC and non-ccRCC	Sorafenib Sorafenib	1 year 3 years	DFS
EVEREST: Everolimus	1,537	Pathological stage intermediate or very high–risk cc and non-ccRCC patients with full or partial nephrectomy	Everolimus	9 treatment cycles	RFS
PROTECT: Pazopanib	1,540	Patients with moderately high or high risk after nephrectomy of localized or locally advanced ccRCC by AJCC TNM v.2010	Pazopanib	1 year	DFS
ATLAS: Axitinib	700	High-risk, nonmetastatic ccRCC with nephrectomy by AJCC TNM v.2010	Axitinib	3 years	DFS

Abbreviations: AJCC, American Joint Committee on Cancer; ccRCC, cc renal cell carcinoma; DFS, disease-free survival; HR, hazard ratio; RFS, recurrence-free survival; TNM, tumour-node-metastasis staging system; UISS, University of California LA Integrated Staging System.

It is worth noting several differences in eligibility among the various trials, including the allowed TNM groups, and risk stratifications using prognostic nomograms. For example, ASSURE,[13] SORCE,[11] and EVEREST[16] included more patients with lower-stage disease than S-TRAC,[15] PROTECT,[14] and ATLAS.[12] SORCE used the Leibovich prognostic nomogram to define risk,[6] whereas ASSURE, PROTECT, S-TRAC, and EVEREST all used modified UISS[17] to define risk. ASSURE, SORCE, and EVEREST all included patients with non-clear cell RCC although all had primary endpoints powered to the clear-cell population.

There remains debate about the usefulness of small molecule inhibitors in the adjuvant setting for several reasons: A first concern was that there were 4 similar negative trials and only one positive trial; thus, was it the patient population that explained these differences? To address the concern raised about the inclusion of patients with lower-stage disease in the ASSURE trial,[18] the authors thought to determine a potential DFS benefit in the subgroup of patients with pT3, pT4, N+ clear cell RCC (the entry criteria for S-TRAC). However, no difference was found with respect to DFS or OS in this high-risk population.[13] Similarly, a recently updated analysis of the subgroup of patients with sarcomatoid RCC did not show any improvement in DFS or OS with adjuvant therapy.[19] The hazard ratios for the 5-year DFS were 0.74 (95% CI, 0.45–1.20) for sunitinib versus placebo and 0.82 (95% CI, 0.53–1.28) for sorafenib versus placebo.

A second concern was that roughly 60% of patients participating in the five VEGFR-TKI trials experienced grade 3 toxicity, and there was significant dropout in many of the trials due to intolerance or toxicity. ASSURE, SORCE, and PROTECT all amended their trials to start at reduced dosing with recommended escalation, but most patients did not increase their doses. The PROTECT trial pharmacokinetic analysis determined that patients who achieved a higher trough had an improved DFS, but this was not related to dose or toxicity.[20] Differences in incidence of toxicity were observed in trials conducted with predominantly Caucasians. In contrast, the ATLAS trial had the highest Asian population enrolled and more cases of hand-foot syndrome (HFS) and proteinuria were observed.[12]

A third concern was that there was no benefit in OS in any of the VEGFR-TKI trials, even in longer follow-up. According to an updated analysis of the PROTECT trial,[21] the benefit of adjuvant sunitinib was observed across risk groups. The authors also described patterns of recurrence: the most common sites of recurrence for sunitinib and placebo were the lung (n=40 and n=49) followed by lymph nodes (n=21 and n=26) and liver (n=11 and n=14, respectively). The updated OS was based on an additional 10 months of follow-up, but the median OS was still not reached in either arm (hazard ratio [HR], 0.92; 95% CI, 0.66–1.28, p=0.6).

Important correlative work is ongoing in these trials including genome-wide association studies, whole-exome sequencing, RNA sequencing, pharmacokinetic analyses, and blood biomarker analyses, which may allow for better prognostication of patient groups for future trials and perhaps identify subsets of patients who might still benefit from adjuvant VEGFR-TKI therapy.

The lone mTOR inhibitor trial, EVEREST SO931, is a randomized, placebo-controlled, phase 3 trial of everolimus (10 mg per day) versus placebo for 54 weeks in patients with clear cell and non-clear cell RCC after nephrectomy or partial nephrectomy (PN). The study started in April 2011 and enrolled a total of 1,545 patients with pathological stage intermediate- or high-risk RCC. The primary endpoint of the trial is recurrence-free survival (RFS). The authors identified significant gender and age-related differences in everolimus trough levels and significant associations between everolimus exposure and toxicity.[22] The authors presented the mature EVEREST data at ASCO 22 and reported that the RFS endpoint was negative at HR 0.85 with p value of 0.0246, but just missing its prespecified p value boundary of 0.022.[144]

In summary, targeted agents have failed to demonstrate a clinically meaningful benefit in the adjuvant-patient setting. Concerns have also been raised by the authors from a meta-analysis that concluded that adjuvant anti-VEGFR therapy has no significant effect on DFS or OS in intermediate- or high-risk patients but that the treatment is associated with substantial toxicity.[23] In conclusion, the imbalance between risk and potential clinical benefit of VEGF inhibitors in the adjuvant setting outweighs the role of VEGF in the pathogenesis of metastasis.

Adjuvant trials with immune checkpoint inhibitors

Immune checkpoint inhibitors (CPIs) targeting the programmed cell death protein 1 (PD-1) pathway, or the cytotoxic T-lymphocyte associated protein 4 (CTLA-4) pathway have revolutionized the treatment of metastatic RCC. Their role in the adjuvant setting is currently under investigation in multiple clinical trials (**Table 3**). These studies differ in terms of inclusion criteria, design (three arms), or endpoints. One of these trials has recently reported the first results.

KEYNOTE-564[8] is a randomized, double-blind, placebo-controlled, phase 3 trial testing the role of the PD-1 inhibitor pembrolizumab in patients with intermediate-high risk, high-risk, or M1–no evidence of disease (NED) status. Intermediate-high risk was defined as pT2+grade 4 or sarcomatoid+N0+M0 or pT3, any grade, N0, M0. High risk was defined as pT4, any grade, any N, M0 or any pT, any grade, N+, M0. The study also included patients who had undergone complete resection of metastasis (M1), within a year of primary surgery. Key eligibility criteria included histologically confirmed clear cell renal cell carcinoma, nephrectomy < 12 weeks prior randomization, no prior therapy, and an ECOG PS of 0 or 1. Patients (n=994) were randomized to receive either pembrolizumab 200 mg or placebo every 3 weeks for 1 year. The primary endpoint was DFS per investigator, with OS as a secondary endpoint. After a median follow-up of 24.1 months (14.9–41.5), the DFS rate at 12 months was 85.7% and 76.2% for pembrolizumab and placebo, respectively, and 77.3% and 68.1% at 24 months (HR, 0.68; 95% CI, 0.53–0.87), p=0.001 (ITT population). The subgroup of patients with M1 NED stage derived the largest benefit from adjuvant treatment (HR, 0.29; 95% CI, 0.12–0.69). OS data was not mature, but the 24-month OS rate was numerically higher for patients who had received pembrolizumab (96.6% and 93.5%, respectively), (HR, 0.54; 95% CI, 0.30–0.96; p=0.0164). Longer follow-up is needed to define a potential OS benefit from pembrolizumab in the adjuvant setting. The authors reported grades 3+4 treatment-related adverse events (AEs) for pembrolizumab and placebo in 18.9% and 1.2%, respectively. No treatment-related deaths occurred. Based on these findings, pembrolizumab has recently received FDA and EMA approval as an adjuvant treatment in patients with RCC and high risk for relapse.

Although this preliminary data is encouraging, the results of other, ongoing trials with CPIs are needed to better define the role of these agents in the adjuvant setting for RCC.

TABLE 3 Ongoing or Completed Adjuvant Trials with Immune Checkpoint Inhibitors in RCC

Name/ID	Drugs	*N*	Duration months	Setting	Risk profile	Endpoint
KEYNOTE-564 NCT03142334[131]	Pembrolizumab	994	12	cc	pT2, G4 or sarc, N0 or pT3, G3-4, N0 or pT4, anyG, N0 or pTany, anyG, N1 or M1 resected	DFS
RAMPART NCT03288532[25]	Durvalumab + Tremelimumab	1750	12	cc + non cc	Leibovich 3–11	DFS OS
CheckMate-914 NCT03138512[26]	Nivolumab + Ipilimumab	1628	24	Cc ± sarc	pT2a, G3/4, N0 or pT2b, anyG, N0 or pT3, anyG, N0 or pT4, anyG, N0 or pTany, anyG, N1	DFS
IMmotion010[24]	Atezolizumab	778	12	cc or non cc + sarc	pT2, G4, or pT3a, G3-4 or pT3b, anyG or pTany, anyG, N1 or M1 resected	DFS
PROSPER adj/ neoadj[27]	Nivolumab	804	1 mo neoadj +9 mo adj	cc + non cc	≥cT2aN0M0 or cTanyN1M0	≥13% RFS improvement

IMmotion010[24] is designed to assess the role of 1 year of a PD-L1 inhibitor versus placebo in high-risk renal cancer. RAMPART[25] and CheckMate-914[26] assess the efficacy of 1 year of combined CTLA-4 and PD-L1 or PD-1 inhibition, respectively, versus PD-L1 or PD-1 monotherapy, respectively, versus placebo in high-risk renal cancer. RAMPART includes patient with non-clear cell histology. PROSPER,[27] which includes both clear cell and non-clear cell histologies, investigates the role of neoadjuvant PD-1 inhibition in priming the intact renal tumour followed by adjuvant therapy for 9 months versus standard-of-care surgery. At the time of this publication, IMmotion010, CheckMate-914, and PROSPER have reported negative results and will certainly lead to revision in thinking about future treatment paradigms in localized stages of RCC.

Neoadjuvant Therapy in RCC

The standard-of-care management of nonmetastatic disease remains surgical resection. However, given the improvement in survival of metastatic RCC patients with advancements in VEGFR-TKI and immuno-oncology (IO) therapy, there is interest in the application of these therapies neoadjuvantly to either locally advanced or localized disease. Neoadjuvant therapy may have several potential advantages for patients: First, the opportunity to allow for nephron-sparing surgery (NSS) in those with reduced renal function, or solitary kidneys. Second, to convert unresectable tumours into resectable tumours. Third, to decrease the height of an inferior vena cava (IVC) tumour thrombus to facilitate surgery. Fourth, response of the primary tumour to therapy can be an indicator of overall response to a particular therapy with improved long-term survival.

Two populations are subject to neoadjuvant therapy: those without evidence of metastatic disease (M0), for whom their planned nephrectomy is curative in intent, and those with metastatic disease (M1) who are receiving preoperative chemotherapy before a cytoreductive nephrectomy (CN) in the setting of more distant metastases. To avoid confusion, it has been suggested that the term "neoadjuvant" refer only to those with M0 disease, whereas therapy in those with M1 disease is described as "pseudo-neoadjuvant".[28,29] While this review focuses on neoadjuvant therapy in the curative-intent setting, we have also included relevant data on patients receiving pseudo-neoadjuvant therapy, as it informs our knowledge on response rates, surgical outcomes, and safety in those who went on to have a cytoreductive nephrectomy, regardless of the current controversy surrounding that approach.[30,31]

Targeted therapy as monotherapy in the neoadjuvant setting

Most data using neoadjuvant VEGF TKI–targeted therapy is retrospective. Proponents of neoadjuvant therapy have argued that tumour downstaging could lead to improved surgical outcomes due to less-complex surgeries and potentially improved long-term survival due to the elimination of micrometastatic disease.[28,32] Concerns about this approach include a delay in definitive therapy that could potentially lead to local or metastatic progression in a potentially curative setting, surgical complications due to impaired wound healing in the case of antiangiogenic agents, and decreased drug effectiveness if required in a future metastatic setting.[33]

Tumour downsizing to allow for nephrectomy on bulky or unresectable primary tumours

The continuing caveat among all solid organ malignancies is there is no standardization on resectability profiles. **Table 4** summarizes all prospective trials investigating neoadjuvant and pseudo-neoadjuvant therapy in patients with M0 or M1 disease, respectively. Importantly, the effect of preoperative therapy on the *in-situ* kidney in patients with metastatic disease still informs the feasibility of this approach; accordingly, Response Evaluation

Criteria in Solid Tumours (RECIST) responses referenced here refer to the effect of therapy on the primary tumour rather than the sites of metastases in any studies involving patients with M1 disease.

TABLE 4 Prospective Studies of Neoadjuvant/Preoperative Targeted Therapy

									RECIST				
Authors (year)	**Drug**	***N***	**Duration (range)**	**Inclusion criteria**	**% M1**	**Histology**	**Median tumour diameter change in cm (range)**	**Median % tumour size change**	**PR**	**SD**	**PD**	**RN (*n*)**	**PN (*n*)**
Hellenthal *et al.*[132]	Sunitinib 37.5 mg	20	90 days	T1b-3, Nany, Many	20	Clear cell (cc)	NA	-11.8 (-27 to +11)	1	19	0	12	8
Silberstein *et al.*[133]	Sunitinib 50 mg	12	12 weeks	cTany, cNany, cMany with indication for NSS	41	cc	-1.5 (-3.2 to -0.2)	-21.1 (-45 to -3.2)	4	10	0	0	14
Bex *et al.*[134]	Sunitinib 50 mg	22	12 weeks	M1 with resectable, asymptomatic primary tumour	100	cc	NA	-9.5% (-36 to +2.2)	1	21	0	18	0
Powles *et al.*[135]	Sunitinib 50 mg	52	12-18 weeks	M1	100	cc	NA	-12% (-35 to +8)	3	46	0	37	0
Rini *et al.*[136]	Sunitinib 50 mg	30	Median 18 weeks (6–120 weeks)	Unresectable primary (large tumour size, bulky LAD, venous thrombosis or proximity to vital structures)	63	All (76% cc)	-1.2	-22% (-100 to +13)	7	21	0	4	9
Cowey *et al.*[137]	Sorafenib 400 mg BID	30	33 days (8–59)	≥cT2, Nany, Many	43	All (70% cc)	-0.8 (-2.6 to + 1.0)	-9.6 (-40 to +16)	2	28	0	30	0
Hatiboglu *et al.*[138]	Sorafenib 400 mg BID	9	4 weeks	cT1-3, N0, M0	0	All (83% cc)	-1.0	-29 (-61.1 to +4.9)	4	5	0	7	5
Karam *et al.*[139]	Axitinib 5 mg BID	24	12 weeks	cT2-3b, N0, M0	0	cc	-3.1	-28.3 (-5.3 to -42.9)	11	12	0	19	5

TABLE 4 Prospective Studies of Neoadjuvant/Preoperative Targeted Therapy *(Cont'd)*

									RECIST				
Authors (year)	**Drug**	***N***	**Duration (range)**	**Inclusion criteria**	**% M1**	**Histology**	**Median tumour diameter change in cm (range)**	**Median % tumour size change**	**PR**	**SD**	**PD**	**RN (*n*)**	**PN (*n*)**
Lebacle *et al.*[140]	Axitinib 5 mg BID	18	60 days (58–114)	cT2aN0M0	0	cc	-1.2 (-2.5 to -0.4)	-17.1 (-4.8 to -29.4)	4	13	0	1	16
Powles *et al.*[141]	Pazopanib 800 mg BID	104	13 weeks (11–14)	M1	100	cc	-1.7	-14.1 (-21.1 to -1.1)	8	86	1	65	0
Rini *et al.*[142]	Pazopanib 800 mg BID	25	8–16 weeks	cT3N0M0	0	cc	-1.8	-26 (-43% to +2)	10	18	0	8	20
Jonasch *et al.*[143]	Bevacizumab: 10 mg/kg q14 days Erlotinib: 15 mg daily	50	8 weeks	M1	100	cc	NA	NA	0	44	1	42	0

Abbreviations: LAD, locally advanced disease; NSS, nephron-sparing surgery; PD, progressive disease; PN, partial nephrectomy; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; RN, radical nephrectomy; SD, stable disease.

The composite analysis of these prospective trials yields a median tumour diameter decrease of 9.5% to 29%. Although modest, this decrease did allow for nephrectomy in some patients who were previously deemed unresectable. Moreover, surgical resectability varies depending on the experience of the surgeon, tumour anatomic location complexity, which is more important than absolute tumour diameter, and the volume of the treating center, all of which are difficult to standardize even in prospective trials. Finally, the percentage of size decrease is less important than achieving tumour shrinkage away from vital structures such as the superior mesenteric artery, proximal pancreas, such as the superior mesenteric artery, proximal pancreas, or other nearby structures.

Tumour downsizing to allow for nephron-sparing surgery

In current surgical guidelines, PN is the treatment of choice for any tumours less than 4 cm (T1a) and preferred over radical nephrectomy (RN) in any tumour < 7 cm (T1b). Tumours larger than 7 cm are typically managed with RN.[34] The opportunity to downsize a tumour to allow for PN is an attractive option in patients at risk for requiring dialysis after an RN due to preexisting renal dysfunction, bilateral renal tumours, or a solitary kidney at baseline. Lane and McDonald both separately published retrospective investigations of the effect of presurgical sunitinib in making tumours susceptible to PN with shrinkage achieved and good results for median ischemia time, transfusion rate, or high-grade 30-day complication rate and in maintaining the glomerular filtration rate (GFR).[35,36] Taken together, these retrospective studies suggested a potential role for preoperative targeted therapy in facilitating PN.

The trials in **Table 4** suggest that neoadjuvant VEGFR TKI therapy may facilitate PN by decreasing tumour complexity, reducing tumour volume, and increasing the distance from the hilar and vascular structures without significantly affecting surgical outcomes. Due to subjectivity in decision-making regarding the feasibility of PN, prospective, randomized data is needed.

Downstaging inferior vena cava thrombus

Extension of the tumour into the adjacent venous system is present in up to 5–10% of all RCC cases.[37,38] Tumour thrombus extension is a predictor of the presence of micrometastases at the time of surgery and the 5-year survival for these patients is around 60%.[39] There is consensus on the correlation between increasing level of tumour thrombus and the rates of perioperative and postoperative complications.[40–42]

A series of case reports documenting the downsizing effects of targeted therapy on tumour thrombi preoperatively first demonstrated proof-of-concept and paved the way for larger, retrospective analyses.[43–52] Cost, Bigot, and others have explored the use of neoadjuvant VEGFR TKI therapy using antiangiogentic drugs on IVC tumour thrombi in retrospective studies of patients with IVC thrombi to above the level of the renal vein.[53–57] The authors of these analyses concluded that there was minimal impact of neoadjuvant targeted therapy on IVC thrombi in a clinically meaningful way. However, data from NAXIVA, the only prospective trial specifically investigating the

impact of neoadjuvant therapy on the extent of tumour thrombus in patients with metastatic and nonmetastatic RCC[58] demonstrated that patients who ultimately underwent surgery required a less-invasive surgical approach than was expected before preoperative therapy. The median reduction in thrombus craniocaudal height was 21.49%. Thus, there may be clinically relevant benefit to the patient if the effect of tumour thrombus reduction can allow for a less-invasive surgical approach. Prospective, randomized data on the impact of tumour thrombus regression on surgical approach and most importantly long-term survival outcomes are needed.

The concern about delaying surgery and the risk for progression capable of changing surgical approach or candidacy while receiving neoadjuvant targeted seems largely unfounded. While 30–80% of patients experience at least grade 3 toxicity while on therapy, these events typically resolve with dose interruption and/or reduction and there are no reports of surgical delay as a result of these adverse events.[29] While there are reports of delayed wound healing, these events were noted in small, single-arm, phase 2 clinical trials without comparison arms in most cases and the large majority of reported events resolved with conservative management. Therapy holiday before surgery tailored to the half-life of the targeted agent appears to reduce this risk.

Immunotherapy and immunotherapy/TKI combinations as neoadjuvant therapy

The efficacy of immunotherapy in the neoadjuvant setting for locally advanced RCC has become a priority area of investigation, both as monotherapy or in combination with other immunotherapy-based or antiangiogenic agents. Neoadjuvant immunotherapy, as in metastatic therapy, enhances antitumour immunity by allowing for the reactivation of exhausted and quiescent cytotoxic T cells. However, by administering the therapy before the primary tumour has been removed, the dominant source of tumour neoantigens capable of stimulating the expansion of T cell clones is present compared to a scenario when immunotherapy is administered in an adjuvant fashion.[59,60] Also in melanoma patients treated with checkpoint inhibitors, it is known that more diverse T-cell clonality in the tumour microenvironment equates to improved responses to anti–PD-1 and anti–CTLA-4 agents.[61] Extrapolating from melanoma, there is now a goal to harness this quality of the immune system to induce a more robust immune response against micrometastatic disease with neoadjuvant immunotherapy, thereby increasing the likelihood of cure. To this end, preclinical data in a mouse breast cancer model showed improved CD8+ T-cell antitumour responses when immunotherapy was administered in the neoadjuvant compared to the adjuvant setting.[62] Lastly, another potential benefit of preoperative immunotherapy lies in overcoming the immunosuppressive tumour microenvironment cultivated by surgery, which may be conducive to the growth of micrometastases postoperatively.[63,64]

The application of immunotherapy in the neoadjuvant setting is early. Gorin *et al.* treated 15 patients with high-risk, nonmetastatic, clear cell RCC (cT2-4, N0) with 3 doses of neoadjuvant nivolumab 3mg/kg given every 2 weeks.[65] All patients completed the 3 doses and proceeded to surgery within the prespecified 7-day window; the single intraoperative complication encountered was not felt to be related to nivolumab. Per RECIST 1.1, all patients had stable disease at the time of surgery, although 1 patient had a 15.7% reduction in their tumour

diameter and evidence of an immune-related pathologic response on the nephrectomy specimen characterized by tumour regression and immune cell infiltration. At median follow-up of 24.7 months, two patients had developed metastatic disease. Importantly, quality of life was maintained during neoadjuvant therapy. Another pilot study of nivolumab was undertaken in 18 patients, every 2 weeks for 4 doses.[66] There were no delays of surgery and all patients had stable disease per RECIST prior to surgery. Two patients had to discontinue nivolumab prior to receiving the full 4 doses due to grade 3 transaminitis and grade 2 arthralgias, respectively; another patient suffered grade 4 colitis 4 months after completion of therapy. Perioperative durvalumab (anti–PD-L1) with or without tremelimumab (anti–CTLA-4) was investigated in a multicohort phase 1b trial.[67] A total of 29 patients with high-risk localized disease (cT2b-T4 or TanyN1) received either a single dose of durvalumab or durvalumab with tremelimumab prior to their nephrectomy followed by adjuvant treatment, which, depending on the cohort, ranged from one dose of durvalumab to a single postoperative dose of both agents followed by 1 year of durvalumab.[67] There were no treatment-related delays of surgery or surgical complications, although the addition of tremelimumab was associated with an excessive incidence of immune-related adverse events (irAEs) and the study was suspended. These studies lack data concerning long-term survival outcomes in those treated with neoadjuvant immunotherapy, which is posited as the primary potential benefit of this approach, as immunotherapies tend to require a longer time to response than targeted agents. Checkpoint inhibitor monotherapy was relatively well tolerated, but the toxicity of combined anti–PD-1 and anti–CTLA-4 blockade may be associated with excessive irAEs to be accommodated in the neoadjuvant setting; notably, there was no signal regarding surgical complications across the studies.

A summary of ongoing trials investigating immunotherapy in the preoperative setting is found in **Table 5**. Just as TKI and immunotherapy combinations have come to dominate the frontline metastatic space, so too are investigators attempting to capitalize on the synergy of these agents in the neoadjuvant setting. Emory investigators have extrapolated from the CLEAR trial and are currently enrolling patients with high-risk localized RCC (cT3Nx or T any N+) in a trial of 12 weeks of neoadjuvant pembrolizumab plus lenvatinib prior to planned nephrectomy (NCT04393350).[68] The PANDORA trial of neoadjuvant pembrolizumab and axitinib in locally advanced RCC (NCT04995016), borrowing from KEYNOTE-426 in the metastatic setting, is enrolling shortly.[69,70] The ongoing NeoAvAx trial of avelumab and axitinib in the neoadjuvant setting (NCT03341845) is built upon JAVELIN Renal 101,[71] just as CheckMate 9ER spurred the currently enrolling CytoKIK trial of neoadjuvant cabozantinib and nivolumab (NCT04322955).[72,73] Although there are excessive immune-related events associated with neoadjuvant durvalumab and tremelimumab in combination, the hope for a tolerable and efficacious dual immunotherapy approach continues in the ongoing SPARC-1 trial of neoadjuvant IL-1b antagonist canakinumab combined with spartalizumab, a novel anti–PD-1 agent (NCT04028245).[74] Finally, PROSPER RCC (NCT03055013) is the only phase 3 trial investigating preoperative immunotherapy (nivolumab) versus observation, and safety, feasibility, and efficacy are not known at this time.[75]

TABLE 5 Ongoing Clinical Trials Investigating Neoadjuvant therapy (± adjuvant component) in Locally Advanced or Metastatic (with Planned Cytoreductive Nephrectomy) RCC

NCT Trial #	Phase	Arm	Drug	Dose	Duration	Goal N	Stage	Histology	Primary endpoint	Status
NCT01263769	2	single	Axitinib	5 mg BID	12 weeks	40	cT2-T3b, No,[b] Mo	clear cell (cc)[c]	ORR[a]	
TKI monotherapy										
NCT03438708 PADRES	2	single	Axitinib	5 mg BID	8–10 weeks	50	TanyNanyMo with strong indication for PN	cc	% reduction of longest diameter of tumour in mm ORR; effect on tumour morphometry R.E.N.A.L score; feasibility of partial nephrectomy	Active, not recruiting
NCT04022343	2	single	Cabozantinib	60 mg daily	12 weeks	17	≥cT3Nx or TanyN+[f]	cc[d]	ORR	Unknown
Immunotherapy or immunotherapy combinations										
NCT04393350	2	single	Lenvatinib and pembrolizumab	Len:18 mg daily Pembro: 200 mg q3w	12 weeks	17	≥cT3Nx or TanyN+[f]	cc[d]	ORR	Recruiting
NCT03680521	2	Single	Sitravatinib and nivolumab	Sitravitinib: oral capsule daily Nivolumab: 24 mg IV q2w	Sitravatinib: 6–8 weeks[e] Nivolumab: 4–6 weeks	25	Locally advanced RCC	cc	ORR and point in treatment course of ORR	Active, not recruiting
NCT04385654	2	Single	Toripalimab and axitinib	Toripalimab: 240 mg IV q3w Axitinib: 5 mg PO BID	6 weeks	40	cT ≥ 2 or cN+	non-cc	Major pathologic response (MPR); pathologic complete response (pCR); pathologic no response (pNR)	Not yet recruiting
NCT04118855	2	Single	Toripalimab and axitinib	Toripalimab: 240 mg IV q3w Axitinib: 5 mg PO BID	Up to 12 weeks	30	T2-3, No, Mo	cc	ORR	Not yet recruiting

TABLE 5 Ongoing Clinical Trials Investigating Neoadjuvant therapy (± adjuvant component) in Locally Advanced or Metastatic (with Planned Cytoreductive Nephrectomy) RCC *(Cont'd)*

NCT Trial #	Phase	Arm	Drug	Dose	Duration	Goal N	Stage	Histology	Primary endpoint	Status
NCT04995016 PANDORA	2	Single	Pembrolizumab and axitinib	Pembrolizumab: 200 mg q3w Axitinib: 5 mg PO BID	12 weeks	18	≥T3Nx or TanyN+[f]	cc[d]	MPR	Not yet recruiting
NCT05024318 NAPSTER	2	Randomized	Stereotactic ablative radiotherapy (SABR) (arm 1) vs pembrolizumab and SABR (arm 2)	Arm 1: SABR: 42 Gy in 3 fractions Arm 2: Pembrolizumab 200 mg q3w x 3 cycles with SABR administered after cycle 1	9 weeks	26	T1b-3, N0-1, M0 or low-volume M1 planned for nephrectomy	cc[i]	MPR	Not yet recruiting
NCT03341845 NeoAvAx	2	Single	Axitinib and avelumab	Axitinib: 5 mg BID Avelumab: 10 mg/kg q2w	12 weeks	40	"non metastatic, completely resectable primary tumour of int to high risk"	cc	Rate of PR	Not yet recruiting
NCT04028245 SPARC-1	2	Single	Spartalizumab and canakinumab	Spartalizumab: 400 mg q4w Canakinumab: 300 mg q4w	8 weeks	14	≥ cT2Nx or cTanyN1	cc[c]	% of patients who proceed to radical nephrectomy[h]	Not yet recruiting
NCT03055013 PROSPER RCC	3	Randomized	Perioperative nivolumab vs. observation	Nivolumab: 480 mg every 14 days x 1 neoadjuvant cycle and up to 9 cycles adjuvantly	7–28 days preoperatively, up to 9 months post-operatively	766	≥ cT2Nx or cTanyN1	any	EFS	Completed
NCT04322955 Cyto-KIK	2	Single arm	Preoperative nivolumab and cabozantinib	Nivolumab: 480 mg every 4 weeks Cabozantinib: 40 mg daily	Up to 12 weeks[g]	45	Metastatic	cc[d]	CR rate	Recruiting

[a]ORR: objective response rate.

[b]RP LNs ≤ 2cm considered N0.

[c]Clear cell must be predominant histology (> 50%).

[d]Clear cell component.

[e]Begins 2 weeks prior to nivolumab.

[f]Or deemed unresectable by surgeon.

[g]First 3–6 subjects will hold cabo for 3 weeks prior to surgery; if safe, all others will hold for only 2 weeks prior.

[h]Feasibility if > 85% proceed.

[i]Including rhabdoid and sarcomatoid differentiation.

The combination of neoadjuvant immunotherapy with radiation therapy in non-small cell lung cancer and melanoma produced an improved antitumour response compared to either modality alone, potentially due to an amplified T-cell response to tumour neoantigens unearthed after cell death from radiation therapy in the presence of checkpoint inhibition.[76,77] Margulis *et al.* showed that neoadjuvant stereotactic radiation therapy for mRCC is safe, with early signs of efficacy and potentially even an abscopal effect on metastatic sites of disease.[78] Building on this potential, the NAPSTER trial of neoadjuvant stereotactic radiation therapy with or without pembrolizumab is set to commence enrollment (NCT05024318), with primary endpoints focusing on the rate of major pathologic response as well as the effect of therapy on tumour infiltrating lymphocytes and other immune cells.

There have been instances of irAEs delaying surgery, including at least one grade 5 AE, although these instances are rare, which underscores the need for biologic markers for patient susceptibility to irAEs.[65–67,79,80] There is data to suggest that checkpoint inhibitors may even be safe to continue through surgery without interruption, although this regimen is debated in clinical practice.[81] The risk for irAEs and surgical complications, including wound healing issues, increases when checkpoint inhibitors are combined with other immunotherapies, radiation, or with VEGFR-TKI therapies. If long-term follow-up shows that the current benefit in disease-free survival seen with pembrolizumab over observation equates to overall survival as well,[8] then we can expect to see more trials incorporating or allowing adjuvant immunotherapy as a standard-of-care component.

Radiology Considerations

Detection of recurrences must be practical, relatively inexpensive, generally available, and safe for patients. As most ccRCC is hypervascular, dual-phase computed tomography (CT) imaging with iodine contrast meets these criteria.[82] Most lesions can be visualized, and some can only be seen in the arterial phase. Ultrasound imaging of the abdomen to detect recurrences in the renal fossa is inexpensive but may be inferior to CT in the detection of recurrence, especially in cases of partial nephrectomy.[83] As the use of intravenous iodine contrast is limited to patients with adequate renal function, magnetic resonance imaging (MRI) with or without gadolinium can be substituted. Nine gadolinium-based contrast agent (GBCA)-like agents are approved for use in the United States.[84] The instability of the earlier (linear) gadolinium-based agents led to gadolinium deposition in the tissue

and nephrosclerosis in patients with impaired renal function However, gadoteric acid (Dotarem®) has been assessed in more than 3,200 renally impaired patients with no reports of nephrosclerosis.[85] Thus, some of the more recent generation agents can be safely used for imaging in the post-nephrectomy patient population.

Other imaging modalities

Several positron emission tomography (PET) imaging approaches have been used in metastatic clear cell renal cancer and warrant discussion here. Carbonic anhydrase IX (CAIX), a transmembrane glycoprotein that interacts with hypoxia inducible factor, is expressed in clear cell RCC and associated with poor prognosis.[86] Girentuximab, a CAIX compound labelled with 124I, was assessed in 195 patients with localized renal masses.[87] In these patients, the compound was able to identify both renal masses smaller than 1 cm and larger than 2 cm and uptake was avid in tumours of clear cell histology while negative in chromophobe and papillary type 1 cancers. In addition, a small molecule targeting CAIX, 18F VM4–037, was investigated in renal cancer.[88] Unfortunately, with both girentuximab and the small molecule, it is difficult to differentiate tumour grade or size and thus the utility in their use in staging primary disease is low, but the small molecule could be used to detect recurrences postresection. As a result, the manufacturer of girentuximab decided to cease development of the antibody.

Prostate-specific membrane antigen (PSMA) is highly expressed in the neovasculature of clear cell renal cancer,[88] and both PSMA gallium and pyL agents have been commercialized recently for use in metastatic prostate cancer. In addition, both approaches have been assessed in metastatic clear cell renal cancer.[89–91] Similar problems with distinguishing size in clear cell renal cancer exist, but these agents could be considered for ruling out metastatic disease preoperatively or for confirmation of recurrence postoperatively.

PD-L1 imaging is of high interest given the use of immune checkpoint inhibitors as treatment in most patients with metastatic kidney cancer. At least 13 targeted antibody and 5 small molecule PD-L1 imaging targets have been tested in human or mouse models in a variety of cancers. FDA-approved versions of humanized pembrolizumab and nivolumab antibodies labelled with ^{89}ZR, ^{111}IN, or ^{64}CU are under investigation. The limitation of labelled antibodies includes slow clearance from the blood and variable penetration of tissues due to their large size. These features result in larger amounts of background noise, the need to image several days after injection, and a larger radiation burden to the patient. Thus, focus is toward development of small molecules targeting portions of PD-L1–binding domains such ectodomains or adnectins.[92,93] While these molecules are early in development, they have the potential to augment the use of immunohistochemistry (IHC) in interpreting which cancers may be more sensitive to anti–PD-1 or PD-L1 therapy. One study has highlighted the ability of these agents to identify tumour heterogeneity not always reflected in IHC.[92] With the approval of adjuvant pembrolizumab, the use of PD-L1 or tagged pembrolizumab imaging could be prospectively studied in patients with intact primary tumours to determine whether there is a correlation with improved DFS in patients with cancers that are PD-1 avid.

Geographic and Economic Issues

Regulatory issues

Uptake of new therapies into routine clinical practice is ideally based on published peer-reviewed evidence, is influenced by international guidelines and recommendations, and is tailored to the needs of each specific patient based on their circumstances and comorbidities. The "real-world" situation is very different: access to and uptake of new therapies is influenced primarily by what is approved and, more importantly, reimbursed in each region. These differences in global systems and equity of access unfortunately mean that use of new treatments is often restricted to those with the financial resources to pay for it themselves. This is ultimately not sustainable at a societal level.

Australian regulations

New agents must be approved by the Therapeutic Goods Administration (TGA), but reimbursement for most of the population is generally through the Pharmaceutical Benefits Scheme (PBS). PBS reimbursement means that the bulk of the cost of the agent is carried by the Federal Government in its single-payer public health system, with each patient paying only a small fee and pharmacy-dispensing charges, or nothing at all if the treatment is administered in a public hospital. PBS reimbursement indications are generally more stringent than TGA approval indications, and usually reflect the eligibility criteria for the pivotal trials that led to approval. It is not legal in Australia to claim PBS reimbursement if the prescribing criteria are not met; physicians may prescribe the medication as "non-PBS," but the patient will pay the full cost in that situation.

Canadian regulations

The Health Products and Food Branch (HPFB) regulates drug approval in Canada. If the HPFB decides not to grant a marketing authorization, the drug's sponsor has the option of providing additional information or resubmitting its submission at a later date with additional supporting data. Additionally, HPFB has a Special Access Program that allows physicians to gain access to drugs that are not currently available in Canada provided it deems the argument legitimate and the Sponsor agrees to provide the drug. The Kidney Cancer Research Network of Canada reviewed the results of ASSURE, PROTECT, and S-TRAC and 4 other adjuvant trials for renal cancer and issued a consensus statement that did not support the use of VEGFR-TKI therapy in the adjuvant setting.[94]

European regulations

The European Medicines Agency (EMA) is responsible for the scientific evaluation of applications for centralized marketing authorizations in the European Union (EU). The European drug regulatory system is based on a network made up of around 50 regulatory authorities from the 31 countries of the European Economic Area (EEA) (the 28 Member States of the Union, plus Iceland, Liechtenstein, and Norway), the European Commission, and the EMA. Each evaluation of a new drug or new indication is performed by the EMA's Committee for Medicinal Products for Human Use (CHMP). Once the marketing authorization has been granted, decisions relating to the price and reimbursement are taken at the level of each Member State, pending on the potential role and use of the drug within the national health system of the country. In United Kingdom, a specific evaluation of the drug may be considered by the National Institute for Health and Care Excellence (NICE), on demand of the Department for Health and Social Care.[95–97]

The negative opinion for sunitinib as adjuvant therapy was stated on February 22, 2018, and the recommendation was a refusal of a change to the marketing authorization for the agent, including the indication in patients at high risk for renal cell carcinoma recurrence after surgery. It was considered that the benefits did not outweigh the risks of sunitinib according to the data of S-TRAC. Thus, the ongoing evaluation of NICE, started in December 2016, was suspended in December 2018.[98] More recently, the appraisal of pembrolizumab in the adjuvant setting started on August 8th 2019, and publication of the results from NICE is pending on July 20th 2022.[95]

US regulations

The United States Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER) is the entity responsible for review of new drug applications before they can be marketed. Within CDER, the Office of Oncologic Diseases oversees the approval of drug and biologic treatments for cancer and hematologic malignancies. At its discretion, the FDA will seek expert advice from an independent advisory panel in situations where additional guidance may prove helpful. The Oncologic Drugs Advisory Committee (ODAC) provides expert recommendations to the FDA to help the agency in its decision of whether to approve a new drug. ODAC comprises experts in relevant fields including general oncology, pediatric oncology, hematologic oncology, immunologic oncology, and biostatistics. One voting member is identified with consumer interests while one non-voting member is identified with industry interests. While ODAC itself does not ultimately decide on drug approval, its recommendations and perspectives are of high value to the FDA in its approval decisions.

The FDA's approval of sunitinib in November 2017 for adjuvant use based on the results of the S-TRAC trial represented the first approval of an adjuvant treatment for RCC.[15] The approval was not without controversy.[99] Members of ODAC were split on their recommendation for approval, 6 in favour and 6 opposed. The disease-free survival had been used for adjuvant drug approval in other cancers, but its validity as an endpoint for adjuvant treatment of RCC was unknown. The lack of overall survival data was concerning for some reviewers, while others felt that the potential for DFS benefit to eventually translate into overall survival benefit was sufficient to

recommend approval.[100] The negative results of the ASSURE and PROTECT trials also brought into question the consideration of the totality of the evidence regarding adjuvant use of tyrosine kinase inhibitors in RCC.[13,14] In the end, the FDA's approval of sunitinib set a precedent for DFS as an acceptable endpoint for adjuvant RCC studies seeking US regulatory approval.

In November 2017, the FDA and the National Cancer Institute held a public workshop to develop consensus on adjuvant trials in RCC. The substantial variability in the design, conduct, and analysis of trials in this disease state prompted this effort. A group of US-based experts in genitourinary cancer clinical trials were invited and discussion was focused on eligibility criteria and radiographic determinants of recurrence.[9] Subsequently, in October 2020, the FDA issued draft guidance for industry for the development of adjuvant RCC treatments based on recommendations from the 2017 workshop.[101] The impetus was a need to develop consistency within and across trials remove these two words to facilitate interpretation of results. Among recommendations for trial eligibility were the inclusion of patients with non-clear cell histology, and those with microscopically positive margins, and exclusion of patients with residual or recurrent malignant disease based on biopsy confirmation or clearly prespecified radiographic criteria. Biopsy confirmation of suspected recurrent lesions was suggested whenever safe and feasible, and prespecified radiographic criteria for recurrence based on organ site was emphasized. The guidance document focused on DFS as the primary efficacy endpoint, reinforcing the precedent of DFS as acceptable for adjuvant RCC trials based on the sunitinib approval. The guidance stated that a number of factors may influence the magnitude of DFS benefit required to support drug approval, including trial design, toxicity profile, study population, and overall risk-benefit evaluation of the therapy. Additionally, interim analyses of DFS were not recommended, and it was suggested that an interim analysis of overall survival be conducted at the time of the final DFS analysis and that a favourable trend should be observed to ensure that OS is not negatively impacted by the treatment. It should be emphasized that guidance documents issued by the FDA only represent current thinking by the Agency and are to be interpreted as recommendations, not requirements.

In November 2021, the FDA approved pembrolizumab for adjuvant treatment of RCC in patients who are at intermediate-high or high risk for recurrence after surgery. The approval was based on results of the KEYNOTE-564 study using investigator-assessed DFS as the major efficacy outcome.[8] Like the S-TRAC study, overall survival data were not mature at the time of the analysis. The FDA gave the application priority review designation, in which 6 months (rather than the standard 10 months) was allocated to take action on the marketing application. Priority review designation is granted in situations in which the proposed drug would show a significant improvement in safety or effectiveness of a treatment for a condition.[102] The review of the pembrolizumab submission was also conducted under Project Orbis, an initiative that facilitates concurrent review of oncology products among international partners, allowing for simultaneous decisions in all countries. The Australian TGA, Health Canada, and Swissmedic participated in this review.

The approval of pembrolizumab redemonstrated the FDA's acceptance of DFS as a regulatory endpoint for adjuvant RCC trials. Long-term overall survival results from these studies remain important in determining the overarching clinical significance of adjuvant treatments and how such results might influence the FDA in its evaluation of future trials.

Racial or ethnic issues

Drug levels, metabolism, and elimination can all be affected by various factors including pharmacogenomics or body habitus. Differences in ancestry or in socioeconomic status can therefore lead to differences between populations with respect to toxicity or efficacy. For example, clearance of sunitinib is slower in Asian patients, resulting in greater drug exposure, leading to a higher frequency of adverse events, and also possibly explaining an apparently higher rate of response to therapy.[103] A meta-analysis of clinical trials of sunitinib in renal cell carcinoma examined data from 33 publications involving 9,977 patients of Caucasian or Asian ancestry.[104] Asian patients had more toxicity of all grades, particularly HFS, fatigue, and thrombocytopenia. Anticancer efficacy was similar in this study, although South Asians may have poorer outcomes that are more similar to those of European descent.[104] Efficacy of pazopanib is similar between patients of Asian or European descent, but the patterns of adverse events differ: Asians tend to have more hematological and less gastrointestinal adverse events than Europeans.[105,106] No difference in terms of treatment effect of axitinib has been reported between the Asian and non-Asian subgroups in the adjuvant setting. Nevertheless, more Asian patients than non-Asian patients had an AE resulting in permanent discontinuation, 27.3% versus 15.0% respectively, p=0.014. The dose reduction needed was also significantly more frequent in the Asian population (58.8% vs. 46.0%; p=0.028), with more frequent nasopharyngitis and proteinuria reported.[107]

Various physiological factors affect drug levels and elimination. Membrane transporters influence drug absorption, and various enzymes affect drug metabolism. Sunitinib and pazopanib are substrates for P-glycoprotein and BCRP efflux transporters in the gut, influencing absorption; they are also involved in efflux across endothelial cells into tissues or into bile canaliculi for excretion. Cytochrome P450 enzymes such as CYP3A4 produce extensive first-pass metabolism of drugs in the liver such as sunitinib, pazopanib, cabozantinib, sorafenib, and axitinib, often producing biologically active metabolites. Variants of these enzymes can have profound effects on drug levels and hence on efficacy or toxicity. Asian populations more frequently have variants associated with reduced clearance or metabolism of sunitinib, to the extent that it is standard practice to commence treatment at a lower dose (37.5 mg).[108]

Limited information is available regarding racial or ethnic differences in terms of rates of response or incidence of immune-related adverse events for patients with renal cell carcinoma receiving immune checkpoint inhibitors. This lack of data is due in part to under-representation of various populations in large-scale clinical trials. One study of 293 patients with various cancers suggested a higher incidence of immune-related adverse events in Caucasians compared to African-Americans.[109] As in other studies, those with higher rates of immune-related adverse events had indications of better outcomes, with improved progression-free survival and overall survival. These findings remain to be confirmed and, if real, for the biologic mechanisms of these differences to be defined.

Using Other Cancer Adjuvant Trials to Develop Trials

The therapeutic index is always relevant for studies of new experimental agents. This index is even narrower in the adjuvant setting. The major challenge is to select the population with the highest risk for recurrence or death, with in parallel the highest chance of sensitivity to a given drug. This should be supported by strong biological information or high-level confidence in data coming from neoadjuvant or metastatic treatments, but frequently this information is limited. If the design or management of drugs or trials could be improved by analogy between tumour types, this approach could streamline trial design and avoid repeating the same mistakes.

Level of toxicity deemed acceptable in solid tumour adjuvant trials

Evaluation of an acceptable level of toxicity in solid tumour adjuvant trials is in part limited by the absence of data about long-term side effects, especially when they could be confounded by other medical events. This effect upon quality of life counterbalances quantity, and ultimately efficacy, at least by DFS and/or OS. It is hoped that real-world studies can correct this over time.

Patient-reported outcomes can help inform investigator-reported toxicity grades, especially in capturing functional side effects such as grade 2 side effects, which are usually not reflected by NCI Common Terminology Criteria for Adverse Events (CTCAE) toxicity.[110] Another measure of unacceptable toxicity may be appreciated indirectly as the number of patients who could not continue treatment due to toxicity or required interruption of dose reduction of therapy.

Other trial designs used perioperatively currently not being tested in RCC?

There are currently no validated biomarkers that will enable more effective molecular classification and risk definition to improve selection of patients for adjuvant therapy.

Issues Important to Patients

The scientific issues discussed in this chapter are critically important considerations for clinicians involved in assessment of the science and in providing advice and care to their patients. It is important also to consider aspects of these issues from the perspective of the patient, which in many cases can differ substantially from those of the providers.

Adjuvant therapy

Adjuvant therapy given after definitive therapy with curative intent can be likened to life insurance: "a bet you do not want to win." A life insurance policy is essentially saying to a company, "I bet I die," and the company saying, "We bet you don't." A decision to undertake adjuvant therapy employs similar thinking. Patients with no apparent residual disease will be offered adjuvant therapy to reduce their theoretical risk for recurrence and death from cancer. Most patients who receive adjuvant therapy cannot benefit from it. Some patients will have micrometastatic treatment-resistant disease from the outset, while others will be cured of their disease; adjuvant therapy cannot benefit these patients, and they will take on the risk of treatment toxicity without a corresponding improvement in outcomes. There is only ever a relatively small population of patients with disease that was initially destined to kill them, but now will not because they received early treatment that was able to wipe out lethal potential repopulating cancer cells, and the patient has survived any effects of the treatment. However, unless this small population can be reliably identified, all patients must receive treatment and take on its risk of toxicity, which in some cases may be fatal. It may be possible to increase the proportion of treated patients who can benefit (Box 1).

BOX 1 Factors predicting increased relative benefit compared to harm from adjuvant therapy

Increased probability of benefit:
• Higher risk for recurrence based on clinical features (stage, grade, other)
• Biomarkers identified before or after definitive treatment:
• Indicators of minimal residual disease
• Predictors of treatment sensitivity
Decreased probability of toxicity:
• Low comorbidity scores
• Absence of polypharmacy
• Absence of frailty
• Good performance status
• No known pharmacogenomic characteristics adversely affecting drug pharmacokinetics

This paradigm of thinking about adjuvant therapy provides a conceptual framework for discussion with patients making decisions about their treatment. It does not consider the effects of life-prolonging therapies given at the time of cancer recurrence, which is a critical consideration for clinicians in the selection and timing of treatment. The long natural history of some cancers, and the existence of potentially life-prolonging therapies in the metastatic setting, complicate the design and interpretation of clinical trials of adjuvant therapies. Most adjuvant therapy clinical trials, including almost all of those published for renal cell carcinoma, use a primary endpoint of disease-free survival. It can be argued that this is a valid surrogate for anticancer benefit: only those patients who relapse will die of the cancer; delay in relapse is likely to lead to some delay in death, assuming that the kinetics of cancer progression after adjuvant therapy are the same as for patients who did not receive the therapy. This may be sufficient to sway patients and clinicians in favour of adjuvant therapy, particularly when the therapy has low toxicity. However, if no overall survival benefit has been demonstrated for adjuvant therapy, and a life-prolonging therapy is available in the metastatic setting, then patients who relapse can still benefit by not receiving adjuvant therapy, and those who do not need it will be spared the risk of toxicity. It could similarly be argued that if an overall survival benefit is demonstrated for adjuvant therapy, then it must be considerably greater than when patients with metastases are treated; if it is similar, then there is no advantage to treating the entire population, most of whom cannot benefit. This is a complex calculus for decision-making, and the challenge for clinicians is to understand the science, understand the patient and their specific circumstances, provide information and advice in a way that can be understood, and allow patients to make informed decisions.

Neoadjuvant therapy

The issues relating to decision-making for neoadjuvant treatment prior to definitive treatment with curative intent are very different to those for the adjuvant setting. Neoadjuvant therapy is “a bet you want to win”—an investment in treatment now, while cancer is still detectable, to try to improve outcomes from definitive treatment such as surgery. Currently for patients with renal cell cancer, this approach is nearly always in the context of a clinical trial, as its benefit as of yet is unproven.

Patient preferences

Clinicians and the patients for whom they care often have different goals for treatment and expectations of outcomes, even in the setting of apparent joint decision-making. This is particularly the case for treatment in the adjuvant setting, where definitive therapy with curative intent has already been undertaken, there is risk for recurrence, but there is no current evidence of detectable residual or metastatic disease. People with cancer at the commencement of their treatment will often decide that even very small probabilities of improved survival are worth the potential risk for treatment toxicity. Clinicians tend to require larger evidence of benefit before recommending adjuvant therapy. The situation is further complicated by the fact that patients and clinicians perceive and report adverse events very differently. Toxicity assessments in most trials until recently were based on clinician assessments without validated tools to report the patient’s experience or their symptomatic or

functional outcomes; and often collected data only during trial participation.[111] The balance and weighting of all these factors is likely to be very different for a patient contemplating adjuvant treatment compared to one with known overt metastatic disease.

Patients will often have other generic preferences regarding treatment. They prefer settings where it is possible to tell whether the treatment is working; this is not possible for adjuvant therapy. They want minimal toxicity and minimal inconvenience; these cannot be guaranteed. The SORCE clinical trial[11] included a patient preferences substudy that aimed to understand what degree of improvement in survival would be judged by participants as sufficient to justify their participation and potential side effects from treatment with sorafenib.[112] This "PAS in SORCE" substudy included 233 participants from Australia and New Zealand and some selected sites in the United Kingdom. It used a validated questionnaire to determine the minimum survival benefits the participants judged to be sufficient to warrant treatment with adjuvant sorafenib for 1 year (compared to observation) or 3 years (compared to 1 year of active sorafenib treatment), according to theoretical reference survival times, or theoretical survival rates at 5 years. This study showed that participants required that treatment for 1 year should provide at least an extra 9 months of survival beyond 5 years and an extra 1 year of survival beyond 15 years; alternatively, it should provide improvements in theoretical 5-year survival from 65% to 69%, or from 85% to 88%. Three years of treatment, with its predicted attendant toxicity, required greater benefits to be justified: an extra year beyond both 5 and 15 years. Clinical investigators in SORCE required larger theoretical benefits than the participants.[113]

In the context of contradictory results of S-TRAC and ASSURE, the European Association of Urology (EAU) Renal Cell Carcinoma Guidelines Panel and the Kidney Cancer Research Alliance (KCCure), conducted a survey in 450 patients treated for kidney cancer.[114] Toxicity was not a main driver of decision-making for the patients—18% would use it in case of moderate toxicity, 14% no matter of toxicity, 9% only in case of no toxicity. Considering efficacy, 26% of the patients would use adjuvant treatment if it prolonged survival, but patients did not make a difference between DFS and OS. 30% would use it after more information is provided. Finally, only 4% of the patients will not use adjuvant treatment. Moreover, patients with a history of systemic therapy rely on the physician's recommendation in contrast to patients without a history of systemic therapy ($p<0.0001$). Finally, patients on systemic therapy had a significant higher acceptance of toxicity ($p<0.0001$).

Clinical trial design

Design of adjuvant clinical trials in renal cell carcinoma should ideally involve extensive community consultation to ensure the study procedures and outcomes align with community expectations and needs. People with metastatic cancer often participate also in the hope of a good outcome for themselves through reduction in cancer burden and the hope of cure. These goals are much more abstract for a patient who has already undergone definitive therapy with curative intent and has no evident residual disease. Such patients might be less willing to undergo inconvenience, incur cost, or experience adverse events, as the direct benefit to them personally is more difficult for them to visualize. People often participate in clinical trials due to altruism, hoping to improve outcomes for

those who come after,[115] but other factors include scientific interest, fear of cancer recurrence, or fear of missing out. It is important to ensure that trials are designed appropriately and that recruitment and consent processes are not coercive for such patients.[116]

Unmet needs

The most obvious unmet need in the context of clinical trials for renal cell carcinoma is for effective therapies. None of the trials so far have demonstrated a survival advantage, including perhaps the most promising data with pembrolizumab in the KEYNOTE-564 trial.[8] Certainly, there is no evidence that adjuvant therapy can improve outcomes substantially more than existing life-prolonging therapies. Although several agents are approved for adjuvant use in various regions, it is also reasonable to advise our patients that the standard of care remains observation, with access to potentially life-prolonging therapies in the event of relapse. Other needs might be even more difficult to meet. Patients want not only better treatments and outcomes but also results more quickly.[117–120] They want trials that examine and report the patient experience, rather than investigator-assessed outcomes. These are all considerations for future trial designs, but they also apply to everyday treatment decision-making.

Future Directions

Several issues need to be considered when designing clinical trials of adjuvant therapy in renal cell carcinoma.

- Nature of the therapy: Is there a biological rationale?
- Primary endpoint: Is it clinically relevant?
- Control arm: What is the current best standard of care?
- Need for placebo: What is the risk of bias or confounding if an open-label design is used? Is there untoward risk or inconvenience for patients receiving placebo (e.g., prolonged courses of intravenous administration)?
- What are the implications for subsequent treatment sequencing? Will early use of an agent compromise outcomes by restricting future treatment options, if needed?
- Can the study population be enriched for those most likely to benefit? Counterpoint: Would enrichment unfairly exclude some patients who might still benefit (e.g., selection based on tissue PD-L1 expression)?

Statistical designs for the trials

There is equipoise in arguments for randomized control trials (RTCs) versus multi-arm multistage (MAMS) designs for adjuvant trials. In general, RCTs are preferred in industry and ask a well-defined controlled question. This approach gives confidence that the trial will be delivered in the projected timescale and the simple design is easy for patients and physicians to understand and enroll in. But adjuvant studies are long and costly and progress can be slow. MAMS trials are ideal for academic consortia and are able to ask multiple questions simultaneously and in sequence and to adapt to new data. Rapid advancements in prostate cancer have been made using this approach via STAMPEDE and more recently in kidney cancer via RAMPART (same MRC group). This model

adopted by the UK allows adaptions that include adding arms, dropping arms, and changing control arms in light of new data. Although initially less attractive for commercial support, this approach, which demonstrated speed and quality of data and low cost, could be compelling.

Trial endpoints

The ultimate aim of adjuvant treatment is to improve the cure rate or at least to prolong healthy life. Overall survival remains the gold standard but in event-driven trials, this will either take a long time (generally 3 to 4 years to accrue and 3 to 7 years for maturity) or will require very large numbers of patients. This massively increases costs and slows potential progress. It does not require a blinded independent central review (BICR). Moreover, there is expenditure of patients who may not ultimately need therapy (possibly pT2 high grade) and perhaps undertreatment of very high-risk patients (i.e., M1-resected disease). Thus, disease-free survival has become a *de-facto* approach and was an accepted endpoint for S-TRAC and KEYNOTE-564. However, in a recent meta-analysis encompassing 13 studies and more than 6,400 patients treated with adjuvant therapies for RCC, correlation between 5-year DFS and OS rates was modest, suggesting DFS is not a good surrogate marker for OS.[121] These results underline the difficulty of choosing the good primary objective in designing an adjuvant clinical trial in RCC.

Essential requirements for future trials include cost-effectiveness: we need to encourage innovation in therapies that will reduce healthcare costs, including the medium (such as oral CPIs instead of intravenous), the duration of therapy, and access to care. Finally, quality of life remains underappreciated: the diarrhea and dysgeusia and fatigue experienced from VEGF TKIs continue to have poor remedy, and the autoimmune side effects from CPIs can be permanent (such as diabetes and hypophysitis).

Biomarkers needed

Contemporary metastatic clear cell cancer trial designs have failed to address whether both immune CPIs and antiangiogenic therapy are necessary for individual patients. Both pure angiogenic trials (which have been largely negative) and pure immune-checkpoint monotherapy trials have been applied (with one positive trial so far) to the adjuvant setting with continued uncertainty as to who would benefit from adjuvant therapy or neoadjuvant therapy and for how long. With the availability of molecular signatures, which could improve prognostication, there is opportunity to design smarter trials. Transcriptomics—which identified seven clusters of genes (angiogenesis, immune, cell-cycle, metabolism, and stromal signatures, and mutational analyses of PBRM1 and other epigenetic genes) that appear to indicate sensitivity or resistance of some renal cancers to immune CPI or antiangiogenic therapy in the metastatic setting[122]—need validation and could be used to select treatments when indicated. The PROSPER trial is undergoing such analysis retrospectively, with the hope that these analyses will identify those patients who benefited from nivolumab therapy. Specimens from the ASSURE trial of adjuvant sorafenib or sunitinib or placebo are undergoing whole-exome sequencing and RNA seq. Despite the outcome being negative, analyses of ASSURE specimens are likely to provide further insight into which patients are more

likely to relapse and have worse prognosis, and hence should be offered adjuvant therapy, and may provide insight into any subsets of patients more prone to toxicity or benefit from VEGFR TKIs. Furthermore, an analysis of kidney injury molecule-1 (KIM-1) from blood correlates with detection of recurrence[123] and an ongoing plasma DNA methylation immunoprecipitation analysis are being retrospectively validated to predict recurrence as well in this population as well as in the PROTECT trial.[124] KIM-1 detection and DNA methylation analysis if validated, could be applied to future trials to guide which patients should be offered adjuvant therapy and which might not.

Sequencing of treatments postadjuvant therapy

The new approval and future use of immune CPI adjuvant therapy in some patients affects the design of first-line metastatic renal cancer. The timing of relapse may be important, as it is untested whether patients who relapse while receiving adjuvant therapy might still benefit from VEGFR-TKI monotherapy or VEGF-TKI /IO or IO/IO. Furthermore, should patients who relapse 6 months after IO therapy be considered differently than those who relapse 12 months or 2 years posttherapy, and in which case should the term IO resistant be used? The application of molecular typing becomes essential in this era. The application of tools such as KIM-1, DNA methylation, or circulating tumour DNA (ctDNA) if sensitive enough, could be used for cancer screening, as is in process in GRAIL,[125] to identify cancers at earlier stages and obviate the use of adjuvant therapy in many patients.

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COMMITTEE 13

Therapies in Refractory Metastatic Renal Cell Carcinoma

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Introduction

As the therapeutic landscape for metastatic renal cell carcinoma (mRCC) expands, new challenges emerge for evaluating and treating refractory disease. Assessing and managing refractory disease has several elements: 1) the mechanism(s) of front-line treatment, 2) the timing of progressive disease, 3) the rapidity and sites of progressing disease, 4) the use of adjuvant therapy, and 5) the incorporation of surgical and radiation techniques.

After the initial approval of antiangiogenic agents (tyrosine kinase inhibitors [TKIs] directed against the vascular endothelial growth factor receptor [VEGFR]) in the early to late 2000s, responses were seen in many patients but eventually disease progression occurred and resistance to first-line antiangiogenic agents was first studied. Resistance mechanisms have been elucidated, including further angiogenic drivers (VEGFR1-3, FGFR1-4, PDGF, Ang/Tie2), increased tumour invasiveness signalling (MET or AXL/ GAS6),[1,2] interactions between the tumour microenvironment, and other pathways. Therefore, several second-line trials were conducted for patients who had disease progression after antiangiogenic treatments. Indeed, given the clinical benefit and efficacy of these treatments in the post-antiangiogenic setting, three TKI therapeutics (axitinib, cabozantinib, and nivolumab)[3–5] received their FDA approvals specifically for patients who had progressed after first-line antiangiogenic therapies.

Standard first-line therapy for mRCC is combination immune checkpoint inhibitor (ICI) with VEGFR TKI; however, in the contemporary era nearly all patients with relapsed disease have progressed following exposure to ICI or combination ICI plus VEGFR TKI. Thus, immune resistance has become a new disease state, with a pressing need to define active treatment options for patients who have disease progression past ICI or VEGFR TKIs. Disease that progresses quickly on ICIs, within the first three months on treatment, is termed primary, intrinsic resistance. Conversely, disease progressing after an initial response and subsequent radiologic progression is characterized as secondary, acquired resistance. Limited data exists from prospective clinical trials on the optimal therapeutic strategies for patients with relapsed disease. Additionally, given the lack of validated biomarkers to guide therapy selection, current treatment decisions are based largely on clinical phenotypes of disease progression to determine how refractory disease is managed and which treatments are subsequently used. A better understanding of the essential mechanisms of both primary and secondary immunotherapy (IO) resistance will inform biomarker development and therapeutic strategies in the refractory setting.

This chapter addresses the current understanding of treatment sequencing in refractory mRCC, particularly focusing on treatment options that have prospective clinical trial data, considering refractory mRCC after adjuvant immunotherapy, and incorporating radiation or surgical resection for oligoprogressive disease (**Figure 1**). In addition, we set forth clinical questions for ongoing and future trials that will add to our current knowledge of front-line treatment resistance in mRCC.

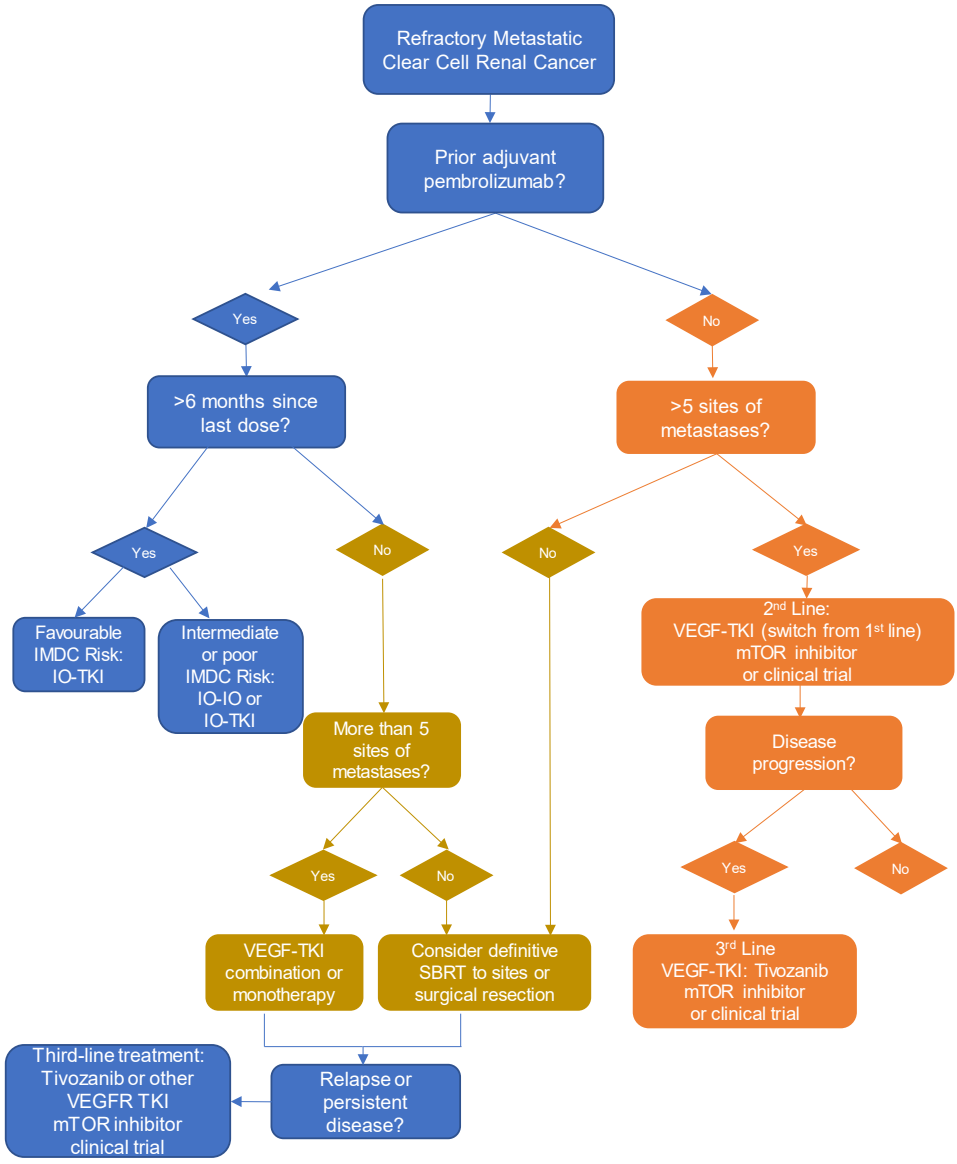
Sequential Treatment After First-Line Antiangiogenic Treatments

The discovery and use of TKIs in the 2000s changed the care of patients with RCC. Oral TKIs primarily target angiogenesis, which is unregulated following the common loss of von Hippel-Lindau (VHL) protein function in RCC.[6] The lack of VHL function allows for accumulation of the hypoxia-inducible factor (HIF) complex and subsequent downstream signalling pathways, such as angiogenesis, metabolism, and proliferation.[7] As of this writing, United States Food and Drug Administration (FDA) approval and National Comprehensive Cancer Network (NCCN) guidelines include eight available oral or infusional VEGF- or VEGFR-targeting therapies: axitinib, bevacizumab, cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, and tivozanib.[8] This category of therapeutics achieves tumour shrinkage and improves progression-free survival (PFS). However, due to resistance mechanisms and limited data for single-agent front-line use, each drug in this class will work for individual patients only months to a few years before tumour progression ultimately occurs.

Several TKI acquired resistance mechanisms have been documented and include upregulation of angiogenesis pathways (VEGFR1-3, FGFR1-4, PDGF, Ang/Tie2), increased tumour invasiveness signalling through MET or AXL/ GAS6,[1,2] and interactions with the tumour microenvironment. Sequential therapy using VEGF inhibitors is based on preclinical rationale and clinical trial data that has shown efficacy in patients who have VEGF-refractory disease. Treatment options in the second- and later-line settings include VEGF inhibition, immune checkpoint inhibition, or combination of VEGF and mammalian target of rapamycin (mTOR) inhibition.

Several clinical trials have been conducted in the setting of second- or later-line therapy showing sequential TKI use demonstrates clinical benefit. The AXIS, phase 3, randomized controlled trial tested axitinib versus sorafenib in the second-line treatment for mRCC, with 54% of these patients having progressed previously on sunitinib and 8% after prior bevacizumab therapy.[3] Axitinib in this second-line setting showed a statistically significant improvement in median PFS over sorafenib (HR, 0.66; 95% CI, 0.544–0.812; $p<0.0001$),[3] suggesting that sequential targeted therapy and perhaps broader inhibition with axitinib (targeting VEGFR1-3, c-Kit, PDGFR) compared with sorafenib led to the demonstrated clinical benefit. Further supportive data for the use of sequential targeted therapy in mRCC comes from the phase 3, randomized controlled trial METEOR, which compared cabozantinib (targeting VEGFR1-3, MET, AXL) with everolimus (mTOR inhibitor) in patients with mRCC who had progression on prior TKI treatment.[4] In this trial, approximately 70% of patients had progressed on one prior TKI and the remaining 30% had progressed following two or more VEGFR TKIs. Cabozantinib showed both a PFS (HR, 0.51; 95% CI, 0.42–0.62; $p<0.0001$) and an overall survival (OS) benefit over everolimus (HR, 0.66; 95% CI, 0.53–0.83; $p=0.00026$).[4] Cabozantinib use for patients with kidney cancer after at least one prior VEGF-TKI therapy suggests that broader VEGFR-TKI inhibition and targeting alternate pathways via MET and AXL receptors is one way to overcome resistance.

FIGURE 1 Treatment algorithm for refractory metastatic clear cell kidney cancer.



Abbreviations: IMDC, International Metastatic RCC Database Consortium; IO, immunotherapy; mTOR, mammalian target of rapamycin; SBRT, stereotactic body radiation therapy; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Furthermore, a retrospective review of the International Metastatic RCC Database Consortium (IMDC) database by Gan *et al.* also looked at the use of cabozantinib from the first-line to fourth-line setting in patients with mRCC.[9] Patients in the refractory setting had been treated with a standard front-line combination using an IO backbone or single-agent TKI, and in this setting cabozantinib showed an objective response rate (ORR) consistently between 22–32% depending on the line of therapy.[9] Furthermore, tivozanib was studied in a randomized, phase 3 trial (TIVO-3) compared with sorafenib in patients who had progressed on at least two prior systemic therapies with at least one prior VEGFR inhibitor. In contrast to earlier-generation VEGFR TKIs, tivozanib was designed to improved VEGFR blockade while reducing off-target toxic effects, causing fewer dose reductions and treatment interruptions.[10] Tivozanib as third- or fourth-line therapy improved median PFS compared with sorafenib (HR, 0.73; 95% CI, 0.56–0.94; p=0.016).[11] Nearly 50% of patients on this trial had progressed on two prior VEGF-TKI therapies, again supportive of the use of sequential treatment with VEGF inhibition. These phase 3 trials all had proven PFS benefit (AXIS, METEOR, TIVO-3) using sequential VEGF inhibition (axitinib, cabozantinib, and tivozanib) and have been approved by the US FDA for treatment in subsequent lines of refractory mRCC.

Targeting alternative biologic pathways such as mTOR with its protumourigenic effects and HIF regulation has also been shown to be beneficial following VEGFR-TKI resistance. In a multicentre, open-label, phase 2 trial, patients who had progressed on prior VEGFR TKIs were randomized to receive lenvatinib monotherapy (targeting VEGFR1-3, FGFR1-4, PDGFR, c-Kit, and RET), the combination of lenvatinib plus everolimus (mTOR inhibitor), or everolimus monotherapy.[12] Lenvatinib plus everolimus significantly prolonged median PFS over everolimus (HR, 0.40; 95% CI, 0.24–0.68; p=0.0005) and trended but was not significantly different to lenvatinib monotherapy (HR, 0.66; 95% CI, 0.39–1.10; p=0.12).[12]

The subsequent development of immune checkpoint inhibition using monoclonal antibodies to block the negative regulatory signal between programmed death 1 ligand 1 (PD-L1) from cancer cells and programmed death 1 (PD-1) on the T cell and other immune cells was tested for use in patients with mRCC. The randomized, open-label, phase 3 trial CheckMate 025 compared PD-1 inhibition with nivolumab with everolimus in the second-line setting for patients with mRCC who had progressed on at least one prior antiangiogenic therapy, with 28% of patients having received two prior VEGFR TKIs.[5] In patients with VEGFR-refractory mRCC, nivolumab showed improved ORR of 23% versus 4% (p<0.001)[5] for patients treated with everolimus, as well as a median OS benefit of 25 months compared with 19.6 months (HR, 0.73; 98.5% CI, 0.57–0.93; p=0.002).[13] Durability benefits of ICI treatment in CheckMate 025 at 64-month follow-up revealed that 26 of 94 nivolumab responders (27.7%) still had benefit.[14] **Table 1** provides a summary of the aforementioned phase 3 trials, highlighting important findings regarding approved treatments for refractory mRCC.

TABLE 1 Key Phase 3 Clinical Trials in Refractory Metastatic Kidney Cancer

	AXIS	METEOR	TIVO-3	CheckMate 025	CANTATA
Treatment	**Axitinib** vs. Sorafenib	**Cabozantinib** vs. Everolimus	**Tivozanib** vs. Sorafenib	**Nivolumab** vs. Everolimus	**Cabozantinib + Telaglenstat** vs. Cabozantinib
mPFS (months)	6.7	7.4	5.6	4.6	9.2
HR (95% CI)	0.66 (0.544–0.812)	0.51 (0.42–0.62)	0.73 (0.56–0.94)	0.88 (0.75–1.03)	0.94 (0.74–1.21)
ORR (%)	19%	17%	12.3%	25%	31%
mOS HR (95% CI)	0.969 (0.800–1.174)	0.66 (0.53–0.83)	0.91 (0.716–1.165)	0.72 (0.57–0.93)	**

**Data not mature at time of presentation.

Abbreviations: HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate.

The treatment landscape for mRCC has become considerably more complex with the approval of front-line IO-based doublets of either IO plus IO or IO plus TKI. There is an ongoing question of how best to sequence VEGFR inhibition after disease progression on now standard front-line combination treatments. Optimal VEGFR-TKI sequencing has been addressed in the phase 2 trial RECORD-3, which supported the use of sunitinib followed by everolimus at progression, thus future clinical trials in refractory mRCC could incorporate this trial design strategy.[15] The decision for the next-line treatment should be based on biologic rationale, prospective and retrospective data, therapeutic side-effect profile, and incorporation of new treatments with novel mechanisms of action, which all result in shared decision-making between the provider and patient.

Sequential Treatments After Initial Immune Checkpoint Inhibition

Following first-line immune checkpoint inhibition for mRCC, resistance mechanisms are difficult to elucidate due in part to lack of serial biopsies. Given the success of cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockade in the front-line setting, several trials have tested the addition of CTLA-4 inhibitors in treatment-refractory mRCC.

Data to support the use of immune checkpoint inhibition following immunotherapy stems from a series of retrospective studies and several phase 2 prospective trials. While the combination of nivolumab plus ipilimumab

has demonstrated improved efficacy compared with sunitinib in the front-line setting,[16] the FRACTION-RCC study tested the efficacy of nivolumab and ipilimumab in heavily pretreated patients (Track 2).[17] The primary endpoints of the study were ORR per investigator assessment, duration of response, and 24-week PFS. The study enrolled 46 patients, of whom 100% had received prior treatment with PD-1– or PD-L1–targeted therapy and 50% had received ≥ 3 lines of prior therapy. The combination of nivolumab plus ipilimumab demonstrated an ORR of 15.2%, though no complete responses were observed. Progressive disease as best response was observed in 32.6% of patients.[17] At a median follow-up of 21.6 months, median PFS was 16.1 weeks.[17]

Given responses observed with single-agent checkpoint inhibition and the toxicity of combination therapy of nivolumab plus ipilimumab, a series of studies (TITAN-RCC,[18] OMNIVORE,[19] and HCRN GU16-260[20]) investigated an adaptive strategy of treatment intensification based on prior PD-1 inhibitor response, in order to maximize efficacy and minimize toxicity in patients with mRCC.

The TITAN-RCC trial enrolled patients with IMDC intermediate- or poor-risk clear cell RCC (ccRCC).[18] All patients initiated treatment with nivolumab and those with early progressive disease or stable disease at week 16 received 2 or 4 "boosts" of ipilimumab. The primary endpoint was investigator-assessed ORR in patients with treatment-naïve or previously treated disease. The study analyzed 109 patients with first-line therapy and 98 patients with subsequent-line therapy for efficacy. After a median follow-up of 12.8 months, the ORR with nivolumab monotherapy was 23% and increased to 33% with the addition of ipilimumab "boost", with an overall complete response rate of 5.3%.[18]

The OMNIVORE trial enrolled patients with clear cell and variant histology RCC having received no prior checkpoint inhibition.[19] Patients were started on treatment with nivolumab monotherapy. If a confirmed partial or complete response was observed within 4–6 months of treatment initiation, therapy was discontinued. However, if stable disease or progressive disease was observed during this time, two doses of ipilimumab were added. The trial enrolled 83 patients, of whom 96% had clear cell histology and 49% were previously treated. Overall, 69% of patients were allocated to receive salvage ipilimumab, of whom two (4%) experienced a response and no complete responses were observed.[19]

The HCRN GU-16260 trial enrolled patients with treatment-naïve disease into two cohorts based on histology (clear cell or variant RCC).[20] All patients initiated treatment with nivolumab monotherapy and those with progressive disease or stable disease at 48 weeks were eligible to receive four doses of ipilimumab. In the clear cell cohort, 123 patients were enrolled, of whom 75% had IMDC intermediate- or poor-risk disease. While the ORR with nivolumab monotherapy was 31.7%, only 34 of 65 eligible patients received salvage nivolumab plus ipilimumab. The ORR with salvage ipilimumab was 13.3% and no complete responses were observed.[20]

In aggregate, these three prospective phase 2 trials demonstrate modest activity of ipilimumab in the salvage setting following nivolumab monotherapy, with limited complete responses in this setting. Therefore, the optimal use of ipilimumab should not be in the nivolumab-refractory setting.

Additional data of the activity of checkpoint inhibition following immunotherapy comes from retrospective series of real-world data. In one series, Ravi and colleagues investigated the efficacy of ICI rechallenge in patients with mRCC.[21] A total of 69 patients were included in the analysis, of whom 39% had received prior ICI monotherapy and 71% had received combination therapy. The ORR to subsequent-line immune checkpoint inhibition was 23%. Additionally, Gul and colleagues investigated the real-world use of nivolumab plus ipilimumab after prior checkpoint inhibition.[22] A total of 45 patients were included in the analysis, of whom the majority had ccRCC (89%) and had received ≥ 3 prior lines of therapy (53%).[22] At a median follow-up of 12 months, the ORR was 20%. There were no observed complete responses, the primary progressive disease rate was 20%, and the median PFS was 4 months.[22]

Thus, for patients previously exposed to ICI therapy, the rechallenge with further PD-1 therapy or combined with CTLA-4 therapy (ipilimumab) results in a modest ORR (5–15%) and limited complete responses. The long-term benefit of such treatments in the refractory setting remains to be defined.

VEGFR-Targeted Monotherapy and Combinations After IO Progression

As reviewed above, most TKIs received regulatory approval prior to the development and widespread use of ICIs. However, data from both retrospective and prospective clinical trials have continued to show efficacy of VEGF-targeted therapies after progression on initial IO therapy. In early retrospective studies of patients who had progressed on ICI combinations (IO plus VEGF TKI or IO plus IO) in the first first-line setting, 70 patients received a mix of VEGFR TKIs including pazopanib, sunitinib, axitinib, and cabozantinib in the second-line setting, where they were noted to have an ORR of 41% and a median PFS of 13.2 months (95% CI, 10.1–NA).[23] Similarly, in patients who had received VEGF plus IO combinations, retrospective studies have also shown an ORR of 25% and a median PFS of 12.0 months (95% CI, 8.2–24.5).[24] Interestingly, for these early retrospective studies, the median PFS appears to be longer than historic experiences with VEGFR-targeted TKIs in the second-line setting.

The prospective evaluation of both cabozantinib and lenvatinib plus everolimus yielded data after progression on IO. The CANTATA study provided the largest VEGF-TKI monotherapy experience for patients who had previously been treated with IO. In this randomized phase 3 study, 444 patients were randomized to cabozantinib plus telaglenastat or cabozantinib plus placebo, including 276 (62%) patients who had prior disease progression on an ICI.[25] In the intent-to-treat population, the ORR was 31.2% for cabozantinib plus telaglenastat and 27.8% with cabozantinib plus placebo, with a median PFS of 9.2 months (95% CI, 7.6–11.1) and 9.3 months (95% CI, 7.6–11.0), respectively.[25] In a subgroup analysis of only patients previously treated with IO, cabozantinib plus telaglenastat demonstrated a median PFS of 11.1 months and cabozantinib plus placebo demonstrated a median PFS of 9.2 months (unstratified HR, 0.77; 95% CI, 0.56–1.06),[25] which was not statistically significant.

Study 218 investigated two different starting doses for lenvatinib (18 mg vs. 14 mg daily) in combination with everolimus, and demonstrated similar safety; however, there was a trend toward worse efficacy with the lower starting dose of lenvatinib (OR, 0.88; 90% CI, 0.59–1.32).[26] A total of 311 patients were randomized to lenvatinib 14 mg starting dose (*n*=156) or 18 mg starting dose (*n*=155), including 82 patients who were previously treated with ICIs (14 mg starting, *n*=43, and 18 mg starting, *n*=39). In IO-pretreated patients, the ORR was 30.2% (95% CI, 17.2–46.1) for the 14 mg starting dose and 51.3% (95% CI, 34.8–67.6) for the 18 mg starting dose, with a median PFS of 12.0 months (95% CI, 8.9–16.7) and 12.9 months (95% CI, 8.4–NE), respectively.[26]

The data for IO-TKI combinations in patients who have previously progressed on IO therapy remains limited and there is debate on whether there is synergism between the VEGFR TKI and IO when used in combination. Therefore, it remains controversial whether continuation of IO therapy after progression on front-line IO plus TKI is beneficial. Prospectively, the combination of lenvatinib plus pembrolizumab was studied in Study111 or KEYNOTE-146. In this single-arm phase 2 study, 104 IO-pretreated patients received lenvatinib plus pembrolizumab. The ORR was 62.5% (95% CI, 52.5–71.8) and the median PFS was 12.2 months (95% CI, 9.5–17.7).[27] However, a key limitation of the study is that this was a single-arm study, so it is not possible to determine the contribution of the individual study drugs used in the combination to the overall observed efficacy.

Currently there are multiple key studies that will likely help us better understand the clinical benefit of continuation of IO therapy after prior IO progression. CONTACT-03 (NCT04338269) is a randomized phase 3 study of cabozantinib plus atezolizumab versus cabozantinib monotherapy in patients who have previously progressed on, during, or after ICI therapy. Dual primary endpoints of PFS and OS will further elucidate the role of cabozantinib plus atezolizumab in the IO-refractory setting. The study has completed enrollment with 500 patients and has an estimated primary completion date in 2022 and estimated study completion date in late 2024. Another ongoing trial, TiNivo-2 (NCT04987203), is a randomized phase 3 trial of tivozanib plus nivolumab versus tivozanib monotherapy in patients who have previously progressed on an ICI. A total of 326 patients will be enrolled, and the primary endpoint is PFS, with an estimated study completion date in 2025. Together, these two large phase 3 studies will determine whether combination therapy with VEGF TKI and either PD-1 or PD-L1 inhibition is superior to TKI monotherapy in IO-refractory mRCC.

Refractory Disease After Adjuvant Therapy

The substantial disease-free survival (DFS) benefit with adjuvant pembrolizumab in patients with ccRCC demonstrated the value of ICIs in this setting.[28,29] Furthermore, despite the conflicting results observed with adjuvant VEGF TKIs,[30] the use of adjuvant sunitinib was FDA approved based on the DFS benefit, observed in the Sunitinib as Adjuvant Treatment for Patients at High Risk of Recurrence of Renal Cell Carcinoma Following Nephrectomy (S-TRAC) trial.[31] One must be aware that no OS has been observed for sunitinib use in the adjuvant setting and this currently has a category 3 recommendation from NCCN.[8] However, further recommendations for treatment decisions after adjuvant ICIs or TKIs have very limited clinical data.

An emerging challenge is how to manage patients with ccRCC whose disease has recurred following either adjuvant ICI or VEGF TKI. The first consideration is whether the recurrence requires systemic therapy or can be addressed with a localized approach? In the latter case, surgery, radiation, or ablation strategies can be used to treat the tumour irrespective of the adjuvant modality used.[32] Subsequently, these patients with no evidence of disease (NED) will still be at high risk for disease recurrence, and the use of additional treatments post-metastases–directed therapy is not recommended in current practice. If a second adjuvant therapy is considered, then ideally it should use a different therapeutic modality than the first adjuvant regimen. For example, adjuvant therapy with pembrolizumab may be a plausible option in patients who recurred following adjuvant sunitinib and were subsequently rendered NED.

If systemic therapy is needed to treat recurrent disease, then the timing of the relapse may provide insights into the degree of resistance to the adjuvant regimen used. Scenarios one can consider include disease progression during adjuvant ICI or VEGF TKI or after treatment is concluded to help make well-informed treatment decisions. While there are currently no data on the efficacy of systemic therapies in recurrent ccRCC following ICIs, a retrospective analysis in melanoma suggested that patients who recurred on adjuvant anti–PD-1 therapy had no responses to subsequent anti–PD-1 regimens and some response to anti–CTLA-4 therapy, whereas those who recurred after completion of adjuvant anti–PD-1 therapy retained sensitivity to anti–PD-1 rechallenge.[33] Furthermore, melanomas recurring during adjuvant anti–PD-1 therapies were similarly sensitive to subsequent targeted therapies (BRAF/MEK inhibitors) compared to those that recurred after completion of adjuvant anti–PD-1 therapy.[33] It is plausible that similar patterns may be observed in ccRCC whereby patients relapsing during adjuvant ICI may benefit more from a VEGF TKI–based regimen rather than rechallenge with a different PD-1 approved treatment. Furthermore, one should consider the degree and type of toxicities that patients may have experienced during adjuvant therapy. For example, a patient who experienced a severe ongoing immune-related adverse event requiring continued immunosuppression at the time of recurrence is unlikely to benefit from the addition of ICI to a VEGF TKI–based subsequent therapy. Moreover, the sites of recurrence can also guide subsequent therapy choice. For example, the intracranial response rates to ICI of ccRCC brain metastases appear to be very low compared with those observed in melanoma.[34,35] Thus, patients with disease recurrence to the brain may benefit more from VEGF TKIs such as cabozantinib, which has demonstrated intracranial activity in several retrospective studies.[36,37]

Radiation Therapy for Refractory Metastatic RCC

The incorporation of radiotherapy (RT) in the treatment paradigm for refractory mRCC is evolving. Current NCCN guidelines support the use of RT in stage IV or relapsed mRCC.[8] Traditionally, RCC has been thought to be radiation resistant, as demonstrated in early clinical trials with conventional external beam RT (CRT) dosing in the neoadjuvant and adjuvant settings with no survival benefits reported.[38–40] However, the metastatic setting incorporated CRT using treatment courses of 30 Gy in 10 fractions to palliate symptomatic metastases (bone, brain), and clinical benefits were observed.[41] In addition, newer radiation techniques are using higher-dose-per-fraction treatments. For example, stereotactic body radiation therapy (SBRT) for extracranial sites and

stereotactic radiosurgery (SRS) for intracranial sites both provide local control for patients with oligometastatic progression and palliative relief to patients, with minimal toxicities.[42–45] SBRT-related mechanisms of tumour control have been associated with endothelial cell damage leading to apoptosis (abscopal effect), whereas CRT typically relies on oxygen-dependent DNA damage.[46–48] Among patients with refractory mRCC, subclasses exist where patients have limited amounts of metastatic disease (typically less than 5 separate sites), thus aggressive management of these sites when progression occurs during systemic therapy may be of some benefit. Hence, SBRT would be an ideal modality to include for these patients, especially if they are unfit for surgical resection. This would allow for local control and continuation of current systemic treatments. Multiple clinical trials have reported local control rates achieved with SRS of over 90%, but these are seen mostly in patients not on systemic treatments.[47,48] Furthermore, a single-arm phase 2 trial demonstrated that definitive RT was safe, feasible, and had low toxicity in 9 patients with oligometastatic RCC who had progressed on prior systemic therapies.[49]

Combining SBRT with systemic therapy in mRCC has also been studied. One study from Group d'etude des tumeurs urogenitalies (GETUG) retrospectively assessed 188 patients who received SBRT after oligoprogression while on first-line VEGF-TKI therapy and reported a median PFS of 8.6 months.[50] Dengina *et al.* studied mRCC patients (*N*=17) who had stable disease with VEGF TKI and incorporated SBRT to manage extracranial lesions; treatment was well tolerated, with radiologic responses in target lesions observed in 76% of patients and complete responses seen in 29% of patients.[51] Newer data suggests that combining SBRT with current IO treatments can overcome resistance through several proposed mechanisms. This is an attractive option for patients with refractory disease or resistance to current IO or IO plus VEGF-TKI combinations to continue treatment if otherwise tolerating well. One phase 2 study explored SBRT in combination with high-dose IL-2, and patients achieved a 40% response rate.[52] Another phase 1/2 trial (RAPPORT) explored the safety and efficacy of total metastatic SABR to oligometastatic mRCC followed by anti–PD-1 treatment. Overall response rate was 63% in 30 evaluable patients, and estimated the 1- and 2-year OS rates were 90% and 74%, respectively.[53] Current clinical trials (CYTOSHRINK [NCT04090710] and SAMURAI [NCT05327686]) are ongoing to study how to effectively combine SBRT or SRS with systemic treatments to improve survival outcomes.

Considerations of Consolidative Surgery in Metastatic Disease

For the refractory second-line setting, systemic treatment is the preferred option, but in selected patients, a consolidative surgical approach could have advantages. Currently, the integration of surgery and systemic therapy represents an active debate and treatment challenge for many patients with advanced disease.

A consolidative surgical strategy may be used in various clinical settings. These situations include 1) after the start of a highly effective systemic therapy such as the new combinations of treatments and deferring cytoreductive nephrectomy for a second stage and 2) at the time of the oligoprogression of the disease with metastasectomy and leaving the patient with either no evidence of disease (NED) or the lowest metastatic burden of disease.

In the case of consolidative nephrectomy, clinicians may take advantage of the high response rates observed with the current first-line immunotherapy combinations, reaching up to 70% objective responses with 16% complete responses.[54–56] In this situation, many studies on consolidative nephrectomy were from the cytokine era, where overall tumour responses were uncommon, and especially rare in the primary tumour; the current evidence on cytoreduction comes from two completed studies: SURTIME and CARMENA. Both studies show that consolidative nephrectomy can be delayed until a stable or partial response is achieved but they used an older and less favoured treatment with sunitinib as first-line therapy where it is now established that IO–VEGF-TKI combinations are a standard approach for mRCC. This strategy, as an initial maneuver, is a valid option for both selected patients with IMDC intermediate- or poor-risk disease and large or voluminous tumours that are not suitable for initial resection and for patients with a high burden of metastatic disease for whom initial resection would not be beneficial. Prospective data using modern treatment (IO–VEGF TKI) is still needed. At least three trials are ongoing (NORDIC-SUN [NCT03977571]; PROBE [NCT04510597]; and CYTO-KIK [NCT04322955]) to answer the clinically relevant questions on optimal timing for consolidative nephrectomy in the metastatic setting.

For oligoprogression in the refractory setting, the evidence for surgery is less clear. Retrospective observational data reveals the potential of metastasectomy to achieve palliation of symptoms as well as long disease-free survival interval.[57] The role of metastasis-directed treatment depends on the correct selection of patients. To choose metastasectomy, patient-specific factors such as size and location of the metastases are important. Among the patient-dependent factors, those in the IMDC favourable risk group, without comorbidities and an adequate frailty evaluation, are the best candidates; on the other hand, those with clear cell tumours with absence of liver, brain, and bone metastases as well the ability for a complete resection are the ideal candidates with survival benefit in several retrospective cohorts.[58–60]

In conclusion, the integration of systemic therapies with surgery represents an option for patients with mRCC as either consolidative treatment or to achieve a disease-free setting for patients who have low-volume metastases. Prospective trials as discussed above will further delineate these approaches.

Conclusions

The treatment landscape for mRCC continues to expand, with multiple immunotherapy-based combinations approved in the front-line setting, and therefore posing important clinical challenges of immunotherapy resistance and sequencing. Managing refractory disease depends on mechanisms of front-line treatment, timing of progression after front-line treatment, and sites of progressive disease. Within this chapter we have described potential treatment strategies for sequencing after either front-line IO-IO or IO-VEGF combinations, as well as considering multimodality management with either radiation or metastasectomy for select patients with oligoprogressive disease. **Figure 1** proposes a treatment algorithm discussing the covered topics in this chapter. Ongoing trials that sequence therapies in the refractory setting, including those with cytoreductive nephrectomies for *de novo* metastatic disease, will provide prospective evidence for maximizing sequential treatments in the current immunotherapy era.

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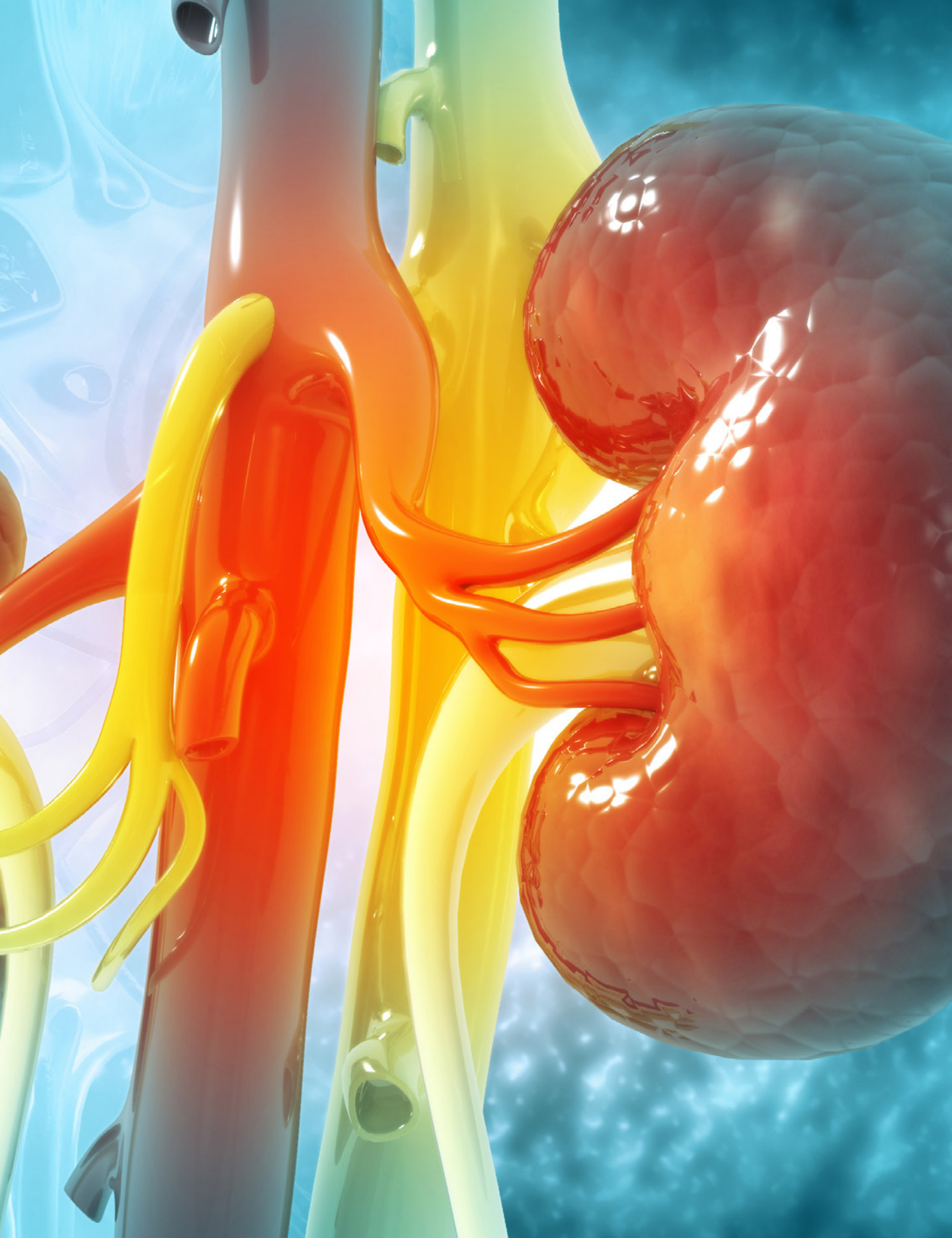

COMMITTEE 14

Novel Agents and Trials in RCC

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Introduction

The management of metastatic clear cell renal cell cancer (RCC) has been transformed by the identification and targeting of biologically important pathways. Combination therapies incorporating immune checkpoint inhibition (ICI) with ipilimumab plus nivolumab[1] or programmed cell death 1 receptor/programmed cell death 1 ligand 1 (PD-1/PD-L1) therapy in combination with a vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) have been adopted as a standard of care.[2–5] Although some patients achieve a prolonged and/or complete remission, most do not derive a durable benefit from therapy. The discovery of yet more novel biological targets in recent years as well as preclinical RCC models demonstrating proof of activity of new drugs provides optimism that outcomes can be further improved. Despite solid rationale, larger studies of many of these compounds have failed to materialize into new therapies. This review summarizes the most promising candidate biological pathways and therapeutics under evaluation in RCC and reviews the evidence supporting their potential future use.

Targeting the HIF Pathway

Hypoxia is a common hallmark of human cancers, including RCC. At a cellular level, hypoxia induces maladaptive changes in cellular metabolism, including a switch from oxidative phosphorylation to glycolysis, increased glycogen synthesis, and a switch from glucose to glutamine as the major substrate for fatty acid synthesis.[6] The transcriptional regulation of this metabolic shift is orchestrated by hypoxia-inducible factor (HIF) transcription factor proteins. The von Hippel–Lindau (VHL) protein functions as the substrate recognition component of an E3 ligase complex that ubiquitylates HIF proteins for subsequent degradation in the proteasome. Loss of *VHL* constitutes a fundamental oncogenic driving event in the development of RCC,[7,8] leading to accumulation of HIF (1α and 2α), resulting in uncontrolled downstream activation of HIF target genes that regulate a range of central cellular processes including angiogenesis, glycolysis, and apoptosis.[9] The 2019 Nobel Prize in Physiology or Medicine was awarded to Drs. William Kaelin, Peter Ratcliffe, and Gregg Semenza recognizing their work detailing hypoxia, oxygen sensing, and the VHL pathway.[7,10]

Upregulation of angiogenic signalling in RCC is the mechanism underpinning the successful targeting of this pathway with VEGF TKIs, mainstays of RCC therapy since the mid-2000s.[11,12] Although targeting VEGF has been clinically effective, hypoxia is an upstream event that regulates multiple active cellular pathways in addition to angiogenesis, thus upstream inactivation of HIF may inactivate multiple important metabolic pathways involved in tumourigenesis and growth of RCC that are missed by VEGF-targeted therapy. As a vital mediator central to the pathogenesis of RCC, the successful inhibition of HIF-2α in particular has become a focus of research and drug development.

Blocking the hydrophobic pocket in the PAS-B domain of HIF-2α disrupts the protein's ability to dimerize, leading to its functional inhibition.[13,14] The first inhibitor of HIF-2α able to accomplish this strategy, PT2385,

strongly inhibited HIF-2α–dependent genes and demonstrated tumour regression in preclinical RCC models.[15] The phase 1 dose-escalation and expansion study of PT2385 in a cohort of 51 pretreated patients with RCC identified no dose-limiting toxicities, and objective responses were recorded with an overall response rate of 14%. Important adverse effects were identified including anemia, fatigue, and peripheral edema.[16] Combination therapy of PT2385 with the PD-1 inhibitor nivolumab was also explored in a phase 1 study of 50 patients, with the combination demonstrating a similar adverse event rate to monotherapy and an overall response rate of 22%.[17]

A second-generation molecule (PT2977, later MK-6482) was developed with a more favourable pharmacokinetic profile compared with the first-generation compound PT2385. In a phase 1/2 study, 55 patients with RCC who had received at least 1 prior therapy were treated with MK-6482 at a dose of 120 mg daily, leading to an overall response rate of 25% and a disease control rate of 80%. Notably, the majority (80%) of responses recorded in this pretreated cohort were durable for more than 6 months.[18] MK-6482 also demonstrated activity in the first-line setting in a phase 1 study of 61 patients with RCC associated with a germline *VHL* mutation (VHL disease). At a median follow-up of 21.8 months, the confirmed overall response rate in this cohort was 49%, with the median duration of response not reached.[19] Based on this promising data, MK-6482 (now named belzutifan) received US Food and Drug Administration (FDA) registration for VHL-associated RCC in 2021.[20]

To evaluate the activity in the broader setting of RCC, a randomized phase 3trial is ongoing in pretreated patients (in the third-line setting and beyond) who must have already received both a VEGF TKI and PD-1/L1 inhibitor. In this study, 736 participants have been included and randomized 1:1 to belzutifan or everolimus, with coprimary endpoints of progression-free survival and overall survival (NCT04195750).[21] If positive, this study may lead to approval of an HIF-2α inhibitor for pretreated patients with RCC.

Given that HIF inhibitors act at a distinct part of the angiogenic cascade compared to VEGF TKIs, there is the potential for combination strategies and synergy with established therapies in RCC such as VEGF inhibition. A phase 2 study is examining the combination of MK-6482 with cabozantinib in untreated RCC patients (cohort A), and those who have received prior immunotherapy (cohort B).[22] Cohort B has reported the outcomes of 52 patients, with 9 partial responses leading to an overall response rate of 22% and disease control rate of 90%. Median duration of response has not been reached and all responses were ongoing as of the data cutoff date.[23] Other novel combination trials are also underway. A phase 3 trial evaluating belzutifan plus lenvatinib versus cabozantinib for second- or third-line therapy in patients with advanced RCC who progressed after prior anti-PD-1/L1 therapy is recruiting.[24]

The first-line treatment landscape for RCC now incorporates combination therapy with an ICI for most patients. To potentially improve outcomes compared to this contemporaneous standard of care, a triplet regimen incorporating belzutifan is enticing given the nonoverlapping toxicity with ICI or VEGF TKI therapy and distinct mechanisms of action. A three-arm, open label, randomized phase 3 study (NCT04736706) in the first-line setting is evaluating novel combinations of pembrolizumab plus belzutifan and lenvatinib (arm A), MK-1308A (a coformulation of pembrolizumab/quavonlimab) with lenvatinib (arm B), against pembrolizumab plus lenvatinib (arm C).[25] Quavonlimab is a cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor that has demonstrated

antitumour activity in non-small cell lung cancer.[26] The trial aims to enroll more than 1,400 adults who will be randomized equally between the arms and assess dual primary endpoints of progression-free and overall survival.

The search for other rational combinations incorporating belzutifan is underway. Preclinical data suggests synergy between cyclin-dependent kinases 4 and 6 (CDK4/6) inhibition and *VHL* inactivation. Synthetic lethality has been observed in the setting of decreased activity of CDK4/6 and *VHL* inactivation in human and *Drosophila* RCC cell lines, suggesting the addition of a CDK4/6 inhibitor to an HIF2α inhibitor may be a rational clinical combination to explore.[27]

The identification of an important biological pathway, development of a targeted therapy, and subsequent clinical application to improve outcomes for patients with RCC represents a significant step forward with this novel class of agents. Moving forward, the multiple trials (**Table 1**) benchmarking these agents to standard therapies in a pretreated and therapy-naïve setting will be essential to define the optimal setting and combination of HIF inhibitors for patients.

TABLE 1 Selected Trials Investigating Hypoxia Induction Factor Inhibition

Investigational product	Combination	Comparator arm	Trial phase (treatment line), NCT number
Belzutifan (MK-6482)	Lenvatinib + pembrolizumab, pembrolizumab + quavonlimab	Lenvatinib + pembrolizumab	3 (1), NCT04736706
	Cabozantinib	Cabozantinib	3 (2), NCT03634540
	-	Everolimus	3 (3+), NCT04195750
	-	-	2 (1), NCT03401788 VHL-associated RCC

Abbreviations: NCT, National Clinical Trial; VHL, von Hippel–Lindau.

Cell Cycle Regulation: PIM Kinase and Cyclin-Dependent Kinase (CDK) Inhibitors

Additional oncogenic pathways have been identified that may be therapeutically targeted in RCC. The proviral integration site for Moloney murine leukemia virus (PIM) kinase family consists of three serine/threonine kinases (PIM1, 2, and 3), which are known to be overexpressed in multiple hematological and solid organ cancers, including RCC. Their activity has been correlated with promoting cellular proliferation, survival, and avoidance of tumoural apoptosis.[28]

Specific to RCC, PIM1 expression is elevated in human RCC cells and its expression has been positively correlated with tumour progression and metastasis. Tissue microarray studies have revealed that a subset (~25%) of RCCs show elevated staining for PIM1 kinase compared to 1% of normal adjacent tissue, suggesting that a subset of RCCs is associated with elevated PIM1 activity.[29] Murine preclinical studies reported that a selective PIM1 kinase inhibitor (SGI-1776) induced tumour regression as monotherapy as well as in combination with sunitinib. Abemaciclib, a potent CDK4/6 inhibitor commonly used in breast cancer, is also a potent PIM1 inhibitor that decreases cell viability and increases apoptosis in RCC cell lines. This effect is potentiated in combination with sunitinib, with similar effects in mouse tumour models.[30]

Based on these preclinical observations, a phase 1b dose-escalation trial is in progress to determine the safety and tolerability of abemaciclib in combination with sunitinib in RCC, including an expansion cohort at the recommended phase 2 dose to evaluate for a signal for efficacy.[31]

Metabolic Pathways and Glutaminase Inhibition

Glutamine is a nonessential amino acid that supplies nitrogen for nucleobase synthesis and carbon for the citric acid cycle (tricarboxylic acid cycle [TCA]) and lipid and nucleotide synthesis. Glutaminolysis results in the conversion of glutamine into various other molecules used by the cell including alanine, aspartate, citrate, carbon dioxide, glutamate, lactate, and pyruvate.[32] The first step is governed via glutaminase (GLS), controlling the conversion of glutamine into glutamate and ammonia. Cancer cells (including RCC) have increased metabolic demands, with increased glutaminolysis activity and higher levels of glutamine and glutamate compared to normal kidney tissue, and increased expression of glutamine importers such as SLC1A5.[33] Preclinical studies suggest dependence on the glutamine metabolism pathway for cancer cell survival, termed glutamine addiction.[34] While incompletely characterized, some oncogenic alterations have been associated with glutamine dependence in RCC, including *Myc*, which can increase glutamine metabolism by upregulating GLS expression.[35]

Given the relative importance of GLS activity to the survival of RCC in preclinical models, there is interest in developing agents that target this pathway such as telaglenastat (CB-839), a selective, oral, first-in-class GLS inhibitor that blocks glutamine utilization. The safety of telaglenastat monotherapy[36,37] was detailed in a phase 1 study that included 15 patients with clear cell RCC. Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or greater toxicity occurred in 7 (20%) of patients, including elevated liver enzymes, elevated creatinine, lymphopenia, and hypoglycemia.[36] One partial response was recorded lasting 7 months, and 4 patients remained on study for more than 10 months.[38]

Preclinical evidence suggested that combination therapy may improve the efficacy of telaglenastat, with synergy between the drug and signal transduction inhibitors such as the mTOR inhibitor everolimus, an established agent in RCC.[39] The resultant phase 2 ENTRATA study[40] randomized 69 patients to receive telaglenastat plus everolimus versus placebo plus everolimus in third-line or greater RCC. Patients had received 2 or more prior lines of systemic therapy for RCC, including 1 or more prior VEGF therapies, and were randomized in a 2:1

fashion to receive telaglenastat (800 mg oral twice daily) or placebo, plus everolimus at 10 mg daily until disease progression or unacceptable toxicity. The study met its primary endpoint of investigator-assessed progression-free survival with a median of 3.8 months for telaglenastat plus everolimus versus 1.9 months for placebo plus everolimus (HR, 0.64 [95% CI, 0.34–1.20], 1-sided p=0.079). Despite the progression-free survival difference, the combination of telaglenastat plus everolimus was not developed further. Combination therapy incorporating other agents was pursued in a less pretreated setting.

Cabozantinib is an effective TKI therapy for advanced RCC, inhibiting multiple targets including VEGFR, AXL, RET, and MET. Similar to the synergy observed in preclinical models with everolimus, cabozantinib combined with telaglenastat resulted in decreased consumption of both glucose and glutamine and synergistic antiproliferative effects.[39] This dual mechanism of inhibiting glucose and glutamine consumption translated into significant activity in a small, phase 1 trial with an overall response rate of 40%, and was further evaluated in the randomized phase 2/3 trial CANTATA. In this trial, 444 patients were randomized to telaglenastat plus cabozantinib or placebo plus cabozantinib until disease progression or unacceptable toxicity. Patients needed to have received at least 1, but no more than 3, prior lines of therapy. Median progression-free survival (the primary endpoint) was similar in the two arms, 9.2 months versus 9.3 months, for telaglenastat plus cabozantinib compared to placebo with cabozantinib (HR, 0.94; 95% CI, 0.74–1.21; stratified log-rank p=0.65). The overall response rate did not differ between the 2 groups. Possible reasons for the lack of any meaningful advantage to the addition of telaglenastat in CANTANA may be related to: (1) lack of synergy between cabozantinib and everolimus with telaglenastat; (2) tumours perhaps being less dependent on GLS in a less pretreated setting; or (3) as yet undefined compensatory mechanisms that may overcome pathway inhibition.

Whether telaglenastat is more active in patients previously treated with immunotherapy is uncertain. A prespecified subgroup analysis from CANTATA for patients pretreated with immune checkpoint inhibition reported a numerical but nonstatistical difference in median progression-free survival of 11.1 versus 9.2 months, respectively (unstratified HR, 0.77; 95% CI, 0.56–1.06), with telaglenastat plus cabozantinib versus placebo plus cabozantinib in this cohort. Competition between tumour and immune cells for nutrients, including glutamine, can create a metabolic checkpoint in the tumour microenvironment that induces local immune suppression. Telaglenastat may support T-cell activity by inhibiting tumour glutamine consumption and increasing its availability for T-cells, resulting in the enhanced antitumour activity of PD-1/PD-L1 inhibitors. A phase 1 trial explored the safety and activity of telaglenastat and the PD-1 inhibitor nivolumab in patients with advanced RCC, melanoma, or non-small cell lung cancer, including cohorts of patients refractory to anti–PD-1/PD-L1 therapy. Although 3 of 16 (19%) immune checkpoint–naïve patients experienced a response to the combination, this is not significantly different to what would be expected compared to nivolumab monotherapy.[41,42] While 3 patients in the melanoma cohort previously treated with immunotherapy developed a response to the combination, no responses to the combination were documented in the RCC cohorts that were refractory to prior immunotherapy.

The future for telaglenastat remains unclear following the reporting of these smaller trials and the larger randomized trial CANTATA. Future trials in this space may explore telaglenastat in non-clear cell RCC, where this metabolic pathway may be more relevant, or in the ICI refractory setting, given the enhanced tumour response noted in the immune-refractory melanoma population.

Tryptophan Pathway Inhibitors

Tryptophan, an essential amino acid, is metabolized by three rate-limiting enzymes: indoleamine 2,3-dioxygenase (IDO) 1, IDO2, and tryptophan 2,3-dioxygenase (TDO).[43] Catabolism of tryptophan mediated by these enzymes results in increased kynurenine, a metabolite that induces T-cell cycle arrest and immune anergy.[44] Substantial increases in the kynurenine to tryptophan ratio were associated with worse outcomes to PD-1 nivolumab monotherapy in patients with RCC or melanoma.[45] Targeting tryptophan metabolism may enhance immune recognition and induction, or restoration of tumour immune recognition. Data from early-phase clinical trials across a range of solid tumours, including advanced RCC, was encouraging. The combination of a selective IDO1 inhibitor epacadostat with pembrolizumab induced partial responses or stable disease in 7 of 11 (64%) pretreated patients.[46,47] However, the failure of a large trial of epacadostat with pembrolizumab compared to pembrolizumab alone in melanoma (ECHO-301[44]) has led to cessation of similar studies in RCC. The future for other IDO inhibitors such linrodostat and a long-acting IDO1 inhibitor in development (KHK2455) remains unclear.[48,49]

Immunotherapy Advances

Despite significant progress secondary to the development of ICI, many patients either do not derive a clinical benefit or do not experience a sustained response to therapy. Looking beyond the PD-(L)1 and CTLA-4 immune checkpoints, multiple promising candidates are emerging using alternative immune checkpoints and cytokines.

Cytokine Therapy

High-dose interleukin-2 (IL-2) formed the earliest active immunotherapy in RCC. IL-2 exerts its antitumour activity through activation of memory effector CD8+ T cells and stimulation of regulatory T cells (Tregs). Some long-term durable remissions were reported following its clinical use (the complete response rate for high-dose IL-2 monotherapy is 7–9%); however, significant toxicity limited its application to highly selected patients and administration was primarily confined to specialized treatment centres and highly selected fit patients.[50] Bempegaldesleukin (BEMPEG/NKTR-214) is a pegylated version of IL-2 with altered pharmacokinetic and pharmacodynamic properties, allowing for a lower dose (with a potential to reduce toxicity) and altered receptor binding, which promotes CD8+ T-cell activation and immune recognition.[51] It has been hypothesized that the combination of pegylated IL-2 and a PD-1 inhibitor could elicit a potent synergistic anticancer immune response.

The combination of NKTR-214 with nivolumab was evaluated in a phase 1/2 study of 162 patients. The combination appeared tolerable and safe, with grade 3 (or higher) treatment-related adverse events observed in 11% of patients. This study included 24 patients with RCC, with an overall response rate in this cohort of 54%.[52] Multiple clinical trials involving patients with RCC are evaluating NKTR-214, including a large phase

3 study examining NKTR-214 in combination with nivolumab versus cabozantinib or sunitinib monotherapy (NCT03729245, PIVOT-9).[53] Unfortunately, a recent press release showed that this trial did not meet the primary endpoints for overall response rate and overall survival for the intermediate-/poor-risk or all-risk populations.[54] Other IL-2 compounds are in preclinical development or early-phase clinical trials.

The Next Generation of Immune Checkpoints

The efficacy of currently approved checkpoint inhibitors has led to intense research interest in targeting other checkpoints that could promote further antitumour immune responses and improve patient outcomes in the checkpoint-naïve or -refractory setting (**Table 2**).

Inhibitory immune checkpoints

T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), a member of the immunoglobulin superfamily, is expressed in numerous immune cells and notably on most exhausted T-cell subsets, suggesting therapeutic potential as a treatment target in RCC. Inhibition of TIM-3 *in vitro* induces proliferation of, and interferon-gamma (IFN-γ) production by, tumour-infiltrating CD8+ and CD4+ T cells. The combination of an anti–TIM-3 antibody with an anti-PD-(L)1 antibody has been investigated across tumour types, with an acceptable safety profile and promising antitumour activity.[55,56] TIM-3 inhibitor-based combinations are currently being evaluated in clinical trials, including studies involving patients with RCC.[56,57]

Lymphocyte activating gene 3 (LAG3), or CD223, is another immune checkpoint under evaluation in RCC. It is expressed on multiple immune cell types, including CD4+ and CD8+ T cells and Tregs, and appears to be required for optimizing T-cell regulation and homeostasis. Chronic LAG3 expression secondary to persistent antigen stimulation in cancer may promote T-cell exhaustion, and the targeting of LAG3 along with stimulation of PD-1 reinduces a T-cell response. The concurrent blockade of PD-1 and LAG3 has been shown to stimulate IFN-γ production in tumour-infiltrating T lymphocytes from patients undergoing surgery for RCC.[58] Drugs such as eftilagimod-α (IMP321) have been tested in a phase 1 clinical trial, which was found to induce activated and effector memory CD8+ T cells.[59] However, no objective responses were recorded in patients with RCC (7 of 8 patients in the high-dose group had a best overall response of stable disease[59]). Clinical trials evaluating the efficacy of LAG3 inhibitors in combination with anti–PD-(L)1 antibodies are currently ongoing.[60,61] Dual inhibition of LAG3 and PD-1 has already shown to provide greater benefit in progression-free survival than inhibition of PD-1 alone in patients with previously untreated metastatic or unresectable melanoma.[62] It is likely that LAG3 inhibitors are going to be developed in RCC, another immunogenic tumour, following this initial positive data in melanoma.

TABLE 2 Selected Trials Investigating Novel Immune Checkpoints in RCC

Investigational product (target)	Combination	Comparator arm	Trial phase (treatment line), NCT number
LY3321367 (TIM-3)	LY3300054 (anti–PD-L1)	-	1 (2+), NCT03099109
Eftilagimod-α (LAG3)	-	-	1 (2+), NCT00351949
Relatlimab (LAG3)	Nivolumab	Nivolumab + ipilimumab	2 (1+), NCT02996110

Abbreviation: NCT, National Clinical Trial.

Inhibitors of anti-inflammatory cytokines

The tumour microenvironment can be altered by inhibitors of anti-inflammatory cytokines or cytokine receptors to reduce the effects of immunosuppressive mediators that dampen the antitumour immune response. The CXCR4 chemokine receptor modulates immunosuppressive cell trafficking that can inhibit antitumour immune responses.[63] Mavorixafor (X4P-001) is a CXCR4 inhibitor that promotes T-cell infiltration and effector function within the tumour microenvironment. The combination of X4P-001 plus axitinib was evaluated in patients with pretreated RCC (48% with 3 or more prior lines of therapy), with an overall response rate of 29%.[64] Other agents modulating anti-inflammatory cytokines and receptors are currently under investigation.

Targeting the Metabolic Immune Microenvironment

Precision immunotherapy approaches

The current immunotherapeutic landscape incorporating checkpoint inhibition remains largely a nonspecific attempt to induce an immune response that will also incur an antitumour effect. The end functions of a broadly heightened response may result in a lack of target specificity that could incorporate off-target effects, which may induce a response against nonmalignant cells resulting in immune-related toxicity. The move toward precision immunotherapy ideally aims to target tumour antigens with specificity as opposed to inducing a broader, generally more heightened immune response.

Target selection for directing the immune response is particularly important and should represent antigens that are uniquely or selectively expressed on RCC cells that allow the development of a targeted immunotherapy. Alternatively, intracellular peptides derived from proteins that become presented on major histocompatibility complex class I (MHC-1), which are subsequently recognized by T-cell receptors, can be utilized for antitumour activity.

Therapeutic vaccines

Therapeutic cancer vaccines aim to induce a durable immune response by developing host immune memory that can mount a sustained response directed only against tumour-specific antigens while sparing host antigen recognition. By selecting tumour-specific antigens, the potential exists to minimize off-target immune-mediated toxicity. Studies attempting to preselect target RCC antigens have not yielded significant responses, but techniques are evolving to become more patient and tumour specific. One approach is to develop a patient-specific vaccine involving the incorporation of all potential antigens from each individual patient's tumour. The phase 3 ADAPT trial used this approach, where amplified tumour RNA was coelectroporated into autologous monocyte-derived dendritic cells, generating a product called rocapuldencel-T. This was administered as a therapeutic vaccine in combination with sunitinib and compared to a standard-of-care arm of sunitinib monotherapy. No significant difference in median progression-free survival (6.0 months vs. 7.8 months) or overall survival (27.7 months vs. 32.4 months) was observed between the two arms.[65] However, there may be synergistic potential to partner the vaccine with immune checkpoint therapy (such as nivolumab and/or ipilimumab), which may prime the immune system and potentiate the effect of the dendritic cell vaccine (now termed CMN-001), and this combination is under evaluation (NCT04203901).[66]

Next-generation sequencing technologies and improved MHC epitope prediction[67] have led to consideration for an alternative approach that targets tumour neoantigens by sequencing an individual's tumour DNA. This sequencing allows for the prediction of which mutations will generate peptides that are likely to bind with that patient's specific human leukocyte antigens (HLAs) and the subsequent generation of a personalized neoantigen vaccine. This approach is feasible and capable of generating neoantigen-specific antitumour immune responses with a favourable safety profile based on prior studies conducted in patients with melanoma or glioblastoma.[68,69]

This strategy is being investigated in patients with RCC in the adjuvant setting combined with locally administered ipilimumab (NCT02950766).[70] In the setting of metastatic disease, preliminary data from a phase 1b study involving an RNA-based neoantigen vaccine (RO7198457) combined with atezolizumab yielded an overall response rate of 22% in a cohort of immunotherapy-naïve patients with advanced-stage solid tumours. Data from patients with RCC is yet to be presented, but significantly the vaccine induced strong CD8+ T-cell responses against a neoantigen in a patient with triple-negative breast cancer.[71] A summary of trials currently investigating vaccine approaches in RCC in presented in **Table 3**.

TABLE 3 Selected Trials Investigating Vaccines

Investigational product (mechanism of action)	Combination	Trial phase (treatment line), NCT number
CMN-001 (dendritic cell vaccine)	Nivolumab + ipilimumab Lenvatinib + everolimus	2 (1), NCT04203901
NEOVAX (neoantigen peptides plus an adjuvant immune checkpoint inhibitor)	Ipilimumab (local administration)	1 (1), NCT02950766
RO7198457 (neoantigen RNA)	Atezolizumab	1 (1+), NCT03289962

Abbreviation: NCT, National Clinical Trial.

Human endogenous retrovirus type E

Most RCCs selectively express a human endogenous retrovirus type E (HERV-E). Antigens derived from this retrovirus are immunogenic, stimulating cytotoxic T cells that kill RCC cells both *in vitro* and *in vivo*. HERV-E expression is restricted to the clear cell subtype of RCC where HIF-2α can serve as a transcriptional factor for HERV-E by binding with the HIF response element. Thus, inactivation of a tumour suppressor gene can result in aberrant proviral expression in a human tumour and give insights needed for translational research aimed at boosting human immunity against antigenic components of this HERV-E.

A trial with HERV-E TCR Transduced Autologous T Cell (NCT03354390) is recruiting, with the primary endpoint being safety by day 21.[72] Secondary endpoints include overall response rate, progression-free survival, and overall survival. Exploratory studies will include persistence of circulating HERV-E T-cell receptor (TCR)–transduced CD8+/CD34+ enriched T cells, changes in immune cell subsets, and activation status of T cells, as well as other immunologic determinants with clinical outcomes at baseline, at different time points during treatment, and at the time of disease progression.[73]

The Microbiome in RCC

Increasing data suggests that the microbiome plays a significant role in modulating the host immune response across a range of solid organ malignancies including RCC, with both specific bacterial species and cumulative microbial diversity driving response. In the search to refine patient selection to enrich for clinical benefit by identifying predictors of response or nonresponse in RCC, the potential for a new biomarker in stool microbiome has become an area of research interest.

The clinical application of observed differences in host microbiome in modulating tumour response to ICI is an area of active investigation. Murine models in melanoma suggest a correlation between ICI activity and pretreatment stool microbiome, which may be therapy specific. Whereas anti–CTLA-4 activity appeared to be dependent on the presence of *Bacteroides* spp.,[74] anti–PD-L1 efficacy was correlated with *Bifidobacterium* spp.[75] Clinical work in melanoma suggests that response to ICI is dependent on the presence of *Ruminococcaceae*, *Bifidobacterium longum*, *Collinsella aerofaciens*, *Enterococcus faecium*, and *Faecalibacterium* spp.[76] In RCC and non-small cell lung cancer, the abundance of *Akkermansia* spp. in pretreatment stool is associated with clinical response to ICI.[77] Dynamic changes may also be an important biomarker of clinical benefit. In a study of patients with RCC where temporal profiling of the microbiome composition was performed, certain species (such as *Prevotella copri* and *Akkermansia muciniphila*) were expanded in patients deriving clinical benefit.[76] In contrast, *Akkermansia muciniphila* decreased in relative abundance in many patients not deriving clinical benefit, suggesting that dynamic assessment of stool microbiome may evolve into a useful biomarker of clinical benefit.

Within the context of RCC, the most advanced evaluation is for CMB-588, a strain of *Clostridium butyricum* that mediates immunomodulatory and anti-inflammatory effects in the intestinal epithelium. This agent is thought to foster the development of a more favourable microbiome by promoting species that are associated with immunotherapy response.

In the randomized phase 1a clinical trial (NCT03829111), treatment-naïve patients with RCC were randomized 2:1 to receive nivolumab and ipilimumab with CBM-588 (dosed orally at 80 mg bid) versus nivolumab and ipilimumab alone.[78] Stool was collected for microbiome analysis at baseline and after 12 weeks on therapy. In contrast to using a clinical endpoint, the primary endpoint was a change in *Bifidobacterium* spp. from baseline to week 12, with secondary endpoints including change in microbial diversity and clinical response (overall response rate and progression-free survival). A total of 30 patients were randomized between April 2019 and Nov 2020. Analysis of paired stool specimens demonstrated an 8-fold increase in *Bifidobacterium bifidum* and a 6-fold increase in *Bifidobacterium adolescentis* in patients randomized to the CBM-588 arm from baseline to week 12. *Clostridium butyricum* was detected only in patients receiving CBM-588. Conversely, pathogenic species such as *Escherichia coli* and *Klebsiella* spp. were more prevalent in patients not receiving CBM-588. Clinical activity favoured the CBM-588 arm, with an overall response rate of 59% versus 11% (p=0.024), and median progression-free survival was prolonged with the addition of CBM-588 to nivolumab/ipilimumab (not reached vs. 11 weeks; p<0.001). No significant difference in grade 3 or higher toxicities was observed between study arms. Limitations to the study included the small number of patients, which may have led to overinterpretation of the secondary clinical endpoints. However, the biological findings and apparent degree of difference in clinical endpoints support further ongoing studies of CBM-588 in RCC.[78,79] Unanswered questions that future studies may answer include the impact of regional variation in diet and composition of the regional microbiome, and whether CBM-588 is best suited to combination therapy with immunotherapy doublets, immunotherapy/TKI therapy, or TKI monotherapy.

Summary

The rapid pace of drug development is transforming the treatment of RCC. Recognition of the biologic diversity of RCC and identification of relevant targets are translating into development of novel agents. The current era of targeted therapy, immunotherapy, and new agent classes such as HIF inhibition is already providing benefit to patients in the clinic today. With the rich investment of our scientific community into molecular research and drug development, the treatment of RCC will continue to evolve, and further improvements in survival outcomes from novel therapies are expected in the coming years.

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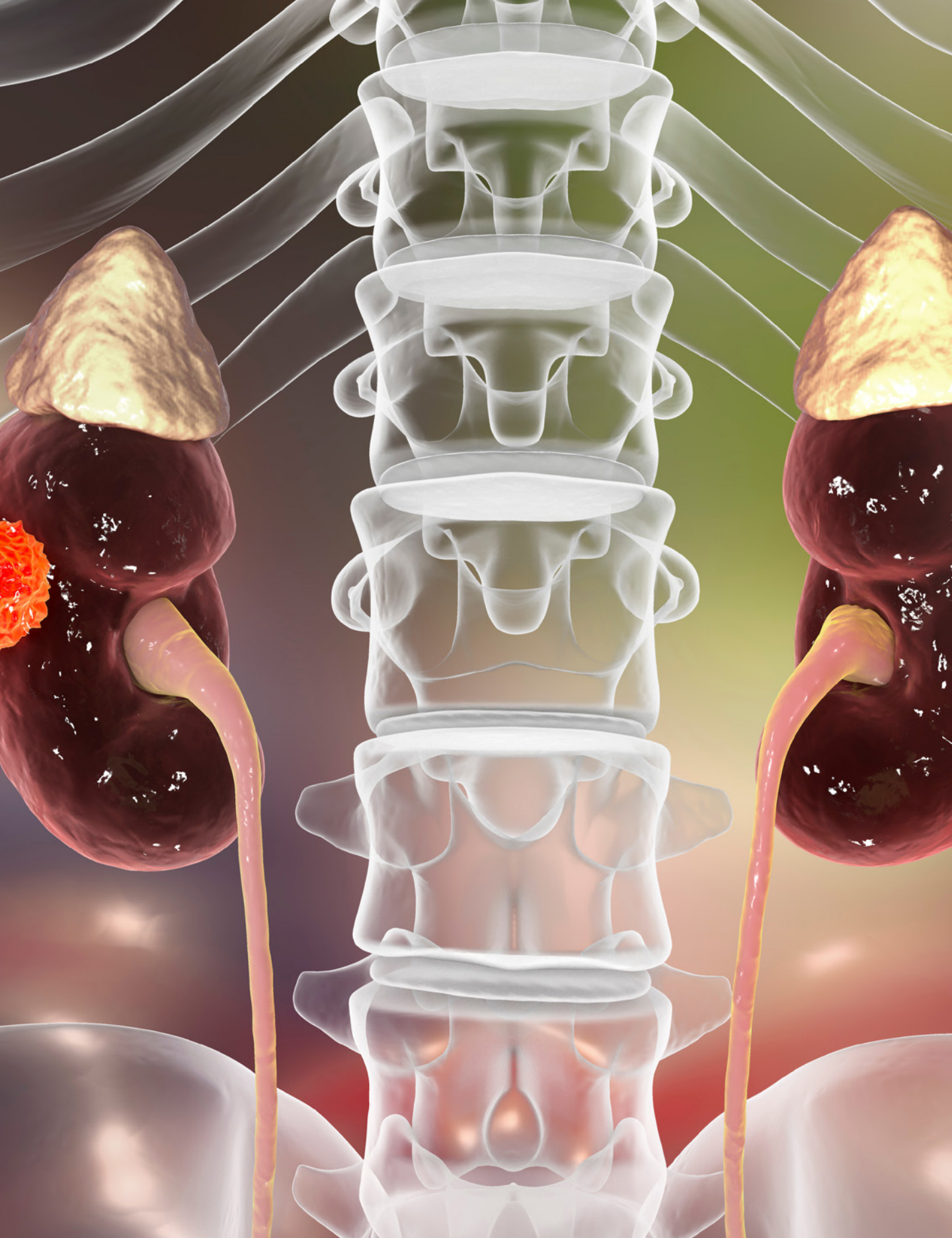

COMMITTEE 15

Management of Toxicity and Side Effects from RCC Therapies

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Introduction

Since the mid-2000s, the introduction of new systemic therapies has transformed the management of renal cell carcinoma (RCC). Vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs), mTOR inhibitors (mTORIs), and most recently immune checkpoint inhibitors (CPIs) have led to dramatically improved outcomes in advanced disease. Immune checkpoint inhibitors are also now approved for high-risk localized disease. However, alongside their beneficial effects, the introduction of these new classes of drug has led to the potential of chronic toxicities. Optimal management of such side effects is essential, both to ensure safe treatment with manageable quality of life for patients for the duration of therapy as well as ensure optimal drug delivery to allow maximum likelihood of effective cancer control. This chapter discusses the management of toxicities associated with these newer therapies, together with emerging data that in future may allow prediction of toxicities at an individual level.

General Principles of RCC Toxicity Management

Prior to initiating any systemic therapy for mRCC, it is standard clinical practice to consider each individual patient, their fitness, past medical history and existing comorbidities, and any concurrent medications. This may highlight patients who could be at greater risk for toxicity and may trigger targeted pretreatment investigations, such as evaluation of cardiac status, and endocrine, gastrointestinal, or respiratory conditions, among others. It will also identify patients taking medications that may interact with the planned RCC treatment such as cytochrome P450 3A4 (CYP3A4) enzyme inducers (e.g., glucocorticoids and some anticonvulsants) or inhibitors (e.g., some antimicrobials, H2 antagonists, and calcium channel blockers). This will help anticipate and thus minimize the side effects and risks of treatment.

Should toxicity arise, the approaches to consider are implementing supportive therapies to alleviate the symptoms or impact of any side effect, together with modifying the treatment itself. Treatment interruption, dose or schedule modification, and treatment cessation each have a role to play in specific scenarios, according to the drugs being used and the severity or "grade" of the toxicity. Toxicities are graded according to the Common Terminology Criteria for Adverse Events (CTCAE).[1] CTCAE grading is recommended to guide the management of each toxicity. Ongoing assessment of toxicity grade can be helpful in monitoring and documenting improvement. CTCAE grading was not developed for immune-related adverse events (irAEs), and these toxicities should be evaluated using CTCAE in conjunction with irAE guidelines as described later in this chapter.

Coupled with these approaches, good patient education and support are enormously beneficial. Early recognition and intervention are required for the effective management of treatment-related adverse events (TRAEs), and in the case of irAEs, prompt immunosuppression is required. Also, alongside the better effectiveness of these treatments, increasingly patients may be taking these therapies for many years, during which time they have to live with chronic side effects. Patient education regarding potential toxicities and proactive management

is therefore essential to minimize the risks of these treatments and to ensure optimal tolerability and clinical outcomes. Although this is particularly important in the first few months after treatment initiation, ongoing vigilance is required throughout, especially for CPI-induced toxicities, which can emerge late into treatment or even after its discontinuation. Moreover, support and education for general physicians and oncologists, and the development of specialized networks of teams with an interest in irAEs are hugely beneficial in successful multidisciplinary management. Optimal toxicity management for the different classes of drugs and regimens is discussed in further detail below.

Toxicity of VEGFR TKIs

Oral TKIs that target VEGF receptors remain some of the most effective treatments for advanced RCC, both as single agents and in combination with other therapies. Collectively, these have led to a marked improvement in survival.[2–7] Guideline-recommended VEGFR TKIs for first-line therapy as single agents in specific situations include sunitinib, pazopanib, tivozanib, and cabozantinib. Axitinib, cabozantinib, and lenvatinib are approved in the first line as VEGFR TKIs within TKI/CPI combinations as described later in this chapter. Second-line VEGFR TKI options also include axitinib, cabozantinib, and lenvatinib in combination with the mTOR inhibitor everolimus.[8]

Mechanism, spectrum, and frequency of VEGFR TKI–associated toxicities

VEGFR TKIs have varying potency and selectivity for VEGFRs and inhibit several other tyrosine kinase receptors, including platelet-derived growth factor receptor (PDGFR), MET, AXL, and c-KIT, which contributes to differences in their toxicity and clinical profiles. Nearly all patients experience some side effects, with TRAE rates for all-grade toxicity of >98% in the registration clinical trials. Severe toxicity is less common; with the exception of hypertension, grade 3 or 4 toxicity typically affects fewer than 10–15% of patients. The TRAEs most frequently encountered with VEGFR TKIs in clinical practice are skin, gastrointestinal, stomatitis, hypertension, and other cardiovascular toxicities, hematological abnormalities, fatigue, and endocrine dysfunction. Other important toxicities include renal effects such as proteinuria. There are some differences in the reported safety endpoints across these trials. From published data, dose interruptions have been reported in 19–40% of treated patients, dose reductions in 14–46% of patients, and treatment discontinuation in 4–21% of patients. **Table 1** describes the most common toxicities reported for each medication according to their registration clinical trials.

TABLE 1 Safety Outcomes Reported in Pivotal Clinical Trials of Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors in Metastatic Renal Cell Carcinoma

	Sunitinib		**Pazopanib**		**Tivozanib**		**Cabozantinib**		**Axitinib**		**Lenvatinib**	
	1st line, NCT00083889, *n*=375		1st or 2nd line, NCT00334282, *n*=290		1st or 2nd line, NCT01030783, *n*=260		1st line, NCT01835158, *n*=78		1st line, NCT00835978, *n*=56		2nd line, NCT01136733, *n*=52	
	17215529		20100962		24019545		28199818		24140184		26482279	
TRAE leading to discontinuation in %	8		NR		4		21		4		25	
Death due to TRAE—*n* (%)	NR		4 (1)		NR		3 (4)		None		1 (2)	
Adverse event in %	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Diarrhea	53	5	52	4	23	2	72	10	59	11	71	12
Fatigue	51	7	19	2	19	5	86	6	44	5	50	8
Nausea	44	3	26	<1	12	<1	32	3	37	5	62	8
Stomatitis	25	1	-	-	11	<1	36	5	16	0	25	2
Hypertension	24	8	40	4	44	27	81	28	61	30	48	17
Vomiting	24	4	21	2	-	-	-	-	30	5	38	4
Hand-foot syndrome	20	5	-	-	14	2	42	8	33	4	15	0
Anorexia	-	-	22	2	18	3	47	5	27	7	48	6
Back pain	-	-	-	-	14	3	-	-	23	5	21	0
Decreased appetite	-	-	-	-	10	<1	-	-	37	5	58	4
Lower respiratory tract infection	-	-	-	-	-	-	-	-	-	-	8	8
Laboratory abnormality												
Neutropenia	72	11	34	1	11	2	15	0	-	-	-	-
Thrombocytopenia	65	8	32	1	18	<1	40	1	7	0	-	-
Lymphopenia	60	12	31	4	-	-	-	-	-	-	-	-
Leukopenia	60	5	0	0	-	-	12	0	-	-	-	-
Increased AST	52	2	53	8	37	2	62	3	7	2	-	-

TABLE 1 Safety Outcomes Reported in Pivotal Clinical Trials of Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors in Metastatic Renal Cell Carcinoma *(Cont'd)*

Laboratory abnormality *(Cont'd)*												
Increased lipase	52	13	-	-	46	11	-	-	-	-	-	-
Increased ALT	46	3	53	12	28	1	55	5	7	2	-	-
Hyponatremia	-	-	31	5	-	-	-	-	-	-	-	-
Proteinuria	-	-	-	-	72	3	-	-	20	4	31	19
Hypothyroidism	-	-	-	-	-	-	-	-	32	0	37	2

Table 1 shows the safety outcomes that were reported in the referenced pivotal registration trials. All adverse events grade 3 or worse that occurred in at least 5% of patients in one of the trials are reported.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; NR, not reported in cited publication; TRAE, treatment-related adverse event.

General principles for management of VEGFR TKI–associated toxicities

General principles of managing VEGFR TKI–induced toxicities involves consideration of supportive approaches, treatment interruption, dose reduction, and, particularly with sunitinib, planned schedule modification. Treatment discontinuation is reserved for the most severe toxicities. The combination of these strategies selected depends on the VEGFR TKI being used, the specific toxicity, and its grading. Grade 1 and 2 toxicities can often be managed with supportive approaches in the first instance but may benefit from temporary treatment interruption. For significant treatment-related toxicities of ≥ grade 3, treatment interruption is usually required, other than for some laboratory abnormalities. Subsequent dose reduction or schedule modification may be needed.

Sunitinib and axitinib have specific dosing nuances that can also be exploited in therapy management. Most VEGFR TKIs are administered on a continuous dosing schedule. Sunitinib, however, is routinely administered on a dosing schedule that incorporates treatment-free periods: its approved starting dose and schedule is 50 mg daily for 4 weeks followed by a 2-week treatment break (4/2). Several nonrandomized studies have shown that the alternate schedule of 2 weeks continuous dosing followed by a 1-week treatment break (2/1) reduces toxicity.[9–11] This was recently confirmed by the prospective SURF study.[12] SURF randomized 226 patients who developed toxicity on the standard sunitinib dose and schedule (50 mg; 4/2) to either a dose reduction (37.5 mg 4/2) or altered schedule (50 mg 2/1) and found this was effective at reducing toxicity with no apparent compromise to efficacy. This schedule is not recommended at initiation of sunitinib but can be a useful switch option for those experiencing side effects, especially those that worsen incrementally over the 4-week course.

Axitinib as a single agent is commenced at a dose of 5mg twice daily with dose increase or reduction individualized according to safety and tolerability. Patients who tolerate axitinib at 5 mg twice daily for at least 2 consecutive weeks with no adverse reactions above grade 2 according to CTCAE and are normotensive and not receiving antihypertension medication should have their dose increased to 7 mg twice daily and further to 10 mg twice daily using the same criteria.[13] This is an unusual situation whereby a complete lack of side effects may in fact be problematic, as it may indicate that those patients are not receiving a sufficient dose. Blood pressure rise in particular is somewhat correlated with axitinib serum concentration. Correct axitinib dose titration according to the approved recommended dose has been shown to be associated with improved response to treatment,[14] although further research has indicated that this alone is insufficient to guide optimal axitinib dosing and other toxicities should be considered.[15] Like with other VEGFR TKIs, dose reductions should be considered for toxicity management.

Management of VEGFR TKI–associated toxicities

Recognized guidelines for VEGFR TKI–driven toxicities should be followed where available. However unlike for toxicities associated with immune CPIs, there are no regularly updated consensus guidelines for VEGFR TKI toxicity management and recommendations are primarily derived from clinical expertise rather than strong evidence. Practical recommendations for common VEGFR TKI–associated toxicities are therefore outlined below and summarized in **Table 2**.

Hypertension and other cardiovascular toxicities

Due to the intrinsic effects of VEGFR TKIs on multiple downstream signalling pathways, almost all patients commencing these medications will experience a dose-dependent elevation in blood pressure (BP). Pretreatment evaluation of BP and cardiovascular risk are essential, and preexisting hypertension should be well controlled before starting treatment. All patients should have regular BP monitoring. Management of VEGFR TKI–induced hypertension should follow established national and international guidelines for hypertension. Angiotensin-converting enzyme (ACE) inhibitors or calcium-channel blockers are commonly used first line for treatment-emergent hypertension. Non-dihydropyridine calcium-channel blockers such as verapamil or diltiazem are cytochrome CYP3A4 inhibitors and are ideally avoided.[16] During VEGFR TKI treatment breaks, BP may normalize and antihypertensive medication may also be discontinued. The risk for cardiac toxicity resulting in clinically significant decreases in cardiac left ventricular ejection fraction (LVEF) correlates with baseline cardiac risk and may be precipitated by uncontrolled hypertension or thyroid dysfunction. Treatment-related deterioration in LVEF is generally reversible with drug interruption and prompt management.

Gastrointestinal toxicity

Diarrhea is a common side effect of VEGFR TKSs but can often be managed with supportive approaches and temporary treatment interruption. General dietary recommendations can be made for grade 1 symptoms, such as the “BRAT” diet (bananas rice, grated apple, toast) and an increase in fluid intake. Probiotics have been shown

to reduce the severity of chemotherapy-induced diarrhea; however, they have not specifically been evaluated in TKI-induced diarrhea.[17] Loperamide or codeine are commonly recommended to improve persistent symptoms; pancreatic enzyme supplementation can also be considered in specific cases. Fecal microbiota transplantation has recently shown promising results for the treatment of TKI-induced diarrhea.[18]

Stomatitis may result in a significant reduction in food intake and quality of life. Prior to starting treatment, patients should be advised to maintain good oral hygiene and report symptoms promptly. Oral rinses (saline, sodium bicarbonate, or nonalcoholic mouthwash) can be used for mucosal erythema (grade 1). Grade 2+ mucositis will usually require dose interruption/modification; topical anesthetics, mucosal coating agents, and/or benzydamine may be administered as needed for pain, together with systemic analgesia in severe cases.[19]

Dermatologic toxicity

Hand-foot syndrome (HFS) or palmar-plantar erythrodysesthesia is also common with VEGFR TKIs. Patients should be advised to keep their skin moisturized and to report symptoms as they arise. For grade 1 erythema, self-care plus moisturizing creams, and 20–40% urea creams are recommended. The development of pain (grade 2) will require dose interruption or modification, with addition of mild steroid ointment such as clobetasol 0.05% plus topical or systemic analgesia as required. Grade 3 symptoms limiting self-care will always require dose interruption and dose reduction.[20] Other dermatologic effects include skin and hair color changes, which are relatively common and can be surprising if unexpected. Patients starting VEGFR TKI treatments should be counselled accordingly.

Hypothyroidism

Hypothyroidism is a common target effect of VEGFR TKI therapy potentially contributing to treatment-related fatigue and increasing the risk for cardiac dysfunction. Thyroxine stimulating hormone (TSH) should be measured at baseline and monitored typically every 12 weeks during treatment. Thyroxine replacement should be considered for patients with TSH above 10 IU/mL and in all symptomatic cases.[21]

Fatigue

Fatigue is common in patients receiving VEGFR TKIs for advanced RCC and is often multifactorial. Monitoring for and treatment of anemia, hypothyroidism, cardiac dysfunction, diarrhea, hypophosphatemia, and low testosterone levels in male patients can help to reduce fatigue levels. Aerobic exercise as tolerated has also been shown to improve fatigue. However, some patients will require dose reduction if, despite correcting all these factors, fatigue continues to impair quality of life.

TABLE 2 Management Recommendations for Key Toxicities Associated with VEGFR Tyrosine Kinase Inhibitors

Toxicity	Management recommendations
Hypertension	Blood pressure should be monitored regularly with initiation of antihypertensive therapy ≥140/90 mmHg according to clinical practice guidelines. Non-dihydropyridine calcium-channel blockers that inhibit CPY3A4 (verapamil, diltiazem) should be avoided.[16]
Fatigue	Aerobic exercise reduces fatigue in fit patients. Hypothyroidism should be corrected if present. Check testosterone in male patients.
Diarrhea	Dietary adjustment (BRAT diet: bananas rice, grated apple, toast) and increase in fluid intake. Probiotics have been shown to reduce the severity of chemotherapy-induced diarrhea; however, they have not specifically been evaluated in TKI-induced diarrhea.[17] Fecal microbiota transplantation has recently shown promising results for the treatment of TKI-induced diarrhea.[18] Loperamide or pancreatic enzyme supplementation can also be considered in specific cases.
Stomatitis	Good oral hygiene. Oral rinses (saline, sodium bicarbonate, or nonalcoholic mouthwash) can be used for mucosal erythema (grade 1). For grade 2+ mucositis requiring dose interruption/modification, topical anesthetics, mucosal coating agents, and/or benzydamine HCl may be administered as needed for pain.[19]
Hand-foot syndrome	Preventive advice includes avoiding unnecessary friction/removing hyperkeratosis prior to treatment, and avoiding excessively hot water. For erythema (grade 1), recommend self-care plus moisturizing creams and 20–40% urea creams. Pain (grade 2) will require dose interruption/modification with addition of clobetasol 0.05% ointment/topical or systemic analgesia as required.[20]
Hypothyroidism	Thyroxine stimulating hormone should be measured at baseline and monitored during treatment at least every 3 cycles. Replacement with thyroxine should be considered for patients with TSH above 10 IU/mL.[21]

Table 2 summarizes management recommendations for common or drug class specific toxicities VEGFR tyrosine kinase inhibitors.

Abbreviations: TKI, tyrosine kinase inhibitor; TSH, thyroxine stimulating hormone; VEGFR, vascular endothelial growth factor receptor.

Toxicity of mTOR Inhibitors

After more than a decade of experience with the mTORIs temsirolimus and everolimus in the treatment of renal cell carcinoma, the toxicity profile of these drugs and its management are well established.[22–24] mTORIs are usually well tolerated with low rates of grade 3 and 4 adverse events.[22–25] Common side effects of mTORIs include asthenia, stomatitis, skin rashes, pulmonary toxicity, metabolic changes, and infections.[26] An association between certain class-effect toxicities, such as pneumonitis and metabolic changes, and treatment efficacy has been postulated.[27] While this association is of interest, it does not impact practical management.

General principles for management of common mTOR inhibitor–associated toxicities

The most common and most notable toxicities reported with mTORIs include stomatitis, skin rash, infections, noninfectious pneumonitis, and biochemical abnormalities particularly hyperglycemia and hyperlipidemia. As for VEGFR TKI–related toxicities, the general principles of managing the side effects from mTORIs are to consider treatment interruption, dose reduction, and use of supportive therapies. Although relatively uncommon, treatment cessation may be required for grade 3 and 4 toxicities. Key recommendations for the management of common mTORI-associated toxicities are discussed below and summarized in **Table 3**.

Management of specific mTOR inhibitor–associated toxicities

Stomatitis

Stomatitis is one of the most common TRAEs caused by everolimus and temsirolimus. This TRAE presents as an aphthous stomatitis that is somewhat different from cytotoxic-induced mucositis.[28,29] In the RECORD-1 trial, 43% of patients suffered from stomatitis, but grade 3 or higher toxicity was rare (3%). Stomatitis will usually occur within the first 2 months of treatment. Management includes mouth wash with local anesthetic, with or without steroids, and treatment interruption for grade 2 or higher stomatitis.[30]

Skin rash

Skin rash is a common side effect seen in about 25% of patients taking everolimus, but grade 3–4 toxicity is rare.[22,23] Skin rashes usually present as papulopustular or maculopapular eruptions that can sometimes be pruritic. Patients should be instructed to avoid heavy sun exposure and to apply pH-neutral and fragrance-free skin care products. Mild skin rashes can be treated with topical moisturizers and cortisone creams if required.

Systemic steroids may be used for grade 3 or worse erythema, usually starting at a low dose of about 10–25 mg prednisone daily.

Infections

mTORIs increase the risk for infection such as candidiasis, pneumonia, and invasive fungal infections, and the reactivation of latent viral hepatitis. Infection rates are constant across the entire treatment period. Patients with a high risk for infection or reactivation of infections should be identified prior to treatment initiation. Hepatitis and HIV serology should be checked in endemic areas and prior TB exposure should be evaluated. Monitoring of hepatitis B virus (HBV) DNA is recommended for patients with latent hepatitis. Active infection should be treated, and mTORIs should be interrupted or discontinued in patients with severe infections.

Noninfectious pneumonitis

Noninfectious pneumonitis (NIP) is an mTORI class–related adverse effect characterized by noninfectious, nonmalignant pulmonary inflammatory infiltrates.[31] Typical symptoms include coughing, dyspnea, and hypoxemia, which can be accompanied by fever and fatigue; however, about half of patients will be asymptomatic and have radiographic changes only, which do not necessitate any dosing changes and can simply be monitored. Higher grades of NIP may be associated with deterioration in lung function tests. A retrospective analysis of the pivotal trial for temsirolimus revealed signs of pneumonitis in 29% of patients, typically occurring in the first 6 months of treatment.[32] Treatment of NIP includes monitoring, dose adjustment, treatment interruption, and treatment with corticosteroids.

Endocrine toxicities

Hyperglycemia (overall 50%, 11% at grade 3) and hyperlipidemia (overall 76%, 3% at ≥ grade 3) are common side effects of mTORIs. Glucose and lipids should be measured at baseline and monitored throughout treatment. If endocrine levels are elevated, treatment should follow standard guidelines.[33,34] Hypophosphatemia is also seen in 32% of patients.[23] It is usually mild or asymptomatic; if symptomatic or severe, phosphate replacement should be administered.[35]

TABLE 3 Management Recommendations for Key Toxicities of mTOR Inhibitors

Toxicity	Management recommendations
Stomatitis	Grade 1: Modified diet and alcohol-free mouthwash may alleviate symptoms. Grade 2 and above: Treatment should be interrupted and can be restarted at full (grade 2) or reduced (grade 3) dose. Grade 4: Treatment should be discontinued permanently in most cases. Investigation to rule out herpes and fungal infection may be helpful.
Skin rash	Grade 1 (covering <10% BSA) and grade 2 (covering >10% to <30% BSA) toxicity can be managed with topical moisturizers and steroids. Grade 3 toxicity (covering >30% BSA) may require dose interruption and treatment with low-dose systemic steroids (e.g., 10–20 mg prednisolone).
Noninfectious pneumonitis	For patients with preexisting pulmonal morbidity, baseline LuFT is recommended. Grade 1 (radiological findings only): Clinical follow-up is sufficient. Grade 2 (cough, SOB, no oxygen requirement): Workup for other causes of symptoms including chest imaging should be conducted. Grade 3 (interference with ADL or oxygen requirement): Interrupt treatment and start steroids (prednisolone 0.75–1 mg/kg). Treatment can be restarted with a reduced dose. Grade 4 (life-threatening pneumonitis): Start treatment with intravenous steroids (e.g., methylprednisolone 2–5 mg/kg). Discontinue treatment permanently. Workup including BAL is recommended.
Hyperglycemia	Educate patients regarding symptoms of hyperglycemia. Grade 2 and 3 hyperglycemia (glucose > 8.9 mmol/L): Treat according to guidelines, focus on avoiding symptomatic hyper- and hypoglycemia.

Table 3 summarizes management recommendations for common and drug class–specific toxicities of mTOR inhibitors.

Abbreviations ADL, activities of daily living; BAL, bronchoalveolar lavage; BSA, body surface area; LuFT, lung function test; SOB, shortness of breath.

Toxicity of Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are a well-established component of the treatment paradigm for RCC, and their efficacy has now also been demonstrated in the adjuvant setting.[36–39] While CPIs are well tolerated by many patients, immune checkpoint blockade is associated with a unique collection of irAEs. These irAEs behave very differently from the more predictable toxicities oncologists are accustomed to managing with chemotherapy

or targeted therapies, occurring any time between initiation of treatment to many months after its cessation, waxing and waning in severity, affecting every organ system in the body with potentially permanent and, on rare occasions, life-threatening consequences.

Mechanism, spectrum, and frequency of CPI-associated toxicities

Mechanisms of immune-related adverse events

The exact mechanisms responsible for the development of irAEs are not fully understood. The immune checkpoint proteins cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 receptor (PD-1) play important roles in immune homeostasis and self-tolerance, acting to suppress T-cell function. CTLA-4 signalling reduces T-cell proliferation early in the immune response, and PD-1 signalling inhibits activated T cells in peripheral tissues.[40] While inhibiting these pathways enables the immune system to recognize and attack the patient's cancer, the inflammation of normal tissues through the production of cytokines, autoreactive T cells, and autoantibodies may occur and lead to irAEs.[41,42]

Range of immune-related adverse events

The spectrum of irAEs experienced depends upon the CPI in question, whether the CPI is used in combination or alone, and according to the malignancy being treated, along with yet poorly understood host factors such as an individual's genetics, epigenetics, and microbiome. Overall, dermatological, gastrointestinal, endocrinological, musculoskeletal, and pulmonary irAEs are more common, while renal, hematological, ophthalmological, cardiac, and neurological irAEs are rarely seen.[43,44] Colitis, hypophysitis, and rash are more frequently observed with anti–CTLA-4 antibodies, whereas pneumonitis, hypothyroidism, arthralgia, and vitiligo are more often associated with anti–PD-1 antibodies.[45] In practical terms, these distinctions are relative and the spectrum of irAEs may occur with any of the CPI agents. Across solid tumour types, patients treated with a single-agent anti–PD-1 antibody have the lowest rates of irAEs (grade ≥3 irAEs, 6%), followed by a single-agent anti–CTLA-4 antibody (grade ≥3 irAEs, 24%); patients receiving combination therapy having the highest rates (grade ≥3 irAEs, 55%).[46] In addition, irAEs tend to present earlier with combination regimens.[46]

IrAEs demonstrate specific patterns of presentation, with dermatitis and colitis typically presenting early in treatment, followed by hepatitis and endocrinopathies, and then pneumonitis and nephritis presenting later.[46,47] However, it should be noted that these irAEs have a variable, overlapping, and wide range of onset times, and physicians must always have a high index of suspicion for their presence in patients being treated with CPIs. Fatal irAEs are fortunately rare with CPIs, with reported rates ranging from 0.36% with anti–PD-1 antibodies, 1.08% with anti–CTLA-4 antibodies, to 1.23% in combination.[48] Myocarditis has the highest irAE fatality rate, although the leading cause of CPI-related death is due from colitis with anti–CTLA-4 antibodies and pneumonitis with anti–PD-1 antibodies.[48]

Frequency and severity of immune-related adverse events

The frequency and severity of irAEs do not appear to be dose dependent and there is no role for dose reduction following CPI toxicity, although higher rates of toxicity have been reported with the increased doses of ipilimumab used in melanoma treatment. For example, in early phase trials in RCC, a better safety profile resulted with the lower dose of ipilimumab (1 mg/kg rather than 3 mg/kg) being selected for the phase 3 combination study, CheckMate-214.[37,49] This finding has not been replicated with nivolumab. As oncologists gain experience with CPIs in different solid tumours, certain irAEs are reported to more likely occur in some tumour types than in others. In a systematic review including 573 patients with RCC, pneumonitis and dyspnea were reported to be the more common irAEs in RCC patients treated with anti–PD-1 antibodies than in melanoma patients, but arthralgia, hypothyroidism, rash, pruritis, and diarrhea were more common in the melanoma patients.[45]

Immune-related adverse events in RCC

Multiple clinical trials have now specifically investigated the use of CPIs in RCC. Their safety outcomes and summarized in **Table 4**. CheckMate 025 investigated nivolumab versus everolimus as second- or subsequent-line treatment in patients with advanced RCC.[36] Grade ≥3 TRAEs occurred in 19% of patients on nivolumab versus 37% of patients on everolimus, with fatigue being the most common, affecting 2% patients of nivolumab. TRAEs leading to nivolumab discontinuation occurred in 8% patients, but there were no treatment-associated deaths in the nivolumab arm. CheckMate 214 investigated the combination of nivolumab and ipilimumab versus sunitinib in the first-line treatment of patients with advanced RCC.[37] Grade ≥3 TRAEs occurred in 46% of patients on combination immunotherapy and in 63% of patients on sunitinib, with fatigue (4%) and hypertension (16%) being the most common TRAEs, respectively. TRAEs leading to discontinuation occurred in 22% of patients on immunotherapy and in 12% of patients on sunitinib, with <1% TRAEs leading to death in both groups. KEYNOTE-564 investigated adjuvant pembrolizumab versus placebo following nephrectomy.[38] Grade ≥3 TRAEs were reported in 18.9% of patients on pembrolizumab and in 6% of patients on placebo, with diarrhea being the most common grade ≥3 TRAE in patients treated with pembrolizumab (1.6%). TRAEs led to treatment discontinuation in 17.6% of patients on pembrolizumab, with no treatment-associated deaths.

The frequency of adverse events reported in these pivotal trials of CPIs in RCC are outlined in **Table 4**.[36–38] Safety results from the recently published extended follow-up for the CheckMate 025 and 214 studies are consistent with these data, with no new safety signals or treatment-related deaths reported.[50,51] These landmark clinical trials demonstrate that CPIs are generally well tolerated in patients with RCC, with small percentages of patients experiencing grade 3 or 4 toxicities and <1% patients dying because of treatment. Furthermore, studies considering patient-reported outcomes have noted that with both single-agent and combination-immunotherapy treatment, patients with advanced RCC experienced fewer symptoms and reported a better health-related quality of life (HRQoL) than with single-agent everolimus and single-agent sunitinib, respectively.[51,52] The toxicity of CPIs in combination with small-molecule tyrosine kinase inhibitors is considered later in this chapter.

TABLE 4 Safety Outcomes Reported in Pivotal Registration Clinical Trials of Immune Checkpoint Inhibitors in Renal Cell Carcinoma

	Nivolumab mRCC, 2nd or later-line, CheckMate 025, NCT01668784,[36] *n*=406		**Nivolumab & Ipilimumab** mRCC, 1st line, CheckMate 214, NCT02231749,[37] *n*=547		**Pembrolizumab** adjuvant setting, KEYNOTE-564, NCT03142334[38] *n*=488	
TRAE leading to discontinuation in %	8		22		21	
Death due to TRAE—*n* (%)	None		8 (1)		2 (<1)	
Toxicity in %	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Any	79	19	93	46	79	19
Fatigue	33	2	37	4	30	1
Pruritis	14	0	28	<1	23	<1
Nausea	14	<1	20	1	16	<1
Diarrhea	12	1	27	4	25	2
Decreased appetite	12	<1	14	1	-	-
Rash	10	<1	22	1	20	1
Cough	9	0	-	-*	16	0
Dyspnea	7	1	-	-*	-	-
Pneumonitis	4	1	-	-*	-	-
Hypothyroidism	-	-	16	<1	21	<1
Asthenia	-	-	13	1	10	<1
Vomiting	-	-	11	<1	-	-
Arthralgia	-	-	-	-	22	<1
Headache	-	-	-	-	14	0
Hyperthyroidism	-	-	-	-	12	<1
Increased creatinine	-	-	-	-	10	<1

Table 4 shows safety outcomes that were reported in the referenced pivotal registration clinical trials.

*While cough, dyspnea, and pneumonitis were not reported, in the combination arm of the CheckMate 214 study, 1 patient died from pneumonitis, 1 with pneumonia, 1 with immune-mediated bronchitis, and 1 with lung infection.

Abbreviations: NR, not reported in paper; TRAE: treatment-related adverse event.

Management of CPI-associated toxicities

General principles for management of immune-related adverse events

The management of irAEs in patients with RCC is the same as that in other solid tumours and detailed guidelines are available from ESMO, American Society of Clinical Oncology (ASCO), Society for Immunotherapy of Cancer (SITC), and the National Comprehensive Cancer Network (NCCN).[44,54–56] The guidelines have been developed based on consensus opinion from physicians from multiple disease specialties who manage autoimmune conditions, alongside oncologists' experience from clinical trials. These guidelines are more detailed than those available for toxicities from targeted therapies. Readers are strongly encouraged to use these to guide management of specific toxicities, particularly in this actively evolving field in order to ensure they are following the most up-to-date approach. Therefore, this section describes the principles of managing irAEs rather than discussing specifics of toxicity management by organ system, which should be taken from one of the above guidelines.

The overarching principle of management is to control the inflammation that has precipitated the irAE. In the guidelines, irAEs tend to be graded according to the CTCAE used in clinical trials but it is important to note that these criteria were not developed for irAEs and may over- or underestimate severity and at times be difficult to apply.[44] Depending upon the severity of the irAE, management may involve prompt use of immunosuppression, usually in the form of corticosteroids, together with interrupting or permanently discontinuing treatment. Hospitalization and specialist management are required in the more serious cases. Indeed, referral to a disease specialist is recommended in all cases not responding rapidly to simple steroid treatment, particularly for neurological, cardiac, and pulmonary irAEs, where early specialist treatment may be life-saving.

Corticosteroids and sparing-sparing agents in immune-related adverse events

In general, for CTCAE grade 1 irAEs, corticosteroids are not required, and immunotherapy may be continued.[44] For grade 2 irAEs, oral prednisone (or equivalent) may be considered, starting at 0.5–1 mg/kg daily. If there is no improvement, the dose may be increased to 2 mg/kg daily. Immunotherapy is paused until the irAE has resolved to grade 1 or less and the steroids have been weaned, usually over 4–6 weeks. For grade ≥3 irAEs, oral prednisone at 1–2mg/kg daily, or equivalent intravenous methylprednisolone, is started and immunotherapy is withheld. If there is no improvement in 2–3 days, alternative immunosuppressants are required. Following grade 2 irAEs, a 4–6 week steroid taper is initiated after the irAE improves. Restarting immunotherapy treatment may be considered on a case-by-case basis after a grade 3 irAE, but immunotherapy is discontinued after grade 4 irAEs. Most irAEs are reversible with steroid treatment, but endocrinopathies, especially hypothyroidism, may require lifelong hormone replacement. It should also be noted that CPI-induced thyroid disorders and CPI-induced diabetes rarely require steroid treatment.

As outlined above, in severe or refractory cases where the irAE is not responding to corticosteroid treatment, or where steroid sparing is desirable, other immunomodulatory agents may be considered. These agents may have specific immune targets such as TNF-α (infliximab), IL-6 (tocilizumab), and α4 integrin (vedolizumab) or be nonselective (mycophenolate mofetil, cyclophosphamide, methotrexate, azathioprine, intravenous immunoglobulin, and plasmapheresis).[57] In such cases, liaising with specialist physicians, ideally with an interest in both the affected organ and irAEs, is of paramount importance.

Treatment rechallenge after an immune-related adverse event

In some cases, it may be possible to rechallenge patients with CPI after they have experienced an irAE. Whether to restart treatment will depend on several factors: the severity and control of the irAE, whether the patient is being treated in the metastatic or adjuvant setting, and the availability of other treatment options, as well as the status of the cancer. While in clinical trials, rechallenge after a grade ≥3 toxicity was not permitted, selected patients may benefit from rechallenge, in a carefully considered, case-by-case manner with multidisciplinary support and as described below.[58,59]

RCC outcomes in patients who experience immune-related adverse events

Although the development of irAEs is not required for the patient to benefit from CPI, there are some data to suggest that patients who experience irAEs have better outcomes, particularly with anti–PD-1 and anti–PD-L1 treatment.[60,61] This phenomenon has been reported in patients with RCC, although these studies have tended to be small.[62–65] When required for the management of irAEs, high-dose steroid treatment is not thought to impact outcomes negatively, although there are conflicting reports in the literature and patients receiving high-dose corticosteroids at baseline do appear to experience inferior outcomes.[41,61] Immunosuppression with steroids is also not without risk and may be associated with a myriad side effects including hyperglycemia, weight gain, hypertension, edema, gastritis, anxiety, adrenal insufficiency, osteoporosis, glaucoma, proximal muscle weakness, and opportunistic infections.[41] Supportive therapies must therefore be considered for all patients on steroids, including gastric protection, calcium and vitamin D, and pneumocystis pneumonia prophylaxis, particularly for patients requiring a longer course.

At present, there is little evidence base underlying the current guidelines and within the field there is concern regarding the excessive use of immunosuppression, particularly with corticosteroids. High-quality, prospective studies are required to establish the optimal management of irAEs, ideally based on the pathophysiology of the irAE, and it is likely that guidelines will evolve over the coming years.

Toxicities of Combination VEGFR TKI-CPI Regimens

Regimens that combine a VEGFR TKI with a CPI have become the standard of care in first-line therapy of advanced RCC due to improved cancer outcomes compared with TKI monotherapy. Four different TKI-CPI regimens are now approved and used in practice globally.[66–69] Collectively, these regimens are regarded as having acceptable

safety profiles with manageable toxicity. The studies that have reported HRQoL (KEYNOTE-426; CheckMate 9ER) have shown superiority over the previous standard of sunitinib monotherapy. Given the impressive cancer control conferred by these regimens, patients are often on treatment for many months or years, thus good toxicity management is of great importance for durable good quality of life.

Spectrum and frequency of toxicities with TKI-CPI combination regimens

The registration trials of approved TKI-CPI combinations have reported a variety of safety endpoints and toxicities, each compared with sunitinib monotherapy. Although there are differences across both the trial populations and the toxicity measures reported, the data illustrate the quite good tolerability of each of the regimens in trial populations. These data and the common toxicities reported in each trial are summarized below and described in **Table 5**.

TABLE 5 Safety Outcomes Reported in Pivotal Clinical Trials for the Combinations of Tyrosine Kinase Inhibitors and Immune Checkpoint Inhibitors in First-Line Metastatic Renal Cell Carcinoma

	Axitinib + Pembrolizumab 1st line, KEYNOTE-426, NCT02853331, *n*=429		**Axitinib + Avelumab** 1st line, JAVELIN Renal-101, NCT02684006, *n*=442		**Cabozantinib + Nivolumab** 1st line, CheckMate 9ER, NCT03141177 *n*=322		**Lenvatinib + Pembrolizumab** 1st line, CLEAR, NCT02811861 *n*=355	
Treatment discontinuation for TRAE in %								
Both drugs	8		8		3		13	
Either	26		NR		15		37	
Treatment-related deaths—*n* (%)	4 (<1)		3 (<1)		1 (<1)		4 (1)	
Toxicity in %	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Any	96	63	100	71	100	61	100	82
Diarrhea	54	9	62	7	64	7	61	10
Hypertension	45	22	50	26	35	13	55	30
Fatigue	39	3	42	4	32	3	40	4
Hypothyroidism	35	<1	25	<1	34	<1	47	1

TABLE 5 Safety Outcomes Reported in Pivotal Clinical Trials for the Combinations of Tyrosine Kinase Inhibitors and Immune Checkpoint Inhibitors in First-Line Metastatic Renal Cell Carcinoma *(Cont'd)*

Decreased appetite	30	3	26	2	28	2	40	4
Hand-foot syndrome	28	5	33	6	40	8	29	4
Nausea	29	1	34	1	27	1	36	3
Increased ALT	27	13	17	6	28	5	12	4
Increased AST	26	7	15	4	25	3	11	3
Dysphonia	25	<1	31	1	17	<1	30	0
Cough	21	<1	23	<1	17	0	20	0
Constipation	20	0	18	0	12	1	25	1
Arthralgia	18	1	20	1	18	<1	28	1
Decreased weight	18	3	20	3	11	1	30	8
Proteinuria	18	3	-	-	10	3	30	8
Dyspnea	16	2	20	3	-	-	15	3
Stomatitis	16	1	24	2	17	3	35	2
Headache	16	1	21	<1	16	0	23	1
Vomiting	15	<1	18	1	17	2	26	3
Asthenia	15	3	15	3	22	<1	22	5
Pruritis	15	<1	14	0	19	<1	17	<1
Rash	14	<1	14	1	22	2	27	4
Back pain	13	1	18	1	18	2	17	1
Mucosal inflammation	13	1	14	1	21	1	-	-
Pyrexia	13	0	13	0	12	1	15	1
Abdominal pain	11	1	14	1	16	2	2	2
Dysgeusia	11	<1	13	0	24	0	12	<1
Increased lipase	-	-	-	-	17	6	18	13
Hyponatremia	-	-	-	-	16	9	-	-
Increased amylase	-	-	-	-	15	3	18	9

Table 5 shows the safety outcomes that were reported in the referenced pivotal trials and occurred in at least 15% of patients who received the VEGFR TKI–CPI combination.

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CPI, immune checkpoint inhibitor; NR, not reported in paper; TRAE, treatment-related adverse event; VEGFR TKI; vascular endothelial growth factor receptor tyrosine kinase inhibitor.

Safety outcomes in phase III trials of TKI/CPI regimens

KEYNOTE-426 investigated the TKI-CPI combination of axitinib + pembrolizumab.[67] The rate of of grade ≥3 TRAEs was 63% with the axitinib + pembrolizumab combination, with the most frequently occurring TRAEs being hypertension, raised transaminases, and diarrhea. Discontinuation of at least one of the agents due to TRAE occurred in 26% of patients and discontinuation of both agents in 8%. In HRQoL analyses, no clinically important difference was observed over a 30-week treatment period. JAVELIN Renal 101 investigated axitinib in combination with the anti–PDL-1 inhibitor avelumab.[68] Rates of grade ≥3 TRAEs were similar between the combination and sunitinib arms, at 57% and 55%, respectively. In the combination arm, the most frequently occurring grade ≥3 TRAE was hypertension (24%), while 8% of patients discontinued both study treatments owing to a TRAE. CheckMate 9ER assessed the TKI-CPI combination of cabozantinib with nivolumab.[69] TRAEs of grade ≥3 were reported in 61% of patients with the combination and 51% with sunitinib. The most frequently occurring grade ≥3 TRAEs with the combination were hypertension (11%) and ALT rise (9.8%). Discontinuation of one or both study drugs occurred in 15% and 3%, respectively; 71.9% of patients had at least one nivolumab dose delay and 68.1% had at least one cabozantinib dose delay. HRQoL analyses assessed by FKSI-19, reported a significant difference ($p<0.05$) between treatment groups throughout the study benefitting the TKI-CPI combination arm. CLEAR investigated the TKI-CPI combinations of lenvatinib plus pembrolizumab and lenvatinib plus everolimus compared with sunitinib.[66] Rates of grade ≥3 TRAEs were higher for in both lenvatinib-containing combinations (72–73%) versus sunitinib (59%). For the pembrolizumab-plus-lenvatinib combination, the most common grade ≥3 TRAE was hypertension (25%). Discontinuation of one or both agents occurred in 37% and 13% of patients, respectively.

Management of toxicities associated with TKI-CPI combination regimens

Optimal management of the toxicities from TKI-CPI combination regimens requires appreciation of the expected range of side effects of each agent and knowing how to manage them in accordance with guidelines from ESMO, ASCO, SITC, and NCCN, and the principles described previously in this chapter. However, there is additional complexity, as some toxicities may be caused by both TKIs and CPIs. An approach for identifying the more likely cause is required, where knowledge of expected toxicities from each agent and the half-lives of each drug can be helpful, as can additional diagnostic investigations in select cases.

1. **Common toxicities from each class of agents and timing of onset**
   The common and serious toxicities resulting from VEGFR TKIs and CPIs are described above. For example, hypertension, mucositis, and hand-foot syndrome are more commonly caused by VEGFR TKIs; pruritus, arthritis, and pneumonitis are more commonly caused by CPIs, while toxicities such as diarrhea, and liver and endocrine dysfunction may be caused by both TKIs and CPIs. Toxicity caused by VEGFR TKIs most commonly manifests in the first few weeks following treatment initiation, whereas toxicities caused by immune CPIs can start acutely, many months into treatment, or even after treatment

discontinuation. However, there is considerable variation at the individual patient level, so reliable attribution can be challenging.

2. **Half-lives of the agents**
   VEGFR TKIs have considerably shorter half-lives than CPIs. Axitinib has the shortest half-life at 2.5–6 hours while the half-lives of lenvatinib (28 hours) and cabozantinib (100–120 hours) are somewhat longer. The half-lives of both pembrolizumab and nivolumab are around 26 days. Thus VEGFR TKI–driven toxicity, especially from axitinib, typically starts to improve within a few days of treatment interruption, including when used in an axitinib + CPI combination.[70]

3. **Directed investigations**
   In some cases, directed investigation may help to differentiate the cause, assess impact and severity, and guide management such as: sigmoidoscopy and biopsy for evaluation of colitis; assessment of the pituitary fossa by MRI for endocrine toxicities that may be attributable to hypophysitis; and cardiac MRI to identify immune-mediated myocarditis.

When a likely responsible agent is identified and graded, toxicity should be managed in accordance with the strategies described earlier in this chapter. This includes using supportive therapies as well as treatment interruption, dose reduction (for TKIs but not CPIs), and treatment discontinuation when indicated. As a general principle, grade 1 and 2 toxicities may not require any intervention other than supportive therapies and monitoring. Grade 3 and higher toxicities usually require at least temporary treatment interruption. When treatment interruption of a TKI-CPI regimen is required and there is uncertainty about the cause the following pragmatic approach is suggested:

- First stop the TKI. This allows assessment for improvement in toxicity, which should be seen over a few days if the toxicity is related to TKI treatment.
- If there is no improvement after 5–10 days (3–5 days, or less for axitinib), interruption of the CPI and initiation of steroids should be considered in accordance with the grade of toxicity following a recognized irAE guideline.
- Consider immediate interruption of both agents for severe, clinically significant toxicities.
- Continue to use appropriate supportive measures according to the toxicity.
- Ongoing regular assessment is required until improvement or resolution with vigilance for reemergence during steroid wean or following further treatment.

Toxicities of Novel Therapeutic Approaches

Ongoing clinical trials are investigating new agents and combinations that will require attention to their tolerability and emergent toxicity management as well as their efficacy. COSMIC-313 (NCT03937219) is a fully recruited, randomized trial assessing the triplet combination of cabozantinib plus ipilimumab and nivolumab in 840 patients with intermediate- and poor-risk advanced RCC.[71] While there should be careful scrutiny of the

tolerability of this triplet regimen, the combination has been successfully delivered in a pan-genitourinary phase 1B trial with acceptable tolerability in the trial population.[72]

The hypoxia-inducible factor (HIF)-2α inhibitor belzutifan received approval from the FDA in 2021 for the treatment of von Hippel-Lindau (VHL)-associated mRCC,[73] and its role in sporadic mRCC is being evaluated in a phase 3 trial after promising initial results in a phase 1B study of heavily pretreated patients with mRCC (NCT04195750).[74] Belzutifan is relatively well tolerated, although grade ≥3 AEs were reported in 25% of patients. Common toxicities reported in this study included fatigue (64%), headache (39%), and dizziness (38%). In addition, treatment with belzutifan was associated with grade ≥3 anemia (27%) and hypoxia (16%), thus monitoring and active management of these toxicities is essential. Mechanistically, a decrease in hemoglobin is related to inhibition of the erythropoietin gene by belzutifan.[73] Anemia should be managed according to guidelines including blood transfusion and/or the use of erythropoietin-stimulating agents.[75] Hypoxia may require treatment interruption for oxygen saturation <88% and grade 4 hypoxia should trigger permanent discontinuation.

Ongoing trials are investigating a range of other agents including a variety of new CPIs, agents targeting anti-LAG 3, vaccines, pegylated interleukin (NKTR-214), and others. This promising range of approaches heralds the possibility of other new toxicities with which treating physicians will need to become familiar to optimally manage patients in the future.

Reinitiating Treatments after Toxicity

The presenting grade of toxicity, the speed and degree of toxicity resolution, and the ensuing clinical risk associated with toxicity recurrence potentially at a higher grade, together with current disease status, should be used to guide the appropriateness and timing of restarting treatment. It is possible to reintroduce most agents after a grade 2 toxicity, but treatment reinitiation should be considered more carefully for grade 3 toxicities and is rarely appropriate following a grade 4 toxicity. For patients treated with combination therapy, it may be prudent to consider switching to a single agent for those who have significant comorbidities, are of less good performance status, or have a low burden and/or grade of cancer. In practice, before restarting treatment:

- Allow toxicities to improve to no worse than grade 2 and ideally grade 1.
- If cancer status allows, allow for a longer period to ensure the patient is stable with only mild residual toxicity.
- Before restarting a CPI, corticosteroids should be weaned, usually to no more than 10 mg prednisone or equivalent.
- When restarting VEGFR TKIs, consider whether dose or schedule modulation may play a role in allowing for a better balance between efficacy and tolerability.

A strategy employing the steps described should result in improvement of the toxicity and continuation of treatment in most cases. This approach has been evaluated in a focused hepatic event analysis of the 217 patients

in KEYNOTE-426 who developed liver dysfunction.[76] As expected, a higher rate of grade ≥3 transaminitis was seen with the TKI-CPI combination (22%) compared with sunitinib alone (7%). The study also showed that 120 of the 125 (96%) axitinib-pembrolizumab patients who required treatment interruption for transaminitis had improvement to grade 2 or less. Among the 100 patients who were later rechallenged with treatment, while 45% had recurrence of grade ≥3 transaminitis, all had subsequent resolution and there were no deaths attributable to liver toxicity. These results illustrate that with careful toxicity monitoring and management, including treatment interruption and use of steroids, such toxicities are manageable, and it may be possible to reintroduce treatment successfully.

Patient Selection and Toxicity Prediction

It is widely appreciated that good patient selection is an important tool in ensuring the optimal balance between efficacy and acceptable toxicity and quality of life. The toxicities associated with treatment of RCC are not insignificant, leading to discontinuation of VEGFR TKI therapy in 12–24%,[77,78] combination nivolumab plus ipilimumab in 22%,[78,79] and immunotherapy (IO)-TKI combinations in 6–11%.[66–69] In addition, toxicity rates are typically higher in real-world populations than those reported in trials. Therefore, understanding predictors of toxicity is an important area of research to assist in the personalization of therapy selection, dosing, and maintenance of good quality of life. Most research in this field to date has evaluated clinical and genomic predictors of toxicity to VEGFR TKI therapy. Low body surface area, older age, and female gender have been described as clinical predictors of toxicity to sunitinib.[80] A greater number of dose-limiting toxicities have been noted in patients with a Charlson comorbidity index ≥9 (69 vs. 40%, p=0.004), with the index score also noted to be an independent predictor of dose-limiting toxicity (hazard ratio [HR], 4.30; p=0.002).[81]

Toxicity of RCC therapies in elderly patients and patients with brain metastases

Specific patient groups have been assessed for their ability to tolerate mRCC treatments. Studies in elderly patients with mRCC have demonstrated no significant differences in overall survival or time to treatment failure compared to younger patients treated with TKIs[82,83] or CPIs.[84,85] Older age should therefore not preclude patients with advanced RCC from receiving appropriate therapy. In addition, patients with brain metastases should also not be automatically excluded from treatment with TKIs or CPIs, as demonstrated by a subgroup analysis of the registration study of sunitinib,[86] and the CheckMate 920 study of nivolumab. In this small study of patients with RCC with previously untreated and asymptomatic brain metastases, the safety profile of nivolumab was similar to that seen in the randomized phase 3 trial CheckMate 214, with no new safety signals and with encouraging efficacy.[86,87]

Biomarker and pharmacogenomic predictors of VEGFR TKI–related toxicities

Several studies have focused on the role of single-nucleotide polymorphisms (SNPs) in genes related to pharmacodynamic and pharmacokinetic properties and drug targets of agents such as sunitinib. The largest study of 333 patients sought to validate candidate SNPs that were previously identified in smaller cohorts.[88] In this study, *CYP3A5*1* was significantly associated with a need for dose reductions (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.0–4.0; p=0.039). Although the criteria for significance were not met, the T allele of *FLT3* rs1933437 was associated with a higher risk for leukopenia and the G allele in *VEGFA* rs1570360 was associated with hypertension. In a study of patients with mRCC treated with sunitinib looking specifically at *CYP3A4*, *CYP3A5* and *ABCB1*, the A allele at CYP3A4 rs464637 was associated with a lower rate of high-grade toxicities.[89] However, this same SNP was associated with a higher risk for hypertension in another cohort,[90] without an association with high-grade toxicities. This study highlights the challenge of such analyses in relatively small cohorts. Pharmacogenomic differences may also exist between patients with different ethnic backgrounds. In a study of 97 patients of Asian heritage, a stronger association of the *FLT3 738T* genotype with leukopenia was observed in comparison to previous reports in Caucasian patients. While research has not yet yielded practice-influencing results, it is hoped that large collaborative projects such as the EuroTARGET cohort,[91] incorporating analysis of genomic, transcriptomic, and clinical parameters will produce clinically useful information.

Biomarker predictors of CPI-related toxicities

There are currently no defined biomarkers that predict toxicity to immune CPIs, although some patients are at greater risk of experiencing irAEs. Careful patient selection is therefore important, especially where other treatment options may be available.[41,46] Historically, as patients thought to be at higher risk for irAEs have been excluded from clinical trials, data is lacking; however, as real-world experience grows, multidisciplinary strategies for managing such patients are evolving. Patients with chronic viral infections such as hepatitis and HIV, mild-to-moderate organ dysfunction, autoimmune disease, and even transplant recipients have been successfully treated with CPIs.[59] While there are no absolute contraindications to treatment with CPIs in patients with RCC, a personalized discussion regarding potential risks and benefits is required to enable shared decision-making. This is particularly important in more challenging cases, such as patients with symptomatic autoimmune conditions and transplants, who are at increased risk for irAEs.[41,46] Support from specialist physicians and close surveillance are always required in such cases. One study that focussed on risk factors for CPI-induced acute kidney injury (AKI) showed an association with preexisting lower estimated glomerular filtration rate (eGFR), concomitant use of proton pump inhibitors, and development of extrarenal irAEs. However, when this was limited to stage II and III AKI, a lower eGFR was not predictive.[92] There is growing interest in the role of the gut microbiome in modulating both the efficacy and toxicity of CPI therapy. In patients with advanced melanoma who received ipilimumab plus nivolumab, enrichment with *Bacteroides intestinalis* and *Intestinibacter bartlettii* was seen in patients who developed grade ≥3 adverse events versus those who did not.[93] Investigation of this field continues, including in mRCC.

Future considerations for toxicity from RCC therapies

In the future, as doublet, and potentially triplet, combination regimens are increasingly used, effective strategies to mitigate and minimize additional toxicity will be needed to transfer clinical trial regimens to more diverse real-world patient populations. Strategies include confirming the optimal therapeutic approach in different pathological subtypes of RCC, and in differing RCC risk categories, to ensure that incremental toxicity is merited in terms of additional clinical benefit. In the future, genomic approaches may offer the possibility of refining treatment selection for patients according to expected toxicity profiles. However, at present, there are no robust or validated genomic predictors, therefore patient selection is reliant on traditional measures of performance status and comorbidities. Accurate prediction of treatment toxicity remains a field requiring further research.

Summary

Toxicity management is an essential component of effective cancer control. In the past 15 years, considerable experience has been gained in the management of the side effects of molecularly targeted therapies with strategies including dose modification, schedule modification, switching between agents, and use of supportive therapies. Immune checkpoint inhibitors are also now used widely in the treatment of mRCC. This advance has necessitated oncologists treating patients with RCC to develop an understanding of a new range of toxicities and become familiar with new strategies and algorithms that have evolved to manage irAEs, including use of corticosteroids and steroid-sparing agents, as well as to seek the increased involvement of other organ or system-specific specialists. Combination regimens of CPIs and VEGFR TKIs are now increasingly used. These doublet, and potentially in the future triplet, regimens confer increased frequency and severity of adverse events, which require careful management to balance optimized treatment delivery with tolerable side effects. It is hoped that ongoing research will identify robust means of prospectively identifying those at increased risk for treatment-related toxicities to allow for improved therapy selection at an individual level.

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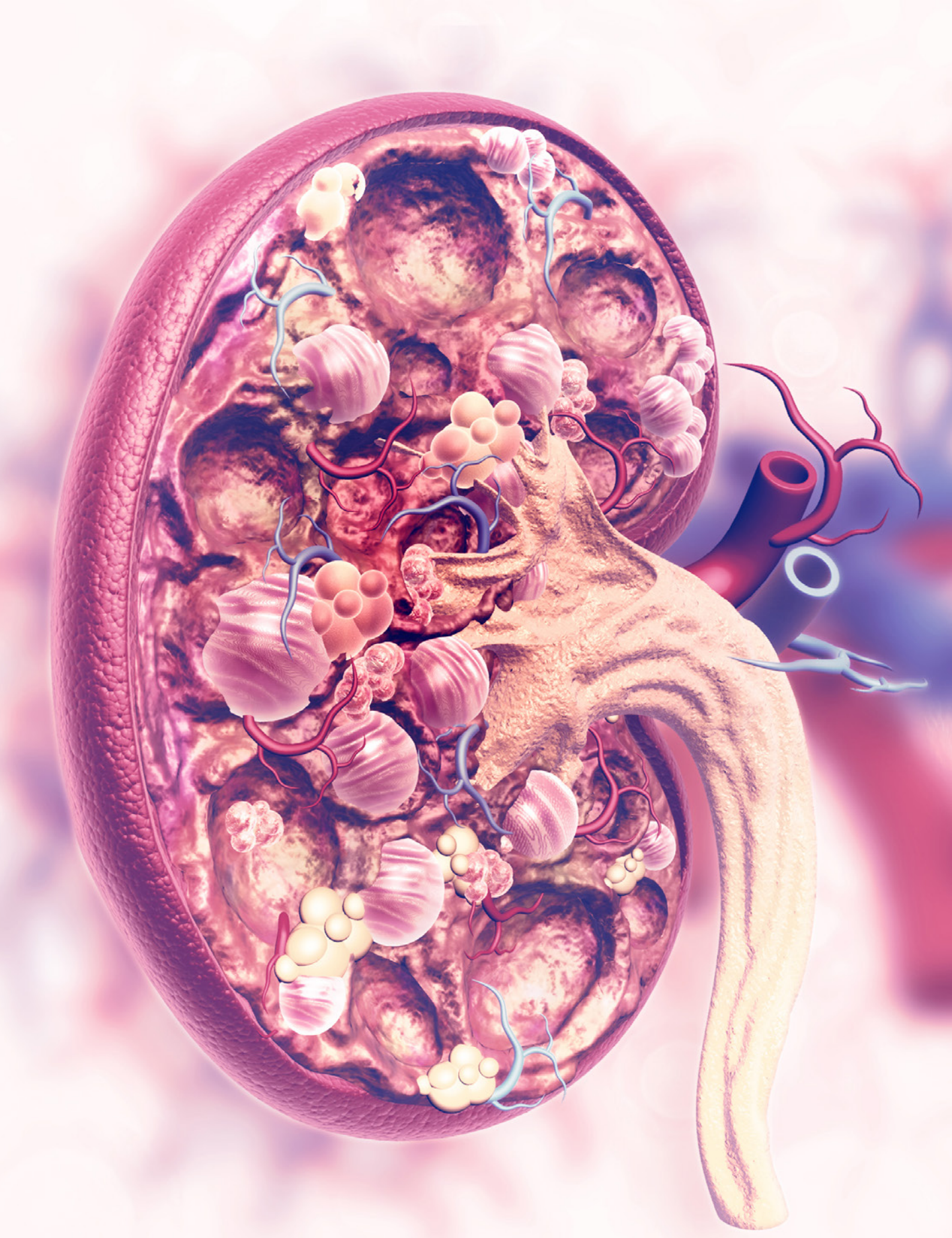

COMMITTEE 16

Cytoreductive Nephrectomy and Metastasectomy

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The chapter is dedicated to Christopher Griffith Wood (1963–2021).

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Table of Contents

Introduction

The question of the place of cytoreductive nephrectomy (CN) in locally advanced or metastatic kidney cancer is crucial. Since the availability of tyrosine kinase inhibitors (TKIs), then immune checkpoint inhibitors (ICIs), and now combinations, the therapeutic sequence becomes fundamental: when to propose CN?

The place of CN in the history of renal cell carcinoma (RCC) is discussed in the section written by Dr. Kazutoshi Fujita and Dr. Hirotsugu Uemura. The role of CN "in real life" is discussed in the next section.

In the following section, Dr. Laurence Albigès contributes with analysis of the literature to see whether the CARMENA results could be extrapolated to ICIs.

In the next section, Dr. Anil Kapoor analyzes retrospective studies and the contribution of nomograms and classifications in determining the value of CN.

Finally, in the last section of this chapter, Dr. Marc-Olivier Timsit analyzes the contribution of metastasectomy and its limitations in the case of oligometastatic RCC (mRCC).

With this short introduction, I wanted to thank so much all the authors of this chapter for their immense work of reading, analysis, consistency, and nuance. Science is moving and we know that today's truth will be outdated tomorrow. Nevertheless, this work of synthesis has had the enormous interest of convincing us that we must always remain humble, curious, moderate, and receptive to all new strategies, critical in the analysis of scientific literature, and attached to the clinical experience that nothing can replace. I would also like to give special thanks to Dr. François Audenet for his help with the layout of the final document.

I would also like to thank the editors for giving me the honor of coordinating this chapter of this prestigious book. Finally, I would like to pay tribute to our friend Christopher Griffith Wood (1963–2021) for his immense scientific contribution to the surgical treatment of kidney cancer. This chapter is dedicated to him.

History of Management of mRCC with Surgery

Renal cell carcinoma represents 4.0% of all cancers and the 8th most common cancer in the United States. Estimated death from RCC in 2021 was 13,780, accounting for 2.3% of all cancer deaths.[1] Death rate from RCC is gradually decreasing since 2000. While 65% of cases are diagnosed as localized disease, 16% of cases have regional lymph node metastasis and 16% have distant metastasis. The prognosis of localized disease is good with more than 90% of 5-year survival, but the 5-year survival of patients with distant metastasis is 13%.[1] The common metastatic sites are lung (45%), bone (30%), lymph nodes (20%), liver (20%), adrenal (9%), and brain (8%). Approximately 60% of patients with mRCC have multiple concomitant metastatic sites.[2]

The systemic therapy for mRCC has been drastically changing over decades. Accordingly, the role of CN has changed. Currently, molecular targeted therapy, such as VEGR-TKI and mTOR-I, immune checkpoint inhibitors, or their combination therapy is available for patients with advanced RCC. The development of these drugs has improved the survival of patients with mRCC. In the era of cytokine therapy, the 5-year overall survival (OS) of patients with metastatic RCC was 18%, while the 5-year disease-specific survival was 22% in the era of molecular targeted therapy.[3] Until the era of molecular targeted therapy, cytokine therapy was the only option for the treatment of mRCC. The anti-tumour effect of interferon-alpha for mRCC was first reported in 1983.[4] In 1985, the remarkable response of the systemic administration of autologous lymphokine-activated killer (LAK) cells and recombinant interleukin-2 for patients with mRCC was reported.[5] However, the response rate of cytokine therapy was low. The response rate of interferon-alpha and interleukin-2 was around 3% and 6%, respectively.[6] Thus, cytoreductive nephrectomy or metastasectomy was the option to manage patients with mRCC. Furthermore, the finding that CN combined with cytokine therapy showed considerable response for mRCC was reported in the 1990s.[7] However, arguments existed on whether CN may improve survival, as CN delays the start of cytokine therapy and tumours progress during the perioperative period. To address this issue, two randomized controlled trials were initiated. The Southwest Oncology Group (SWOG) initiated the prospective randomized controlled trial to test whether CN with cytokine therapy improved OS.[8] A total of 241 patients with mRCC were randomized to the interferon-alone group or the nephrectomy-plus-interferon group. Approximately two-thirds of cases had only lung metastasis. The nephrectomy-plus-interferon group showed significant improvement in overall survival (median survival, 11.1 months) compared with the interferon-alone group (median survival, 8.1 months). This landmark study provided evidence that cytoreductive nephrectomy followed by interferon alfa-2b therapy for mRCC had a survival benefit. The European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group also reported results of randomized controlled trial of CN for patients with mRCC. Eighty-three patients with mRCC were randomly assigned CN followed by interferon-alpha immunotherapy or immunotherapy alone. Five patients showed the complete response in the CN group, and one patient in immunotherapy-alone group. Progression-free survival (PFS) and OS were significantly better in the CN group.[9] The combined analysis of these two randomized trials showed that CN improved OS with a 31% reduction of death.[10] Since then, CN has been recommended in patients with good performance status and the lung-only metastasis and without poor prognostic factors.[11]

After the US Food and Drug Administration (FDA) approved sorafenib for advanced RCC in 2005 and sunitinib in 2006, the era of molecular targeted therapy has begun. Sorafenib and sunitinib are tyrosine kinase inhibitors that inhibit vascular endothelial growth factor receptor-2 (VEGFR-2), VEGFR-3, and platelet-derived growth factor receptor (PDGFR). Sorafenib prolonged progression free-survival in a phase 3, randomized trial in patients with advanced RCC compared with placebo.[12] Sunitinib also showed longer OS compared with interferon-alpha in the first-line treatment of patients with mRCC. The objective response rate (ORR) was 47% for sunitinib compared with 12% for interferon-alpha.[13]

Based on the role of CN in interferon therapy, it was hypothesized that CN followed by molecular targeted therapy improved the survival of patients with mRCC. In fact, several retrospective observational studies showed the CN improved survival.[14–16] In contrast, the rate of CN for patients with mRCC has declined since 2005.[17] In 2001, in

the era of cytokine therapy, approximately half of patients with mRCC underwent CN, but in 2008, in the era of targeted therapy, the percentage of patients who underwent CN had declined to 40%.[18]

The European Society for Medical Oncology (ESMO) 2016 Guideline still recommends CN in patients with good performance status and large primary tumours with limited volumes of metastatic disease and for patients with symptomatic primary tumours.[19] However, the selection bias of the patients who received CN would exist in the retrospective analysis. The patients who are likely to have poor survival may not have received CN by physician discretion. Even after adjustment for various factors, such as age and risk factors, hidden cofounding factors would affect the prognosis. To address this issue, two randomized controlled trials, CARMENA and SURTIME, were initiated for patients with mRCC. The CARMENA trial started in 2009 and randomized 450 patients with metastatic clear cell renal cell carcinoma to CN followed by sunitinib or sunitinib alone. The results showed that sunitinib alone was not inferior to CN followed by sunitinib in OS.[20] The SURTIME trial recruited 99 patients with mRCC from 2010 to 2016. Patients were randomized to immediate CN followed by sunitinib or treatment with 3 cycles of sunitinib followed by CN (the deferred group) Deferred CN did not improve the PFS rate at 28 weeks, but more patients received sunitinib and OS was higher in the deferred-CN group compared with the immediate-CN group.[21] Molecular targeted therapy before CN could identify the patients who are resistant to molecular targeted therapy and do not benefit from CN. Although there are several limitations with these two randomized trials, the results indicate that immediate CN is no longer recommended as a standard of care for patients with mRCC.

The European Association of Urology (EAU) 2021 Guideline strongly recommends not to perform CN in Memorial Sloan Kettering Cancer Center (MSKCC) poor-risk patients and weakly recommends not to perform CN for intermediate-risk patients. CN is weakly recommended for patients with a good performance status who do not require systemic therapy or patients with oligometastasis when complete local treatment of metastasis can be achieved.[22]

The post-hoc analysis of the CARMENA study showed that for patients with two or more International Metastatic RCC Database Consortium (IMDC) risk factors, OS was significantly longer with sunitinib alone than with nephrectomy plus sunitinib (31.2 vs. 17.6 months, respectively; hazard ratio [HR], 0.65; p=0.03). However, in patients with one IMDC risk factor, OS was longer for nephrectomy plus sunitinib versus sunitinib alone, although not significantly (31.4 vs. 25.2 months; HR, 1.30; p=0.2). Patients with only one IMDC risk factor may benefit from CN, and patients with lung metastases only could be the best candidates for immediate CN.[23] The ESMO 2019 Guideline stated that the results of CARMENA and SURTIME should not be used to abandon CN in patients with low-volume metastatic disease, a good PS, and favourable and intermediate risk, who are candidates for initial observation.[24]

In the current immuno-oncology (IO) era, IO therapy improved OS compared with molecular targeted therapy. In 2018, the CheckMate 214 trial showed that 18-month OS of patients with mRCC who received the IO combination therapy ipilimumab plus nivolumab was 75% (95% confidence interval [CI], 70–78) compared with 60% (95% CI, 55–65) for patients who received sunitinib.[25] CheckMate 9ER showed that the OS at 12 months was 85.7%

(95% CI, 81.3–89.1) with nivolumab plus cabozantinib and 75.6% (95% CI, 70.5–80.0) with sunitinib. The ORR was 55.7% in the patients receiving nivolumab plus cabozantinib and 27.1% in those receiving sunitinib.[26]

It remains unclear whether findings in the molecular targeted therapy can be applied to IO therapy in CN, but more potent systemic therapy than sunitinib might decrease the benefit of CN.

In contrast, palliative CN still has a role in improving symptoms. Many patients with mRCC are symptomatic. For local symptoms, gross hematuria was found in 19% and flank pain was in 19%. CN improved these local symptoms in 95% of patients. Patients with mRCC showed general symptoms, such as weight loss, anemia, fever, and fatigue. After CN, the proportion with sign or symptom resolution and improvement was 43% and 71%, respectively.[27] Removal of the primary tumour might affect the general symptoms by eliminating the source of tumour-associated cytokine production. CN improved tumour-associated symptoms, such as anemia, fever, and decreased body weight in a subset of patients with mRCC.[28]

Among patients with mRCC, approximately 27% had tumour thrombus.[29] Patients with tumour thrombus are more likely to receive CN compared with patients without tumour thrombus. Analysis of the National Cancer Database showed that CN improved OS in patients with infradiaphragmatic and renal vein inferior vena cava (IVC) thrombus.[29] Molecular targeted therapy had a minimal clinical effect on tumour thrombus. Only 7 patients (44%) of 25 patients with tumour thrombus had a decrease of tumour thrombus by molecular targeted therapy.[30] **Tumour thrombus is a poor prognostic factor, and the surgical removal of tumour thrombus and primary RCC was recommended for patients with nonmetastatic RCC. The role of CN for patients with mRCC and tumour thrombus remains to be studied.**

In conclusion, the role of CN is changing with the development of new systemic therapy for patients with mRCC. Prospective randomized trials are underway to evaluate the role of CN in combination with IO drugs (NCT04510597, NCT04322955). These results could change the strategy for the patient with mRCC.

Cytoreductive Nephrectomy

Cytoreductive nephrectomy was initially defined as surgical removal of the primary tumour before initiation of systemic therapy (initial or immediate CN). Secondary or deferred nephrectomy was defined as surgical removal of the primary tumour after initiation of systemic therapy and most often in the case of good response. Over time, the term CN has come to be used regardless of whether the surgery is performed before or after systemic therapy. It therefore refers to the local treatment of synchronous metastatic RCC.

The availability of multiple and/or sequential systemic therapies has changed the management of locally advanced and metastatic RCC. The question is, in real life, what is the place of CN?

In 2004, the UCLA team published the UCLA score on a study comparing the OS of 3,119 patients with localized high-risk, intermediate-risk, and low-risk RCC and the OS of 1,083 patients with metastatic high-risk, intermediate-risk, and low-risk RCC. The 24-month OS rate of patients with high-risk, localized RCC and those with intermediate-risk, metastatic RCC was 70% and 40%, respectively.[31] In 2020, Escudier *et al.* published the OS data of patients in the CHECKMATE-214 study according to the number of IMDC risk factors.[32] For patients with 2 IMDC risk factors—that is, intermediate risk—24-month OS rate was 70% for those treated with nivolumab plus ipilimumab. In other words, the prognosis of intermediate-risk metastatic patients has drastically improved over the past 16 years with 24-month OS rates of 40% and 70%, respectively.

In 2021, Correa *et al.* published the OS of high-risk localized and locally advanced RCC patients following surgical resection. The OS rate was 70% at 24 months for high-risk patients.[33] The 24-month prognosis of patients with high-risk, localized or locally advanced RCC has not improved in 17 years. The management of high-risk, localized or locally advanced RCC should be a key area of focus considering the prognosis is now similar to intermediate-risk metastatic patients.

While trials investigating treatments in the neoadjuvant or adjuvant setting are ongoing, it will be key to define the place of CN in treatment sequences to improve the prognosis of these patients.

For patients with synchronous metastatic RCC, the CARMENA and SURTIME studies, the only two randomized, phase 3 studies to date, have questioned the benefit of CN. Many retrospective studies, the main one coming from IMDC, have shown better OS in patients who underwent nephrectomy.[34] The most obvious explanation is selection bias, which gives all these studies a low level of evidence because of the different presentation patterns.

The initial selection of patients is essential to define the best place for CN.

For patients with RCC with a single metastasis or an oligometastatic disease (with a definition that varies from one author to another . . .), CN remains the gold standard according to major recommendations associated with focal treatment of the metastasis and a delay in initiating systemic treatment.[24]

In the CARMENA study, by definition, the patients could only be intermediate- or high-risk as they were metastatic and required a systemic treatment. It was therefore impossible to define a good prognosis group. Initial and final results confirmed that patients treated with sunitinib alone did not have poorer OS.[20] It is essential to remember that patients from CARMENA had exclusively synchronous metastatic RCC, explaining the higher percentage of patients with a poor prognosis compared to patients from registration studies of systemic treatments. The population of these studies is much more heterogeneous than the CARMENA population including asynchronous mRCC patients (defined as patients initially treated with nephrectomy for localized or locally advanced RCC and then progressing to metastatic cancer) and synchronous mRCC with favourable, unfavourable, or intermediate IMDC prognosis. As a result, it is complicated, if not impossible, to select exactly the same population to have comparable results.

When a systemic treatment is proposed, the option to perform CN should be discussed in multidisciplinary team meetings.

In the CARMENA trial, which randomized 450 intermediate- or high-risk metastatic patients, the initial and final results confirmed that patients treated with sunitinib alone did not have worse OS. Nevertheless, in the post-hoc analysis published in 2021, it was possible to identify a group of patients for whom CN could be proposed: patients with low-volume metastatic disease and a single intermediate IMDC risk factor.[23] For the others, systemic treatment was indicated as first-line therapy. However, for patients with a complete or near-complete response at the metastatic sites, a secondary CN should be offered to improve survival. The summary of what we have learned from CARMENA is presented in **Figure 1**. This indication is consistent with the results of SURTIME published in 2019 with post-hoc analyses published in 2021. Although this study was not positive for its primary endpoint (PFS), it demonstrated better OS and disease control in the delayed CN group after systemic therapy.[21,35]

In fact, all these results point in the same direction: the best treatment for metastatic RCC is still CN combined with systemic treatment. Only the sequence remains to be defined on a case-by-case basis. Another information provided by CARMENA and SURTIME is that there is no loss of chance for patients initially treated with a systemic therapy—on the contrary, it allowed better identification of patients likely to undergo a CN under the best conditions.

The question now is whether these results can be extrapolated to immunotherapy or combinations of immunotherapy and targeted therapy? It is already known that these new treatments provide better OS than sunitinib and offer great primary tumour volume reduction (more than 30%) for patients without previous CN.[36,37]

This suggests a continuation of the paradigm established by CARMENA and SURTIME of treating patients who require systemic therapy with their primary tumour in place with the option to perform a deferred CN in the case of response at metastatic sites or local symptoms.

The definitive response will come from therapeutic trials, two of which are currently underway. NORDICSUN (NCT03977571) is an open, randomized, multicentre, phase 3 comparison trial designed to evaluate the effect of deferred CN compared with no surgery following initial nivolumab combined with ipilimumab in metastatic RCC patients with IMDC intermediate and poor risk. PROBE (NCT04510597) is a phase 3 trial comparing the effect of adding surgery to a standard of care immunotherapy-based drug combination versus a standard of care immunotherapy-based drug combination alone in treating patients with metastatic RCC.

Recently a friendly controversy was published in *European Urology Open Science* opening the debate for[38] or against CN.[39] The excellent review by Capitanio *et al.* showed the limits of the exercise as long as the results of randomized studies are not published. Nevertheless, the title of this review was nuanced but logical: "Cytoreductive nephrectomy in 2021: obsolete but necessary".[40]

In conclusion, what are the indications for CN in 2022?

- Single metastasis with clear cell RCC
- Oligometastatic disease (low metastatic volume and 1 intermediate IMDC risk factor) with clear cell RCC
- Complete or near-complete response after first-line systemic treatment with clear cell RCC
- Non clear cell metastatic RCC
- No contributive histology
- Very symptomatic patients (gross hematuria, abdominal pain . . .)
- Enrollment of patients in trials

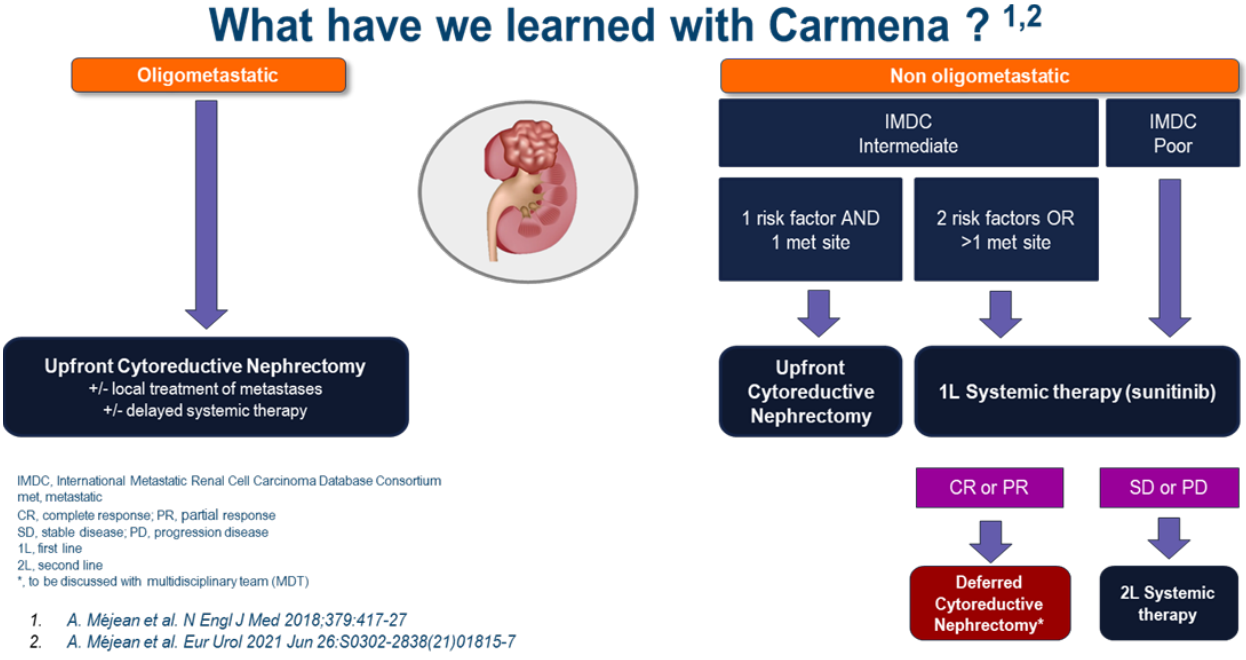

FIGURE 1 What We Have Learned with CARMENA

Source: Courtesy of Dr. Arnaud Méjean, Professor of Surgery, Chair of the Department of Urology, HEGP and Hôpital Necker, APHP, Université Paris Descartes, Université de Paris, Paris, France.

Can We Extrapolate CARMENA's Results to the Immune Checkpoint Inhibitors Era?

Since 2017, the CARMENA trial has changed the daily management of patients with upfront metastatic disease requiring systemic therapy. However, given the approval of 5 new first-line regimens of systemic therapy for metastatic RCC, one critical question has been raised: Would the findings of the CARMENA trial still apply in the immune checkpoint inhibitors (immune-oncology [IO]) combination-based regimens era? To date, no prospective trials have yet answered the question of CN in the IO combination era and retrospective analyses as well as subgroup analysis from pivotal studies have been conducted. Nevertheless, several aspects should already inform our practice.

Combination trials have demonstrated overall survival benefit over single-agent sunitinib

At the time of CARMENA study conduction and results, standard of care for metastatic clear cell RCC was single-agent VEGFR tyrosine kinase inhibitor (VEGFR-TKI).[41] As covered in the systemic therapy chapter of ICUD 2022 e-book, combination trials have transformed the OS of patients with metastatic cancer and established new standards of care in the first-line setting.[42,43] The different regimens either with doublet IO (nivolumab-ipilimumab)[25] or combination of a VEGFR-TKI with an immune checkpoint (axitinib-pembrolizumab, cabozantinib-nivolumab, lenvatinib-pembrolizumab)[26,44,45] demonstrated OS benefits over sunitinib and PFS over sunitinib (axitinib-pembrolizumab, axitinib-avelumab, cabozantinib-nivolumab, lenvatinib-pembrolizumab).[26,44–46] Magnitude of OS benefit currently ranges from 0.65 to 0.68 (HR over sunitinib) on published long-term updates for nivolumab + ipilimumab and axitinib + pembrolizumab, respectively.[47,48] **Given the added benefit of IO combination regimens over sunitinib, it is anticipated that the role of upfront systemic treatment not only remains valid but also may be reinforced with IO-based combination therapies.**

Retrospective cohorts

Retrospective cohorts investigating the role of CN in the IO era have been reported. Singla *et al.* reported on 391 patients, 221 (56.5%) received CN + IO and 170 (43.5%) received IO only. With a median follow-up of 14.7 months, patients who underwent CN + IO had superior OS (median NR vs. 11.6 months; $p<0.001$).[49] IMDC similarly reported among 437 patients, that patients treated with CN followed by IO therapy presented a longer OS versus those treated with IO therapy alone (53.6 vs. 21.4 months; $p<0.001$), and a meta-analysis of these 2 cohorts provided a pooled analysis indicating improved survival with CN (pooled HR, 0.28; 95% CI, 0.16–0.49; I2=21%), with a stronger association in the IO era when compared to pre-IO era ($p=0.01$; I2=0%).[50] Same limitations related to patient inherent bias selection apply to these retrospective series as in the VEGFR-TKI era.

Subgroups analysis from the 5 pivotal studies

Subgroup analysis focusing on the population of patients who did not undergo prior nephrectomy was reported for the 5 pivotal studies leading to IO-based regimen approval. These subgroup analyses are reported in **Table 1**. IO-based combination regimen conferred survival benefits versus sunitinib similar to benefits observed in the overall population. **The benefits of combination regimen over sunitinib remained valid irrespective of prior nephrectomy status.** Notably the population without prior nephrectomy commonly displayed a worse prognosis across these trials as illustrated by the pooled analysis conducted by FDA of the 5 pivotal VEGFR-TKI studies and reported at ASCO 2021 by Fallah *et al.*, with a median follow-up of 15.2 months; patients without prior nephrectomy presented a median OS of 24.5 months (19.6, NR) versus not reached (31.8, NR) for patients with prior CN (HR, 0.53; 95% CI, 0.42–0.68), even after adjusting for established prognostic risk group.[145]

TABLE 1 Summary of IO Combination Pivotal Study—No Prior Nephrectomy Subgroup Analysis

IO-based combination regimen Trial	Total number of patients randomized	No prior nephrectomy population n (%)	Subgroup analyses (HR, 95% CI)	
			PFS	OS
ipilimumab-nivolumab **CheckMate 214**	847	187 (22%)	NA	0.63 (0.42–0.94)
axitinib-pembrolizumab **KEYNOTE-426**	861	143 (17%)	0.68 (0.45–1.03)	0.57 (0.36–0.89)
axitinib-avelumab **Javelin 101**	886	179 (20%)	0.75 (0.48–1.65)	NA
cabozantinib-nivolumab **CheckMate 9ER**	651	196 (30%)	0.63 (0.43–0.92)	0.79 (0.48–1.29)
Lenvatinib-pembrolizumab **Clear**	1,069	272 (25%)	0.40 (0.25–0.65)	0.44 (0.26–0.77)

Abbreviations: CI, confidence interval, HR, hazard ratio; NA, not applicable; PFS, progression-free survival; OS: overall survival.

Timing of cytoreductive nephrectomy

From an oncological standpoint, CARMENA demonstrated the need to use systemic therapy upfront in patients requiring systemic therapy. Such an approach is aiming at treating metastatic disease first: **systemic treatment should be prioritized in the management of patients with upfront metastatic RCC requiring medical therapy**.[16] Therefore, **this concept should remain valid in the combination therapy era**.

TABLE 2 Ongoing Trials

Name of the study	NCT number Study phase	N	Study design	Primary endpoint
Phase 3 trial of Nivolumab and Ipilimumab with or without Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma (PROBE) SWOG-1931	NCT04510597 Phase 3	364	Experimental: nephrectomy and continued systemic therapy Active comparator: continued systemic therapy only	Overall survival
Deferred Cytoreductive Nephrectomy in Synchronous Metastatic Renal Cell Carcinoma: The NORDIC-SUN-Trial (NORDIC-SUN)	NCT03977571 Phase 3	400	Experimental: deferred nephrectomy Surgery after induction therapy (Nivo + Ipi), followed by maintenance therapy (Nivo) Active comparator: no surgery Induction therapy (Nivo + Ipi), followed by maintenance therapy alone (Nivo). All patients will receive induction checkpoint immunotherapy immediately after inclusion. After 3 months or a total of 4 series of nivolumab combined with ipilimumab, whichever comes first, the patient will be discussed for resectability at the multidisciplinary team meeting. Whether the patient is eligible for cytoreductive nephrectomy is at the discretion of the urologist at the local multidisciplinary team meeting. Patients with ≤ 3 IMDC risk factors and deemed suitable for cytoreductive nephrectomy will then undergo randomization.	Overall survival

Ongoing trials in the IO-based combination era

The SURTIME[51] trial, previously presented, raised the questions of delayed CN. The question of delayed CN in the VEGFR TKI has been retrospectively assessed in the IMDC database: among 1,541 patients, 85 (5.5%) received sunitinib followed by delayed CN, at a median of 7.8 months from diagnosis. In multivariable regression analyses, sunitinib followed by delayed CN was significantly associated with improved OS (HR, 0.45; 95% CI, 0.33–0.60]; $p<0.001$) versus sunitinib alone, and these results highlighted that patients who received delayed CN were carefully selected.[52] This question remains valid in the IO combination era and is explored by ongoing studies (PROBE-SWOG-1931 and NORDIC-SUN, **Table 2**). Notably, **on the ground of both CARMENA and SURTIME, these new trials have been designed to optimize patient selection by evaluating tumour response prior to surgery randomization**. In patients specifically experiencing major systemic response (complete response or near-complete response) the question of delayed CN to achieve CR is currently routinely discussed in tumour board and will be prospectively informed by the ongoing trials.

Potential limitations

While both the oncological concept and the magnitude of benefits of IO-based combinations should reinforce the value of upfront use of systemic therapy, several limitations shall be discussed, among which is the activity of systemic treatment on primary tumours and the potential immunomodulating role and tumour burden related to the primary tumour.

Systemic treatment activity on the primary tumour

Cytoreductive nephrectomy remains indicated in patients with symptomatic primary tumours to relieve symptoms. Furthermore, limited antitumour activity on the primary tumour may expose the patient to local disease progression and symptomatic primary tumour.[27] Therefore, the evaluation of primary tumour response to systemic therapy is crucial in the post-CARMENA era.

In the VEGFR-TKI era, a series of 565 patients who received single-agent VEGFR TKI with their primary tumour in place was reported. Among 283 patients receiving first-line VEGFR TKI, the ORR of the primary tumour was 28% (range, 22–33%) in those treated with first-line VEGF-targeted therapy, and 23% (range, 19–28%) in those treated with VEGF-targeted therapy (any line). The primary tumour ORR was 9% (range, 5–13%) and 20% (range, 15–27%) in IMDC poor- and intermediate-risk patients, respectively.[53]

Activity of single-agent IO nivolumab, assessed in 111 heavily pretreated patients as part of the NIVOREN GETUG AFU trial seems limited, with only 6% of ORR on the primary tumour.[54]

Analyses of pivotal studies provided additional insight, with nivolumab-ipilimumab combination therapy providing an ORR on the primary tumour of 35% versus 20% with sunitinib.[55] Similarly, axitinib-avelumab,

reported at ESMO 2019, provided an ORR of 35% on the primary tumour versus 10% with sunitinib alone. And more recently, at ASCO 2021, Grünwald *et al.* reported a reduction of >30% in target kidney lesion in 71% of patients with lenvatinib-pembrolizumab versus 26% with sunitinib. Taken together, these data suggest **that the depth of response on the primary is more important with IO-based combination than sunitinib**.[146] More granularities on symptoms related to the primary tumours and patterns of disease progression are further needed.

Immune system—neoadjuvant and tumour load

The **relation between primary tumour in place and response to IO systemic treatment from an immunological standpoint is not solved**. While a preclinical rationale exists for an IO-based approach in the neoadjuvant setting over adjuvant setting in other tumour models,[56] no models are available specifically for RCC. Ongoing neoadjuvant trials with IO-based combination will explore this approach. However, in the metastatic setting, tumour load has previously been considered to have poor prognostic features in metastatic RCC,[57] and analyses are currently being conducted to investigate whether tumour load itself may hamper the restoration of antitumour immunity by an IO-based regimen.

Conclusion

While the oncological concepts of CARMENA findings seem applicable in the IO-based doublet regimen era, the extended benefit from new combination regimens available reinforces the strategy of potent systemic therapy upfront. The conduction of dedicated phase 3 trials will prospectively answer the question of the role of cytoreductive nephrectomy in the new treatment landscape. Key questions remain around the role of the primary tumour from an immunological standpoint.

Cytoreductive Nephrectomy—Retrospective Trials, Nomograms, and Genomics

Cytoreductive nephrectomy has historically been a standard for patients who presented with metastatic renal cell carcinoma (mRCC). This changed almost overnight with the CARMENA trial and SURTIME trial, which are described elsewhere in this chapter. How did CN become a standard more than 30 years ago? To understand this, we have to go back to early 1990s when interferon alpha-2b and interleukin-2 (IL-2) were used as systemic therapy for metastatic kidney cancer.

Retrospective and prospective trials in the cytokine era

In the early 1990s, cytokine-based therapy was the most effective form of therapy in the armamentarium for patients with mRCC.[8,10] A meta-analysis of more than 6,000 patients from 53 randomized trials confirmed only a 13% probability of either partial or complete response to cytokine-based therapy, underscoring the reality that only a minority will respond.[58]

The role of surgery in mRCC has undergone significant evolution. Historically, in the setting of mRCC, a CN was performed mainly with palliative intent including for palliation of pain, intractable hematuria, and paraneoplastic syndromes.[59,60] Dekernion *et al.* reported in 1978 that nephrectomy alone in the setting of metastatic disease had minimal effect on the survival of patients with metastatic RCC; a widely accepted practice before the cytokine era.[59] The concept of cytoreductive nephrectomy originated from two observations: first, spontaneous regression of metastatic deposits following nephrectomy has been described, although only occurring in less than 2% of the cases.[60,61] Second, in the 1990s with the emergence of cytokine-based immunotherapy, early series suggested an apparent survival benefit in patients found to have had previous nephrectomy.[62–66] **Table 3** summarizes the various retrospective series that have examined the role of CN preceding cytokine-based immunotherapy.[7,67–75]

TABLE 3 Role of Cytoreductive Nephrectomy in Preparation for Immunotherapy in Selected Retrospective Series

Study	Number of patients	Operative mortality n (%)	Unable to receive BRM therapy n (%)	Overall response n (%)	Complete and partial responses n (%), n (%)	Median survival (months)
Rackley *et al.*[67]	37	1 (2.7)	8 (21.6)	3 (8.1)	0 (0.0), 3 (8.1)	12
Wolf *et al.*[68]	23	0 (0.0)	6 (26.1)	3 (13.0)	2 (8.7), 1 (4.3)	23.5
Bennett *et al.*[69]	30	5 (17)	23 (76.6)	4 (13.3)	3 (10.0), 1 (3.3)	30
Franklin *et al.*[7]	63	0 (0.0)	7 (11.1)	19 (33.9)	7 (12.5), 12 (21.4)	22
Fallick *et al.*[70]	28	1 (3.6)	2 (7.1)	11 (39.3)	5 (17.9), 6 (21.4)	21
Walther *et al.*[71]	195	2 (1.0)	74 (37.9)	19 (17.8)	4 (3.7), 15(14.0)	NR
Figlin *et al.*[72]	62	0 (0.0)	7 (11.3)	19 (34.5)	5 (9.1), 14 (25.5)	14
Levy *et al.*[73]	66	2 (3.0)	12 (18.1)	NR	NR	NR
Wood *et al.*[74]	126	3 (2.0)	5 (4.0)	NR	NR	12
Mosharafa *et al.*[75]	32	3.0	21 (65.6)	NR	NR	NR

Abbreviations: BRM, biological response modifier; NR, not reported.

Source: Reprinted with permission Wolters Kluwer Health, Inc., from: Kwan KG, Kapoor A. Cytoreductive nephrectomy in metastatic renal cell carcinoma: the evolving role of surgery in the era of molecular targeted therapy. Curr Opin Support Palliat Care. *2009;3(3):157–165. doi:10.1097/SPC.0b013e32832e466b.*[147]

Table 4 Prospective Randomized Control trials of Interferon-α vs. Interferon-α with Cytoreductive Nephrectomies

		Median survival (months)			Response to therapy (%)				
Trial	Number of patients	Interferon	Surgery + interferon	*P*	Interferon	Surgery + interferon	*P*	Unable to receive immuno-therapy n (%)	Operative mortality n (%)
SWOG[8]	241	8.1	11.1	0.05	3.3	3.6	NS	NR	1 (0.8)
EORTC[9]	8	7	17	0.03	12	19	0.38	NR	1 (2.4)
Combined[10]	331	7.8	13.6	0.002	5.7	6.9	0.60	9 (5.6)	2 (1.4)

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; NR, not reported; NS, not significant; SWOG, Southwest Oncology Group.

Source: Reprinted with permission Wolters Kluwer Health, Inc., from: Kwan KG, Kapoor A. Cytoreductive nephrectomy in metastatic renal cell carcinoma: the evolving role of surgery in the era of molecular targeted therapy. Curr Opin Support Palliat Care. *2009;3(3):157–165. doi:10.1097/SPC.0b013e32832e466b.*[147]

Although nephrectomy alone clearly offered no curative benefit in the setting of mRCC, CN was proposed to have a role when done in conjunction with cytokine-based immunotherapy. Unfortunately, the studies, being retrospective in nature, are all subject to selection bias making conclusions difficult to interpret. The largest series reported included 195 patients who underwent CN with resection of adjacent or contiguous metastases prior to undergoing IL-2 therapy. The overall response rate was 18%, with 4% and 14% complete and partial response rates, respectively. The median survival was not reported in this series. Overall, these retrospective single-institution studies showed a favourable response of 8% to 39%, with a median OS of 12 to 30 months.[7,67–75]

The role of debulking radical nephrectomy was then validated in two prospective randomized controlled trials. In 2001, the results of the EORTC Genitourinary Group Trial 30 947 and the SWOG Trial 8949 showed improved survival for patients who underwent CN before systemic cytokine-based immunotherapy with interferon-α (IFN-α) when compared with patients treated with immunotherapy alone.[8,9] In the pooled analysis of the EORTC and SWOG trials, Flanigan *et al*. demonstrated a median survival duration of 13.6 months for patients in the CN-plus-interferon arm compared with 7.8 months for the interferon-monotherapy arm (**Table 4**).[10]

Cytoreductive nephrectomy seemed to improve the OS in patients with mRCC treated with IFN-α independent of patient performance status, site of metastases, and presence of measurable disease, though these two trials

did not stratify the number of metastatic sites or overall tumour burden. As a result, a transformation in the management of mRCC consisted of CN followed by the administration of biologic disease modifiers such as IFN-α or IL-2.

Historical cytoreductive nephrectomy: the pros and cons

The mechanisms responsible for the survival benefit of CN are still not clearly understood. There are a number of hypotheses and theoretical benefits to performing nephrectomy prior to starting a systemic treatment for mRCC. Nephrectomy removes the symptoms related to the primary tumour such as pain and hematuria, which may in turn improve performance status (PS) and therefore improve prognosis. In addition, palliation of symptoms due to disease burden or paraneoplastic syndromes may be achieved by removal of the primary tumour. It has also been suggested that the reduction in tumour burden itself may enhance the potential of an immune-mediated response to systemic treatment, that removal of the tumour actually benefits the patient as a surrogate for removal of a source of immunological entities that underlie paraneoplastic syndromes. Mosharafa *et al.* reported in their series of 32 patients that 72% had a PS equal to or improved compared to their preoperative status.[75] Furthermore, CN downsizes the overall disease burden, the concept of debulking, which may also remove a source of future additional metastases.[9,76]

It has been documented that the primary lesion in mRCC rarely responds to cytokine-based immunotherapy. In a report of 51 patients who were not candidates for CN prior to IL-2 by Wagner *et al.*, there was only a 6% overall response rate with no responses seen in the primary tumour.[77] Similarly, Sella *et al.* reported 17 patients who underwent IFN-α immunotherapy and 88% of patients had viable tumour at the time of nephrectomy.[78] The SWOG and EORTC trials also reported similar response rates to immunotherapy between the randomized arms (**Table 4**).

Reducing the tumour burden may also remove the immunological "sink" for activated immune cells, taking into account the previously documented spontaneous regression of predominantly lung metastases following nephrectomy.[79] The proposed theory relates to the tumour drawing and trapping antibodies and circulating immune cells, interfering with signal transduction, antigen processing, and expression of major histocompatibility complexes. An additional theory is related to the angiogenic properties of RCC. Increased levels of serum vascular endothelial growth factor as well as other angiogenic growth factors have been documented in patients with RCC. The biology of debulking nephrectomy and the potential immunological and angiogenic consequences in RCC has been reviewed.[80] Other advantages to CRN include the ability to confirm histology and more accurately stage the tumour.[81,82]

The SWOG and EORTC trials suggested that CN in the setting of mRCC can reduce local tumour complications, significantly reduce overall tumour burden, and potentially improve responses to cytokine-based immunotherapy with a lengthened OS time. However, others suggest that there is significant morbidity associated with CN and a potential for serious complications, in particular the presence of metastasis is an independent predictor of

perioperative mortality following open nephrectomy. In instances where intractable hematuria is the indication for nephrectomy, other less morbid and invasive techniques such as angioinfarction are also viable options. Moreover, in the setting of pain, CN rarely alleviates these local symptoms. Some studies reported up to 60% of patients who underwent CN were unable to receive systemic therapy.[83–86] Moreover, patients with rapidly progressive disease are even less likely to derive benefit from CN and will only bear the associated morbidities. In the SWOG and EORTC trials, 20–25% of patients in each arm of the study with rapidly progressive disease died within 4 months of study enrollment.[87]

Prognostic factors and nomograms

Patient selection is a fundamental factor in determining whether CN will be beneficial in the treatment regime. There is no universally accepted clinical prognostic nomogram to determine which patients would be suitable for CN. With the inconsistent response to CN and subsequent therapy, several investigators have attempted to identify characteristics that would predict a favourable response to therapy or outcome. The goal is to define predictors to determine which patients with mRCC would derive the most benefit from CN.

In the Wood *et al.* series, length of stay after nephrectomy, tumour grade, preoperative white blood cell count, and partial thromboplastin time were significant predictors of survival in 126 consecutive patients undergoing CN.[74] Furthermore, the authors suggested that pretherapy tumor biopsy would be warranted to rule out unfavourable histology such as sarcomatoid variants, collecting duct tumours, and other unconventional tumours that traditionally yield a poor prognosis.[88]

Leibovich *et al.* evaluated 727 patients undergoing radical nephrectomy for RCC at the Mayo Clinic who presented with metastatic disease or progressed to metastatic disease.[89] They reported that constitutional symptoms at the time of nephrectomy, presence of bone or liver metastases, metachronous and synchronous metastatic lesions, metastatic disease at nephrectomy, progression to metastatic disease with 2 years after nephrectomy, presence of tumour thrombus, Fuhrman nuclear grade 4, and tumour necrosis were all predictors of poor survival. Complete resection of all metastatic sites was associated with improved survival. The authors recommended an aggressive surgical approach to mRCC with CN and metastasectomy and established a scoring system and algorithm to predict survival in the setting of mRCC.[89]

Another algorithm by Leibovich *et al.* was created based on the retrospective review of 173 patients to predict survival after nephrectomy and IL-2.[90] Multivariate analysis revealed positive lymph node status, presence of constitutional symptoms, location of metastatic lesions at unfavourable sites, sarcomatoid features, and an elevated thyroid-stimulating hormone were all associated with poor survival. Furthermore, in the retrospective series by Fallick *et al.* where patients underwent CN before IL-2, the authors reported central nervous system involvement, bone or liver metastases, poor pulmonary and cardiac function, an Eastern Cooperative Oncology Group (ECOG) PS of 2–3, and a resection of less than 75% of the tumour burden to be poor prognostic characteristics.[70]

Similarly, other series have also shown that the presence of lymph node metastases is associated with poor outcome after cytoreductive nephrectomy and systemic therapy.[91,92] The presence of bone metastases has been shown in other series to be an independent predictor of poor prognosis while others have shown a more favourable prognosis.[93,94] Serum C-reactive protein levels and erythrocyte sedimentation rate have been described as prognostic factors in multivariate analyses.[95,96]

Several authors have also demonstrated that poor performance status is also a powerful predictor of outcome following CN and therefore an ECOG PS <2 has been used as a selection criteria for CN and systemic therapy trials.[97,98] Patients with poor performance status have a limited survival and many are unable to receive adjuvant systemic therapy following CN. In the retrospective series by Mani *et al.*, patients with ECOG PS of 1 have a shorter median survival compared to patients with ECOG PS of 0 (6 vs. 15 months; $p<0.001$).[66] Drawing for the SWOG and EORTC randomized trials that included patients with only an ECOG PS of 0–1, 98% of the patients received adjuvant therapy.

Furthermore, it has been observed that performance status is associated with more aggressive features such as high-grade and -stage disease, lymph node metastases, and sarcomatoid features.[99] In the analysis of 154 patients with mRCC at the National Cancer Institute undergoing CN before IL-2, median survival in lymph node–positive patients was found to be significantly inferior to that of patients with lymph node–negative disease (8.5 vs. 15 months; $p<0.001$).[91]

Several studies have also noted that patients with ECOG PS of 2–3 represent a heterogeneous group. There are those who have impaired performance status due to bony metastases and those with functional decline due to visceral metastases.[99,100] Han *et al.* retrospectively analyzed factors that predict outcome after CN and found that patients with lung-only and bone-only metastases who underwent CN followed by immunotherapy had a longer median survival compared with patients who had multiple metastases (31 vs. 13 months; $p<0.001$).[101] Based on a better response rate to systemic therapy and overall prognosis, the authors concluded that patients with bony-only metastases should be considered for CN followed by immunotherapy and that patients with multiple metastatic sites do poorly overall.

A number of multivariate outcome-prediction models and nomograms have been developed based on patient and disease characteristics as described above.[102–104] One of the most widely used models is derived from a cohort of 400 patients treated with IFN-α at the Memorial Sloan Kettering Cancer Center (MSKCC). Five prognostic factors correlated with OS in patients with metastatic RCC treated with INF-α as initial systemic therapy. The factors were Karnofsky PS, time from diagnosis of RCC to treatment with INF-α , serum lactate dehydrogenase (LDH), corrected serum calcium, and hemoglobin.[105] In 2005, Mekhail *et al.* reported the Cleveland Clinic Foundation (CCF) modified MSKCC prognostic criteria with the addition of two independent prognostic factors: prior radiotherapy and sites of metastasis.[106]

Studies have also evaluated predictors of oncologic outcome in patients treated with targeted therapies.[107,108] Even with the targeted therapies, prognostic variables identified in patients treated with cytokine-based

immunotherapy remain relevant. Motzer *et al.* reported multivariable analyses of baseline characteristics in 375 patients with mRCC treated on the sunitinib arm of a phase 3 trial and found that patient performance status, time to systemic therapy, and corrected serum calcium were independent predictors of PFS.[108] On the basis of outcome data from that trial, the authors developed a nomogram using, in addition to the variables mentioned above, the number of metastatic sites, and the presence of thrombocytosis, for predicting the probability of 12-month PFS for patients who received sunitinib therapy. Although numerous variables have been associated with oncologic outcome after cytoreductive nephrectomy and systemic therapy, there continues to be significant ambiguity with regard to patient selection for surgical debulking.

Cytoreductive nephrectomy in the era of targeted molecular therapy

After the Cytokine era, targeted molecular therapy (TT) emerged as the standard to treat mRCC. The MSKCC criteria[62] and the IMDC criteria[109] stratified patients into good, intermediate, and poor prognosis groups based upon 6 criteria. More than 3 of these criteria conferred poor prognosis, 1–2 intermediate prognosis, 0 good prognosis.

Several retrospective observational studies have investigated the role of CN in patients receiving targeted therapy.[14,15,34,110–119] These observational studies are limited to a varying degree by heterogeneous patient populations, selection bias, and confounding factors, and as a result, the strength of their evidence and related conclusions regarding the benefits of CN are within the limits of these studies. Despite their limitations, nearly all available observational studies have identified a significant survival advantage in favour of CN for patients treated with targeted therapies. In a 2014 analysis from the IMDC, a 40% reduction in all-cause mortality was noted among patients receiving CN after controlling for known biases and adjustment for confounders.[34] In this study, patients with IMDC poor prognosis (3–6 criteria), did not receive benefit from undergoing cytoreductive nephrectomy. Similar findings have been noted across many other multi-institutional and population-based studies.

Cytoreductive nephrectomy in the modern immunotherapy era

Current first-line treatments in mRCC include immunotherapy (IO)–based combinations with nivolumab with ipilimumab in Intermediate- and Poor-risk patients, and IO-TT combinations (pembrolizumab-axitinib, pembrolizumab-lenvatinib, nivolumab-cabozantinib) in Good, Intermediate, and Poor-risk patients. A number of prospective trials are underway to determine the role for CN in the modern IO era. Limited retrospective observational data from the IMDC suggest an OS benefit for patients undergoing CN followed by IO therapy versus IO therapy alone (53.6 vs. 21.4 months, $p<0.001$).

Genomic and molecular biomarkers

Predictors of response with molecular biomarkers are an evolving area of interest. The major driver for mRCC is the genetic or epigenetic loss of von Hippel-Lindau (VHL), which results in the dysregulation of hypoxia-inducible factor (HIF) signalling. Most biomarker research has focused on the VHL pathway, such as VHL mutations, VEGF, HIF, and carbonic anhydrase IX. Other biomarkers studied include Survivin (BIRC5), X-linked inhibitor of apoptosis protein (XIAP), myeloid cell leukemia-1 (MCL-1), nuclear factor-erythroid factor 2-related factor 2 (NRF2), loss of phosphatase and tensin homolog (PTEN) expression, and Kirsten rat sarcoma virus/protein kinase B (KRAS/AKT). Additional mutations involve Polybromo 1 (PBRM1) (40 %), SET domain containing 2 (SETD2) (12 %), and BRCA1-associated protein 1 (BAP1) (10 %).

PBRM1 has been shown to be a predictive biomarker for VEGF TT, with PBRM mutations associated with improved PFS in TT (sunitinib)-treated patients. Positive programmed cell death 1 ligand 1 (PD-L1) expression has been shown to be associated with superior outcomes compared with negative PD-L1 expression in mRCC patients undergoing IO therapy.[120] Tennenbaum *et al.*[121] studied genomic classifiers in patients undergoing cytoreductive nephrectomy. Mutations in SETD2 and KDMSC were associated with a decreased risk for death, while BAP1 mutations were not. Such genomic or molecular biomarkers may help predict patient selection for CN in the future.

Metastasis-Directed Therapy (MDT): Why, When, and How?

Why

The concept of tumour metastasectomy in mRCC has been proposed to defer the use of systematic therapy with encouraging 5-year survival rates of up to 60%.[122] Nowadays, considering the development of metastasis-directed therapy (MDT) options (surgery; stereotactic and image-guided radiotherapy; percutaneous ablation using microwave, radiofrequency, cryotherapy, or electroporation; etc.), along with the impressive ORRs of up to 71% in first-line mRCC obtained with combination therapy,[45] MDT may also serve as a potentially curative treatment in the metastatic setting.

Thus, MDT may be considered: 1) to defer systemic therapy; 2) to improve response rate in combination with systemic therapy, aiming to a complete response; 3) to control progression sites in discordant responses to systemic therapy; and 4) to defer the start of a new line of systemic therapy.

Still, in the absence of randomized controlled trials comparing MDT with observation or systemic therapy, the OS benefit of MDT remains unclear. Considering the inherent bias of retrospective series reporting MDT in mRCC, the current literature allows to assess only feasibility, toxicity, and local disease control rate.

MDT contributes to reach No Evidence of Disease (NED) status, and the comparison of observed OS in NED patients with OS in progressors or partial responders has been proposed as a surrogate to a controlled trial, therefore helping to define indications and modality of MDT in the era of immunotherapy and tyrosine kinase inhibitors (IO/TKI) combinations. Thus, for patients reaching NED after complete removal of metastases, OS ranged from 36.5 to 142 months.[123,124] When merging data from existing retrospective studies, complete metastasectomy was associated with longer median OS compared with incomplete or no metastasectomy (median OS, 40.7 vs 14.8 months, respectively).[125]

Of note, most of studies and trials only included clear-cell histology. Therefore, little is known about MDT benefits for non–clear cell RCC. Considering the limited systemic options in this setting,[126] current practice supports the use of MDT when feasible in non–clear cell metastatic RCC.

When

Prior to the TKI era, patients with solitary site recurrence, disease-free interval greater than 12 months, and age younger than 60 years were considered the best candidates for surgical resection of RCC metastases.[127]

More recently, a large, retrospective, monocentric cohort of MDT in mRCC with patients included from 1989 to 2015 showed an improved (without reaching significance) median cancer-specific survival in treated patients before and after the advent of TKI in 2006 (79.6 and 101.4 months, respectively), suggesting that MDT should be considered whenever complete removal of metastasis could be achieved.[128] In the later study, criteria for reaching NED after MDT on multivariate analysis were: stage < T3, lung-only metastatic site, and absence of sarcomatoid differentiation in the primary tumour. In univariate analysis, impaired renal function (glomerular filtration rate [GFR] < 30 mL/min/1.73 m^2) and presence of multiorgan metastases were adversely correlated to outcome but not the tumour grade of the primary tumour.

Lately, results from KEYNOTE-564 trial investigating the role of adjuvant pembrolizumab after nephrectomy for localized RCC also included oligometastatic patients with NED after cytoreductive nephrectomy and complete resection of metastases.[129] Disease-free survival improvement at 24 months in the treatment arm was markedly observed in the mRCC-NED subgroup (HR, 0.29; 95% CI, 0.12–0.69) showing that surgical resection of metastases remains a valid option in the IO era.

Thus, MDT should be encouraged in: 1) recurrent RCC with solitary site recurrence; 2) *de novo* mRCC with intermediate prognostic factors when cytoreductive nephrectomy and complete resection of metastases are achievable; and 3) for pain management or local symptom control.[125]

Additional data also supports the possibility to repeat MDT in patients with limited site progression and otherwise controlled disease with or without systemic therapy (oligoprogressors). In their retrospective cohort, Holz *et al.*[128] reported on 57 patients with relapse after MDT and initial NED status. Among those, 28% did not recur after second MDT at a median follow-up of 35.2 months, suggesting a potential role for iterative MDT when achieving NED status. Also, in a recently published prospective, single-arm phase 2 trial, MDT using stereotactic radiotherapy was evaluated in oligoprogressors with up to five metastatic sites, reaching its primary endpoint with 93% local control at 1 year.[130] Although encouraging, these results cannot sustain routine MDT in oligoprogressors due to the lack of survival data and to numerous biases: early termination with poor accrual (38 of the planned 68 patients), TKI only as a first-line systemic therapy in the majority of patients, heterogeneity in dose and fractionation schedule, etc.

A Genitourinary Group and French Association of Urology (GETUG-AFU) French, randomized, phase 2 study (Salvage Treatment of OligoRecurrent Nodal Prostate Cancer Metastases [STORM]-O1) is currently recruiting in this setting.

How

MDT can be achieved with invasive and mini-invasive procedures such as surgical resection or thermo-ablation with no existing direct comparison between techniques.

The advent of modern dose-escalated radiation therapy using stereotactic radiotherapy has allowed to reach high doses with low toxicity, breaching the old concept of RCC radio-resistance. Due to its safety profile, stereotactic radiotherapy has been the preferred option in oligoprogressors with multiple sites,[130] whereas surgical resection has the benefits: 1) to provide pathological tissue for biomarker/research purpose; 2) to refine diagnosis and prognosis (for example, thoracic lymphadenectomy associated with lung metastasectomy); and 3) to be associated with additional procedures such as surgical resection of bone metastases associated with cementoplasty to strengthen bone and prevent future fractures.

In the lack of strong evidence for improved survival, MDT should focus on safety and quality of life; thus, choice of MDT technique should be discussed during a multidisciplinary board to personalize options according to the patient's specific situation and to anticipate all additional constraints (tissue biopsy, fiducial marker placement, etc.).

As previously discussed, MDT has been offered to defer the use of systemic therapy or the start of a new line; it has also been proposed to combine MDT with concomitant immunotherapy to improve outcome. Preliminary phase ½ studies have demonstrated the safety of this approach using stereotactic radiotherapy with satisfying cancer control in two different concepts: 1) the use of stereotactic radiotherapy on limited sites as a complement to immunotherapy to obtain an abscopal effect (NIVES and RADVAX trials);[131,132] and 2) the use of stereotactic ablative body radiotherapy with a short course of immunotherapy as a total metastatic ablation to improve cancer control (RAPPORT trial).[133] In the later, 30 patients received SABR to all metastatic sites followed by

pembrolizumab for 8 cycles; despite the heterogeneity of included patients, results showed an encouraging disease control rate at 6 months of 83% with 74% estimated 2-year OS. There were no grade 4 or 5 adverse events, and 13% grade 3 treatment-related adverse events.

Brain metastases

All previously cited studies included mostly extracranial metastases. Patients with brain metastases from RCC experience poor outcome, with a median OS of approximately 10 months and an impaired quality of life.[134]

The limited efficacy of systemic therapies in this setting emphasizes the role for local control. Thus, the largest cohort of mRCC patients with brain metastases treated by sunitinib reported an ORR of 12% with median PFS and OS of 5.6 and 9.2 months, respectively.[135]

More recently, NIVOREN[136] real-life data of patients under nivolumab monotherapy in second or third line, revealed a limited activity of immunotherapy for asymptomatic patients with untreated brain metastases: intracranial response rate was 12%, with no reported objective response in patients with multiple brain lesions or single lesion larger than 1 cm. Median intracranial PFS was 2.7 months and the OS rate at 12 months was 67%. Most patients (72%) needed subsequent focal brain therapy.

Nonetheless, encouraging results have been recently presented with cabozantinib showing an impressive 61% intracranial overall response rate in mRCC patients with progressive brain metastases.[137]

In general, local treatment of brain metastases can consist in whole brain radiotherapy (WBRT) with or without stereotactic radiotherapy, stereotactic radiosurgery (SRS) alone, or surgery.

Stereotactic radiotherapy alone or with WBRT for oligometastatic patients defined by less than 5 brain lesions not greater than 3 cm[138] has been associated with an excellent local control and an overall survival up to 34 months.[139]

With the development of SRS, the benefit of WBRT alone or associated with SRS is unclear.[140] In a trial evaluating the role of SRS and WBRT in brain metastases from RCC, the median OS for SRS-only, SRS-and-WBRT, and WBRT-only was 12, 16, and 2 months, respectively.[141]

Stereotactic radiotherapy may also be associated with surgical resection to improve local control. In a prospective trial including patients with fewer than 4 brain metastases from various primary neoplasms, SRS administered to the resection cavity significantly lowered local recurrence compared with observation alone, suggesting that surgery plus SRS could be an alternative to WBRT.[142] Ippen *et al.* also reported a retrospective series of brain metastases from RCC in 66 patients (77.3% of clear cell type) with single (59.1%) or multiple (40.9%) brain lesions at initial presentation.[143] Data showed an improved OS by combining SRS with surgery. Thus, after stratification by treatment modality (surgery prior to SRS, SRS, and WBRT prior to SRS), the authors reported a median

survival for patients treated with SRS only (n=36) of 13.6 months (95% CI, 6.9–23.5 months) and a median survival of 21.9 months (95% CI, 10.5–70.4 months) for patients who underwent surgical resection (n=24) as an initial treatment. However, the retrospective design of this study cannot allow comparison between treatment modalities.

All together, these data suggest that surgery or SRS might be appropriate to treat a limited number of brain metastases in RCC patients, depending on the individual characteristics and the number, size, and location of brain metastases.

Data are still lacking to robustly assess the benefit of concomitant SRS and systemic TKI/IO combination therapies, but preliminary data recently showed that concurrent IO and stereotactic radiosurgery is a safe approach for the treatment of brain metastases without increasing the risk for radiation necrosis.[144]

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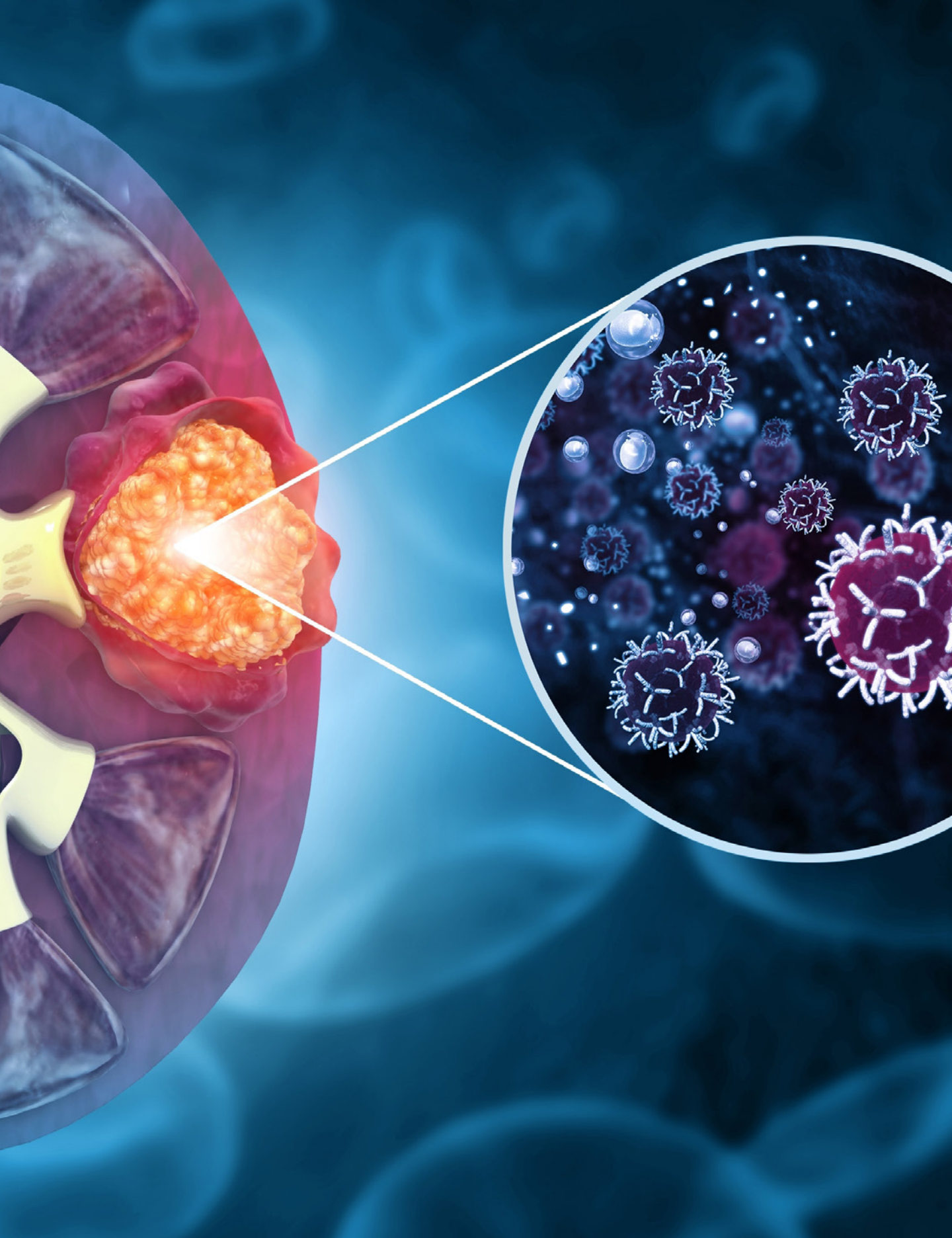

COMMITTEE 17

The Management of Non-Clear Cell Renal Cell Carcinoma

CHAIR

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Abstract

Non-clear cell renal cell carcinoma comprises several rare cancer subtypes that harbour distinct pathological and molecular features. One of their common traits is their poor prognosis in the metastatic setting and their lesser sensitivity to agents otherwise used in clear-cell renal cell carcinoma. Nevertheless, recent developments of targeted therapies with tyrosine kinase inhibitors as well as immune checkpoint inhibitors has helped achieve better antitumour activity and improve outcomes. Combinations of immune checkpoint inhibitors are now being evaluated and may further help patients with papillary renal cell carcinoma, the most frequent of these subtypes. Tailored therapies begin to arise in patients selected for molecular alterations across subtypes. Further improvement in patient management will stem from a better understanding of each tumour subtype, which is still widely unknown and may encompass several molecular entities with different behaviours. These efforts, along with collaborative trials, will be key to implementing better strategies in patients with non-clear cell renal cell carcinoma.

Introduction

Renal cell carcinoma has long been classified into clear cell (ccRCC) and non-clear cell subtypes (nccRCC), the latter encompassing about 25% of all kidney cancer subtypes. These tumours lag clear-cell subtypes in terms of disease comprehension and therapeutic developments, owing to not only their relative rarity but also the complexity of nccRCC biological pathways. Indeed, nccRCC does not represent a single entity, but a heterogeneous set of tumours that harbour differences in ontogeny, molecular features, natural history, and sensitivity to systemic therapies in the metastatic setting.[1]

Multiple histological subtypes have been identified throughout the years: papillary and chromophobe carcinomas being the most frequent and second-most frequent nccRCC subtypes, respectively, while other rare kidney cancers include translocation carcinoma, collecting duct carcinoma, or medullary carcinoma, which are all distinct clinical and pathological entities. Widely used in the clinical practice to guide the treatment of ccRCC, the International Metastatic RCC Database Consortium (IMDC) risk stratification system is the only validated model to predict prognosis in advanced nccRCC.[2,3] Those cancers however share one commonality: nccRCCs exhibit poor prognosis when compared to their ccRCC counterparts in the metastatic setting.[4]

While advances in ccRCC have led to improved outcomes during the past two decades, persistent adverse outcomes in nccRCC have called for new efforts to refine our understanding and develop clinical trials with innovative agents including targeted therapies and immune checkpoint inhibitors. As such, novel therapies have recently emerged, alone or in combination, in several nccRCC subtypes, bringing along novel mechanisms of action and the premise of personalized approaches, raising hopes for better care, and hopefully new opportunities for cure.

The Biological Landscape of Non-Clear Cell Renal Cell Carcinoma

Primary clinical and pathological subtypes of nccRCC

As a highly heterogeneous group of tumours, nccRCCs are primarily made up of clinically and pathologically different tumours, including mainly papillary RCC, chromophobe RCC, collecting duct carcinoma, renal medullary carcinoma, and *MiT* family translocation RCC,[5] with consensus guidelines led by the International Society of Urological Pathology (ISUP) (**Table 1**).[6]

TABLE 1 Main Pathological and Molecular Features of Non-Clear Cell Renal Cell Carcinoma

Non-clear cell renal cell carcinoma subtype	Papillary	Chromophobe	Translocation	Collecting duct	Medullary
Main pathological features	Papillary architecture with fibrovascular cores. Possible psammomma bodies and foam cell macrophages.	Large pale polygonal cells with clear or flocculent cytoplasm, along with smaller cells with eosinophilic cytoplasm.	Pathological aspects may vary depending on the fusion partner. Papillary architecture, possible psammoma bodies. Positive TFE3 expression.	Tubules and papillary structure, infiltrating glandular patterns.	Commonalities with collecting duct carcinoma architecture. Sickled erythrocytes, negative SMARCB1 expression.
Main molecular alterations	*MET* *TERT* *NF2* *SETD2* *FH* *CDKN2A/B*	*TP53* *PTEN* *TERT* *MTOR* Multiple chromosome loss	*TFE3* fusion *TFEB* fusion	*NF2* *SETD2* *CDKN2A*	*SMARCB1*

Papillary renal cell carcinoma

According to pathology, clinical prognosis, and genetic basis, papillary RCC could historically be divided into two main types.[7] Type 1 papillary RCC was characterized by small cells containing basophilic cytoplasm and small oval nuclei with inconspicuous nucleoli.[7,8] For type 2 papillary RCC, the eosinophilic cell within the papillae is much larger and the spherical nuclei are large with obvious nucleoli.[7,8] Clinically, it was acknowledged that the biological behaviour of type 1 papillary RCC was relatively indolent, while type 2 often demonstrated a very aggressive phenotype.[9] Novel insights into the biology of papillary RCC, which resulted in the identification of several distinct molecular profiles, led to a more straightforward classification in 2022 acknowledging only papillary RCC, without specific subtyping. In papillary tumours with former type 2 features, other entities must be ruled out, including translocation carcinoma or fumarate hydratase (FH)-deficient RCC. Compared with ccRCC, papillary RCC is likely to be multifocal although it is localized at diagnosis.[10]

Chromophobe RCC

Derived from the intercalated cell of distal tubules, chromophobe RCC mainly consists of various proportions of two cell types: large and polygonal pale cells with flocculent cytoplasm and smaller cells with granular eosinophilic cytoplasm.[11,12] Although many histological features may predict the chromophobe RCC prognosis such as tumour size, stage, and sarcomatoid differentiation, the World Health Organization (WHO) and ISUP recommended that ISUP grading shouldn't be applied to chromophobe RCC.[13–15] Like for papillary RCC, most patients with chromophobe RCC are at low stage upon diagnosis due to the indolent behaviour of the cancer.[16] Some tumours share radiographic and histological similarity between chromophobe RCC and oncocytoma, and were integrated into the 2016 WHO classification and recommended to be classified as hybrid oncocytic and chromophobe tumours.[17]

Collecting duct carcinoma and renal medullary carcinoma

Different from other RCCs originating from proximal convoluted tubules or from renal pelvis transitional cell carcinoma, collecting duct carcinoma is a highly aggressive epithelial tumour arising from the collecting duct of Bellini.[18] Several architectural patterns may help the diagnosis of collecting duct carcinoma: medullary location, tubules or tubulopapillary structure, infiltrating glandular patterns, desmoplastic stroma, high-grade atypia, and clear-cell RCC or urothelial cancer exclusion.[19,20]

Renal medullary cancer shares similarities with collecting duct carcinoma in terms of prognosis and natural history. It is associated with rhabdoid tumours and arises from patients who are likely to harbour sickle cell disease.[21]

MITF translocation RCC

The 2016 WHO classification established MiT family translocation renal cell carcinoma as a new subtype.[5] These translocation RCCs involve the *TFE3* (Xp11.2) or *TFEB* (6p21) fusion transcripts and are mainly prevalent in

children and adolescents.[22] Historically, MITF translocation RCC was characterized by mixed papillary and nested cells with granular eosinophilic cytoplasm, but pathological presentation may vary.[23] Diagnosis relies on immunoassays targeting TFE3 or TFEB proteins, while fluorescence in situ hybridization (FISH) assays may help make final molecular confirmation.[9,23] Interestingly, *TFEB* gene fusion RCCs are also known for expressing both epithelial immunohistochemical markers and melanoma markers.[9,24]

Main molecular characteristics of non-clear cell renal cell carcinoma

Papillary RCC

About 78% somatic mutations are common within both formerly type 1 and type 2 papillary RCC.[25] According to The Cancer Genome Atlas (TCGA) database, the most common type of somatic change for type 1 papillary RCC is chromosome 7 gains, comprising *MET* gene locus, followed by frequent gains of chromosomes 12, 16, 17, and 20.[7,25–27] Although somatic *MET* mutation occurs in only 13–15% of sporadic type 1 papillary RCC subjects,[28,29] the total rate of *MET* alterations including chromosome 7 copy number gains could reach up to 81%. In addition, *MET* mRNA expression and protein phosphorylation levels may also be significantly elevated in type 1 papillary RCC.[7] However, it's necessary to note that type 2 papillary RCC also harbours a high *MET* mutation rate at nearly 50%.[25,30] In addition to *MET* mutations, both types also share the *TERT*, *CDKN2A/B*, and *NF2* mutations in another larger cohort.[31] Recently, two studies revealed that *NF2* tumour suppressor gene inactivation may be related to the progressive behaviour of papillary RCC.[32,33]

Other subgroups have been identified through the analysis of former type 2 papillary RCC. Those include tumours with *CDKN2A* silencing, with a mutation rate of 25%.[7] Another group demonstrated a high rate of alterations in some chromatin-modifying genes such as *SETD2*, *BAP1*, and *PBRM1*. Interestingly, *PBRM1* mutations were frequently concurrent with *SETD2* mutations. A subset also harboured a CpG island methylator phenotype, which was frequently associated with a fumarate hydratase (FH) gene mutation.[7] The latter entity of fumarate hydratase–deficient RCC will now appear as a distinct RCC subtype in the WHO 2022 classification.

Chromophobe RCC

The TCGA, together with some other reports, have validated frequent whole chromosome loss as the most characteristic pattern of chromophobe RCC, including chromosomes 1, 2, 6, 10, 13, and 17 in more than 80% tumours.[34] *TP53* (32%) and *PTEN* (8%) are the most frequently mutated genes and the mTOR pathway is the most enriched pathway of mutated genes.[27] High heteroplasmy truncating (nonsense or frameshift) mutations of mitochondrial DNA are significantly more frequent in chromophobe RCC samples. In addition, expression of genes involved in metabolism, including the Krebs cycle, electron transport chain (ETC), and pyruvate dehydrogenase complex (PDC), are frequently expressed.[27]

Translocation RCC

MITF translocation RCC involves the translocation of *TFE3* on Xp11.2 as the most common type. Many common fusion partner genes with translocation of TFE3 have been reported, including *ASPL*, *PRCC*, *SFPQ*, *CLTC*, *PARP14*, *LUC7L3*, and *KHSRP*, with new partners still being recently discovered.[35,36] Another type is *TFEB* translocation RCC, and it is relatively rare and reported sporadically. In addition to most common partner fusion genes such as *MALAT1*, genomic analyses have discovered some other partner genes such as *KHDRBS2*, *CADM2*, *COL21A1*, *ACTB*, *EWSR1*, and *CLTC*.[37]

Collecting duct and renal medullary carcinomas

Comparative genomic hybridization has found that recurrent DNA losses at 8p, 16p, 1p, and 9p, and gains at 13p are more frequent with collecting duct carcinoma as compared with other renal tumours and urothelial cancers.[38] Overall, *NF2* is described as the most common type of gene mutation (29%), followed by *SETD2* (24%), *SMARCB1* (18%), and *CDKN2A* (12%), although data is limited in these rare tumour subtypes.[39] Another study revealed recurrent alterations of *CDKN2A* and an altered *CDKN2A*-mediated p53/RB1 pathway.[40] Transcriptomic analyses have shown immune or metabolic deregulations that define collecting duct carcinoma subgroups.[41] Renal medullary carcinomas are characterized by biallelic loss of *SMARCB1* with low mutation frequency of other genes. Aberrant expression *OCT3/4*, a germ cell tumour marker, has also been reported in 71% patients.[42–44] Some reports indicate that renal medullary carcinoma may have commonalities with urothelial carcinomas, including upregulation of long noncoding RNA (lncRNA) urothelial cancer associated 1 (*UCA1*) and dysregulation of the NOTCH pathway.[45]

The immune landscape of non-clear cell renal cell carcinoma

There is much interest in the use of immune checkpoint inhibitors as therapeutic agents in various solid tumours, with renewed interest for immune context and expression of immune pathways. The expression of programmed cell death 1 ligand 1 (PD-L1) on tumour cells has been explored within nccRCC in a retrospective cohort, and it has been reported in up to 30% of translocation RCC, 20% of collecting duct carcinomas, 10% of papillary RCCs, and 6% of chromophobe RCCs.[46]

Each subtype of nccRCC may harbour unique tumour microenvironment phenotypes. Papillary RCC appears to be infiltrated by a large number of macrophages and is associated with immune tolerance, while collecting duct carcinoma has high levels of T and B cells.[47] Additional works indicate however that CD8-infiltrating lymphocytes may also be frequently exhausted in the context of nccRCC.[48] The clinical relevance and predictive value of these data remain unclear but may be first steps to investigating response patterns to immune checkpoint inhibitors. Additional markers known to be associated with response to immune checkpoint inhibitors include tumour mutational burden as well as microsatellite instability status, but several studies reveal that nccRCC harbours a low tumour mutational burden (TMB) and mostly stable miscrosatellites.[49,50]

Hereditary syndromes related to non-clear cell renal cell carcinoma

While most nccRCCs are sporadic, rare familial nccRCC syndromes have also been identified. The activating germline mutations of *MET* result in hereditary type 1 papillary RCC, an autosomal dominant disease.[51] Caused by inactivated mutations of *FH*, hereditary leiomyomatosis and renal cell cancer (HLRCC) is typically classified as type 2 papillary RCC.[52] Other syndromes, including Birt-Hogg-Dubé, characterized by folliculin gene mutations, as well as succinate dehydrogenase subunit mutations, may be responsible for the onset of oncocytic or chromophobe tumours. Overall, genetic testing must be considered for any papillary or chromophobe RCC.

The Uprising of Systemic Therapies in Metastatic Non-Clear Cell Renal Cell Carcinoma

The development of molecular targeted agents

First activity data of molecular targeted agents and historical trials

The biological correlates and ontogeny of nccRCC have been poorly understood, and as such, the development of systemic therapies for metastatic disease first mimicked developments in ccRCC. Since 2006, vascular-endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) as well as mammalian target of rapamycin (mTOR) inhibitors have been developed for use in clear cell and non-clear cell RCC subtypes (**Table 2**).

The VEGFR-targeted TKIa sunitinib and sorafenib first demonstrated activity in retrospective cohorts, achieving objective responses in patients with papillary or chromophobe nccRCC subtypes and prompting dedicated clinical trials.[53,54] The first prospective data stemmed from the phase 2, single-arm study SUPAP, which evaluated sunitinib in papillary RCC and demonstrated an objective response rate of up to 15% in both type 1 and 2 subtypes.[55] Median progression-free survival (PFS) in this trial reached 5.5 and 6.6 months and overall survival (OS) was 12.4 and 17.8 months in type 2 and type 1 papillary RCC, respectively.[55] In a similar timeframe, the phase 2 RAPTOR trial was the first prospective study specifically evaluating the mTOR inhibitor everolimus in nccRCC of papillary subtype.[56] This trial demonstrated evidence of activity of everolimus in papillary carcinoma, with a PFS of 7.9 and 5.1 months in type 1 and 2 papillary RCC, respectively. Overall, median OS reached 21.4 months, with 65% of patients experiencing stable disease.

TABLE 2 Activity of Targeted Therapies in Non-Clear Cell Renal Cell Carcinoma

Agent	Trial phase	Histology	Setting	Patients (*N*)	Reponse rate (%)	Median PFS (months)	Median OS (months)
Sunitinib vs. Everolimus[1]	Phase 2	All nccRCC	L1	108	18 vs. 9	8.3 vs. 5.6	31.5 vs. 13.2
Sunitinib vs. Everolimus[12]	Phase 2	All nccRCC	L1	68	9 vs. 3	6.1 vs. 4.1	16.2 vs. 14.9
Sunitinib vs. Everolimus[3]	Phase 2	All RCC	L1	471	–	7.9 vs. 10.7	–
Everolimus[4]	Phase 2	pRCC	L1	Type 1: 14 Type 2: 43	–	Type 1: 7.9 Type 2: 5.1	Type 1: 28 Type 2: 24.2
Sunitinib[5]	Phase 2	pRCC	L1	Type 1: 15 Type 2: 46	12	Type 1: 6.6 Type 2: 5.5	Type 1: 17.8 Type 2: 12.4
Axitinib[6]	Phase 2	pRCC	L1	44	28.6	6.6 Type 1: 6.7 Type 2: 6.2	18.9 Type 1: NR Type 2: 17.4
Foretinib[7]	Phase 2	pRCC	L1/L2	74	13.5	9.3	NR
Crizotinib[8]	Phase 2	Type 1 pRCC (MET driven and not MET driven)	≥ L1	MET driven: 4 Not MET driven: 16	MET driven: 50 Not MET driven: 11	MET driven: NR Not MET driven: 3	MET driven: NR Not MET driven: 14.5
Savolitinib vs. Sunitinib[9]	Phase 3	pRCC with MET driven	≥ L1	60	27 vs. 7	7 vs. 5	NR vs. 13.2
Lenvatinib + Everolimus[10]	Phase 2	All nccRCC	L1	31	25.8	9.23	15.64
Sunitinib vs. Cabozantinib vs. Crizotinib vs. Savolitinib[11]	Phase 2	pRCC	≥ L1	147	4 vs. 23	5.6 vs. 23	16.4 vs. 20
Bevacizumab + Erlotinib[12]	Phase 2	pRCC with FH deficient (germline or sporadic)	≥ L1	83 HLRCC: 42 Sporadic: 41	51 HLRCC: 64 Sporadic: 37	14.2 HLRCC: 21.1 Sporadic: 8.7	NA

Abbreviations: chRCC, chromophobe carcinoma; FH, fumarate hydratase; HLRCC, hereditary leiomyomatosis and renal cell cancer; NA, not applicable; nccRCC, non-clear cell renal carcinoma; NR, not reported; OS, overall survival; PFS, progression-free survival; pRCC, papillary renal cell carcinoma; tRCC, translocation carcinoma; unRCC, unclassified renal carcinoma.

These single-arm trials brought the first evidence of the relevance of targeted molecular therapies in nccRCC. Three trials ultimately compared everolimus and sunitinib in nccRCC in the first-line setting: the ASPEN trial,[57] the ESPN trial,[58] and the RECORD-3 trial.[59] The ASPEN trial, unlike the previously described SUPAP, AXIPAP, and RAPTOR trials, included chromophobe and unclassified carcinomas in addition to papillary nccRCC subtypes. In this trial, PFS was improved with sunitinib over everolimus, with a respective median PFS of 8.3 months versus 5.6 months. It's worth noting that heterogeneity was described depending on histological subtypes, with chromophobe subtypes appearing to derive lesser benefit from sunitinib, although the limited number of patients with chromophobe carcinoma (n=16) may hamper definitive conclusions. The ESPN trial reached similar results, with a PFS benefit of approximately 2 months with sunitinib as compared with everolimus across nccRCC histologies. The RECORD-3 trial compared the sequence of sunitinib-everolimus versus everolimus-sunitinib in both clear cell and non-clear cell RCC subtypes, demonstrating similar benefit in the subgroup of patients with nccRCC.[60] A meta-analysis of these three trials confirmed the alleged benefit of sunitinib over everolimus in terms of progression-free survival, with a hazard ratio (HR) of 0.71.[61]

Overall, published evidence has led to the emergence of VEGFR inhibitors, led by sunitinib, as a gold standard for the first-line treatment for nccRCC. It is however worth stressing that the overall activity data reported in these studies remains disappointing. Overall response rates struggled to reach 10% while median PFS hovered around 6 months for any agent tested. The alleged benefit of sunitinib over everolimus in these studies also translates neither into overall survival benefit nor into significant response rate benefit,[61] while the rarity of non-papillary nccRCC subtypes also hindered assessments of best therapeutic sequences in these patients. As such, further developments of targeted molecular therapies remain a key endeavour for improving the care of patients with nccRCC.

Novel developments with targeted molecular therapy

Other VEGFR-targeted TKIs have then been evaluated in settings similar to those of previously described trials. Axitinib was evaluated in papillary RCC within the AXIPAP trial across 42 patients, demonstrating interesting response rates that reached nearly 40% in the subset of patients with type 2 papillary RCC, although the median PFS of ~6 months was similar to that previously described for sunitinib in both type 1 and 2 subtypes.[62] Other trials attempted the dual inhibition of the VEGFR and mTOR pathways. The multitargeted TKI Lenvatinib, in combination with everolimus, demonstrated an overall response rate of 26% in 31 patients with nccRCC.[63] Interestingly, the response rate climbed to 44% in patients with chromophobe subtypes (N=9), which constitutes promising activity despite the small number of patients involved. Other combinations targeting angiogenesis and mTOR pathways included bevacizumab and everolimus, with an objective response rate of 37% in papillary and unclassified RCC.[64]

Novel understanding of nccRCC biology and notably the widespread involvement of *MET* alterations in papillary RCC have led to several efforts in targeting this specific pathway. Crizotinib, a *MET*, *ALK*, and *ROS1* inhibitor, demonstrated activity in a nonrandomized phase 2 trial of patients with type 1 papillary carcinoma, although responses were largely restricted to papillary RCC with *MET* alterations, at 50% versus 6% in non-*MET* altered tumours.[65] Foretinib was another *MET*-directed TKI, now discontinued, that demonstrated an overall response rate of 13% in papillary RCC, which increased to 50% in patients with germline MET alterations.[66,67] The most advanced *MET*-targeted agent currently in development is savolitinib, which showed activity in a nonrandomized trial of an 18% overall response rate in patients selected for *MET* alterations, but no activity in patients without these alterations.[68] Savolitinib was thus developed in *MET*-altered (*MET* mutation or amplification, *HGF* amplification) papillary carcinoma and compared against sunitinib in the phase 3 SAVOIR trial.[69] Savolitinib provided higher response rates compared with sunitinib (27% vs. 7%), but PFS and OS were not significantly different despite a trend favouring savolitinib (HR for PFS and OS of 0.71 and 0.51, respectively).

The SWOG 1500 / PAPMET trial, in the context of renewed interest regarding *MET* inhibition, evaluated three agents with MET-targeted activity crizotinib, savolitinib, and cabozantinib against sunitinib in unselected patients with papillary RCC.[70] In this trial, only cabozantinib, a nonselective TKI with potent MET, AXL, and VEGFR inhibitory activity, improved outcomes against sunitinib, with respective response rates of 23% versus 4%, and a median PFS of 9.0 months versus 5.6, respectively. As cabozantinib demonstrated the best activity despite being less selective for *MET* targeting, the real impact of MET inhibition on outcomes is unclear for patients with papillary RCC. These interesting results however confirmed the benefit of cabozantinib in unselected patients with papillary RCC, and cabozantinib can be considered the standard of care in this population. Activity of cabozantinib in other nccRCC subtypes is also hinted through retrospective cohorts, in which responses could be observed in approximately one-third of patients regardless of nccRCC histology.[71] Prospective data in any nccRCC subtype will likely emerge from the CABOSUN2 trial evaluating cabozantinib versus sunitinib in untreated nccRCC (NCT03541902).

Other novel interesting targets involve tumor metabolism. It has been described that epidermal growth factor receptor (EGFR) activity may impact glucose uptake, thus becoming a potential target in tumours with metabolic alterations. Such tumours include papillary RCC, notably in the context of HLRCC with *FH* alterations involved in the tricarboxylic acid cycle.[72] The EGFR inhibitor erlotinib, in combination with bevacizumab, demonstrated response rates from 35% in sporadic papillary RCC to 72% in papillary RCC with germline *FH* alteration. Importantly, duration of responses was 17.5 and 19.3 months, respectively, providing a clinically meaningful benefit of the combination and validating the proof-of-concept of EGFR inhibition in selected patients.[73]

The novel role of immune checkpoint inhibitors, alone or in combination

Immune checkpoint inhibitors targeted against programmed cell death 1 receptor (PD-1)/PD-L1 entered the stage in ccRCC after demonstrating overall survival benefit against everolimus after previous TKI treatment.[74]

Immune checkpoint inhibitors are now upfront standard of care in ccRCC, in combination with either a TKI or a cytotoxic T-lymphocyte antigen 4 (CTLA-4) targeted agent, after demonstrating overall survival benefit over sunitinib.[75–78]

Development of immune checkpoint inhibitors also emerged in nccRCC, in a setting where reportedly high PD-L1 expression advocated for the evaluation of immune-based approaches (**Table 3**).[79] Several retrospective trials evaluating immune checkpoint inhibitors as monotherapy have been reported, showing encouraging response rates ranging from 11% to 20% across all histologies, with reportedly higher response rates in nonchromophobe subtypes.[80–82] The phase 2 KEYNOTE-427[83] and CheckMate-374[84] trials, evaluating respectively pembrolizumab and nivolumab in untreated or minimally treated nccRCC, demonstrated objective responses in 24.8% and 13.6% of patients, respectively, with responses described in patients with any histological subtype. The KEYNOTE-427 trial however hints at a lower likelihood of response in patients with chromophobe histology, with less than 10% of objective responses among 21 patients.[85]

First results of immune checkpoint inhibitors combined with VEGF-targeted agents came from a phase 2 trial of anti–PD-L1 atezolizumab and bevacizumab, which yielded a 26% overall response rate across lines of therapy.[86] The CALYPSO trial evaluated the combination of savolitinib and anti–PD-L1 durvalumab with a response rate of 27% in papillary subtypes, regardless of PD-L1 expression or *MET* alterations.[87] Most compelling data to date however stems from the combination of cabozantinib plus nivolumab, a combination that is already approved in ccRCC, and which demonstrated objective response rates of 48% in patients with papillary, unclassified or translocation renal cell carcinoma, and a median PFS of 12.5 months.[88] Of note, this phase 2 trial included a second cohort of patients that comprised only chromophobe carcinomas and was terminated early, as no objective responses were reported despite some degree of disease control in several patients. These results corroborate another phase 1b trial combining cabozantinib and atezolizumab, and demonstrating less than 12% of responses in chromophobe carcinoma, although the overall response rate in the entire nccRCC cohort was 31%.[89] Overall, these results indicate that patients with nccRCC may also benefit from immune checkpoint inhibitor combinations, and that patients without chromophobe histology may derive the most benefit.

Confirmatory studies to support these promising data are needed and are underway, evaluating combinations of TKIs and immune checkpoint inhibitors, or dual checkpoint inhibition in the first-line setting and beyond. The MK-3475-B61 trial will provide prospective data on the pembrolizumab-plus-lenvatinib combination (NCT04704219), while SAMETA is currently evaluating savolitinib plus durvalumab against sunitinib or durvalumab in *MET*-driven papillary RCC (NCT05043090). The CONTACT-03 trial evaluates the activity of cabozantinib plus atezolizumab after previous immune checkpoint inhibitors and allows the inclusion of patients with papillary RCC (NCT04338269). Dual immune checkpoint inhibition targeting PD-1 and CTLA-4 has been evaluated in only a retrospective context as of today, with a response rate of 33% across histologies,[90] but results are awaited from the SUNNIFORECAST trial assessing nivolumab plus ipilimumab versus standard of care in nccRCC (NCT03075423).

TABLE 3 Activity of Immune Checkpoint Inhibitors in Monotherapy or in Combination Therapy in Non-Clear Cell Renal Cell Carcinoma

Agent	Trial phase	Histology	Setting	Patients (*N*)	Reponse rate (%)	Median PFS (months)	Median OS (months)
Nivolumab[13]	Retrospective	All nccRCC	≥ L1	41	20	3.5	NR
Nivolumab[14]	Retrospective	All nccRCC	≥ L1	48	21.6	4.9	21.7
Nivolumab, Atezolizumab, Pembrolizumab[15]	Retrospective	pRCC, unRCC	≥ L1	57	11	3.5	14
Pembrolizumab[16]	Phase 2	pRCC, chRCC, unRCC	L1	165	All patients: 26.7 pRCC: 28.8 unRCC: 30.8 chRCC: 9.5	4.2	28.9
Nivolumab[17]	Phase 2	All nccRCC	≥ L1	44	13.6	2.2	16.3
Nivolumab + Cabozantinib[19]	Phase 2	Cohort 1: pRCC, unRCC, tRCC Cohort 2: chRCC	L1/L2	Cohort 1: 40 Cohort 2: 7	Cohort 1: 48 Cohort 2: 7	Cohort 1: 12.5 Cohort 2: NA	Cohort 1: 28 Cohort 2: NA
Atezolizumab + Bevacizumab[20]	Phase 2	All nccRCC and ccRCC with sarcomatoid features	≥ L1	60	All patients: 33 nccRCC: 26	All patients: 8.3	NR
Savolitinib + Durvalumab[21]	Phase 1/2	pRCC	≥ L1	42	27	3.3	NA
Nivolumab + Ipilimumab[18]	Retrospective	All nccRCC	≥ L1	18	33.3	7.1	NA

Abbreviations: chRCC, chromophobe carcinoma; NA, not applicable; nccRCC, non-clear cell renal carcinoma; NR, not reported; OS, overall survival; PFS, progression-free survival; pRCC, papillary renal cell carcinoma; tRCC, translocation carcinoma; unRCC, unclassified renal carcinoma.

Approaching rarer non-clear cell renal cell carcinoma subtypes

Rare entities such as renal medullary carcinoma or collecting duct carcinoma historically shared similarities in their natural history and their sensitivity to anticancer therapies. The chemotherapy-based regimen with gemcitabine plus cisplatin has been tested in a prospective, multicentre, phase 2 study in 23 patients with collecting duct carcinoma, showing a response rate of 26%, a median PFS of 7.1 months, and a median OS of 10.5 months.[91,92]

There is very limited data regarding the activity of TKIs in these subtypes apart from retrospective reports.[93] Most reliable data stems from the phase 2 trial of cabozantinib in collecting duct carcinoma, which demonstrated a response rate of 35% and a median PFS of 6 months.[94]

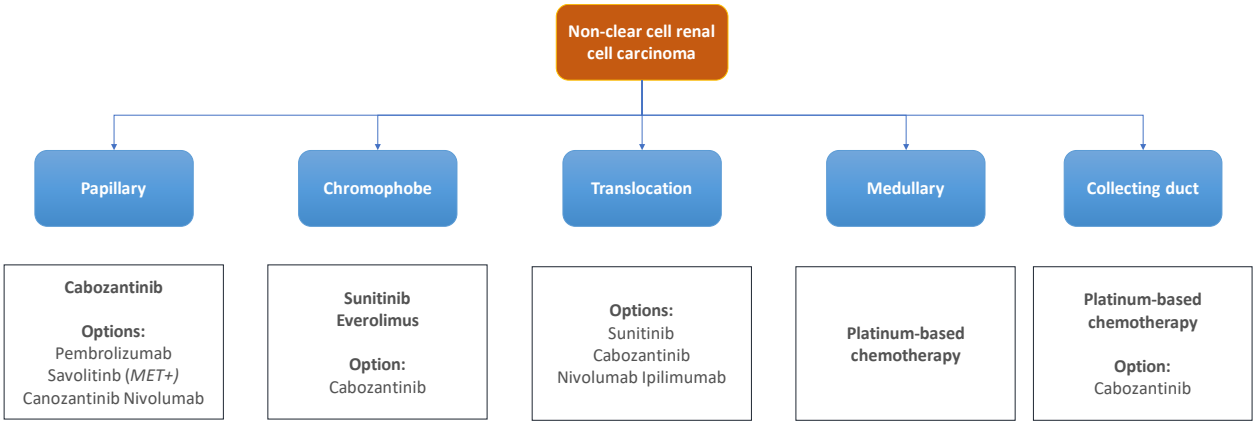
Renal medullary carcinomas harbour bi-allelic *SMARCB1* alterations, involved in chromatin remodelling, and share this molecular context with other rhabdoid tumours. As such, the evaluation of agents targeting *EZH2*, a component of the chromatin-remodelling complex PRC2 that already demonstrated activity against other rhabdoid tumour types[95] is underway in this population (NCT02601950).

Considerations for Systemic Therapeutic Strategies in Non-Clear Cell Renal Cell Carcinoma

Papillary renal cell carcinoma

Papillary RCC has been the most explored nccRCC subtype, with the most readily available data on systemic therapies. Current evidence with prospective randomized trials demonstrates the highest level of evidence for the use of cabozantinib as a standard of care in the first-line setting, with improved progression-free survival over other TKIs (**Figure 1**).[70] Other TKIs including sunitinib remain an option for further lines of therapy.

FIGURE 1 Systemic Treatment for Non-Clear Cell Renal Cell Carcinoma According to Histological Subtypes



Other options that demonstrated compelling activity should also be considered, although formal comparisons are not available. Immune checkpoint inhibitors as monotherapy, or in combination with TKIs, have demonstrated an interesting likelihood of antitumour response with potential for long-term disease control, and as such may also be considered upfront on a case-by-case basis.[88]

Some systemic therapies may be preferred in specific papillary RCC subtypes. Savolitinib is an option only in *MET*-driven papillary RCC, including *HGF* amplification, *MET* amplification, *MET* kinase domain mutation, or chromosome 7 gain.[69] Erlotinib and bevacizumab should be considered as standard of care in the rare context of HLRCC and germline *FH* mutations considering that most patients will experience response and long-term disease control.[73] This combination may also be considered on a case-by-case basis for papillary RCC without *FH* mutations, as prolonged disease control has been reported in subsets of patients.

Chromophobe carcinoma

Chromophobe carcinoma, contrary to papillary subtypes, has been associated with little benefit from immune checkpoint inhibitors, even in a combinatory approach.[94] As such, the standard of care still relies on targeted therapies evaluated in historical trials, namely sunitinib or everolimus.[57,58] Retrospective data suggests that other TKIs such as cabozantinib may also provide interesting disease control and may be a viable option.[71] Further lines of therapy may be considered on a case-by-case basis, as there is no robust standard and prognosis remains poor.

Translocation carcinoma

Translocation carcinomas are rare entities occurring in younger populations with little activity of systemic therapies, for which there are no established standards. Retrospective cohorts indicate that cabozantinib as

well as immune checkpoint inhibitors may provide individual responses in subsets of patients with prolonged survival.[96,97] Translocation carcinomas have also been included in combination trials, with individual responses observed with cabozantinib plus nivolumab.[88] All these insights may be discussed to better guide therapy on a case-by-case basis.

Renal medullary carcinoma and collecting duct carcinoma

Cytotoxic chemotherapy remains the mainstay of systemic treatment for renal medullary carcinoma and collecting duct carcinoma, which remain hard-to-treat tumours with aggressive behaviour.[98] Immune checkpoint inhibitor activity is disappointing in both settings, as is TKI activity with less than 10% objective responses.[99] Recent data from the BONSAI trial may propel cabozantinib as an alternative in patients with collecting duct carcinomas, although long-term follow-up is yet to be reported.

Focal Therapies in the Metastatic Setting

Focal therapy for oligometastatic disease

It has long been shown that systemic therapies have more limited activity in nccRCC compared with ccRCC. As such, development of focal therapies may be an interesting alternative for patients with low tumour burden. The importance of achieving NED (*no evidence of disease*) status with focal therapies has already been described in ccRCC, with patients deriving very long-term disease-free intervals.[100] Such an approach in nccRCC may also be valid. In a retrospective cohort of patients, one patient with papillary RCC had metastasectomy after responding to TKI and achieved a disease-free interval of 13 months, and counting.[101] This proof-of-concept indicates that focal therapy may be interesting for patients achieving disease control, with only residual oligometastatic disease. Other datasets address the question of upfront focal treatment of oligometastases and show among ccRCC and nccRCC that the median time to first systemic treatment can be deferred for more than a year.[102] Notably, among 6 patients with nccRCC, 2 were alive with no systemic therapy after 2 years of follow-up. Such an approach may thus be proposed to select patients.

Surgery of the primary tumour in the metastatic setting

Understanding the debate on the use of cytoreductive nephrectomy in ccRCC may help considering this approach in the light of nccRCC. It has long been reported that cytoreductive nephrectomy in ccRCC may improve overall survival in the metastatic setting, thanks to prospective data stemming from the cytokine era,[103] or from retrospective datasets in the TKI era.[104] However, a large prospective trial in the TKI era did not confirm these findings, and as such cytoreductive nephrectomy is no longer a standard in ccRCC.[105] These findings highlight the fact that the activity of systemic therapy may impact the potential relevance of a surgical approach, and that retrospective datasets harbour biases that may hamper formal conclusions.

The current situation in nccRCC is that of a changing treatment landscape, with very few data on cytoreductive nephrectomy. A large retrospective dataset including patients with papillary RCC showed that cytoreductive nephrectomy was associated with a nearly doubled overall survival.[106] Patients with cytoreductive nephrectomy were younger and had better performance status, showing that favourable clinical profiles are selected in clinical practice for surgical approaches in the metastatic setting. While these data cannot be considered as robust as a prospective trial, as demonstrated in the context of ccRCC, such results may indicate that cytoreductive nephrectomy may be a valid approach in eligible patients.

A Role for Systemic Therapy for the Management of Localized Disease?

Patients with localized nccRCC are candidates for surgical strategies. So far, no perioperative treatment strategy has been shown to improve outcomes after surgical management of localized nccRCC. Experience stemming from ccRCC showed that TKIs could not provide any overall survival improvement when used in the adjuvant setting.[107–110] New hopes stem from the first results of the KEYNOTE-564 adjuvant trial of pembrolizumab in ccRCC, which demonstrated improved disease-free survival in patients with a high risk of relapse, with an HR of 0.68.[111] So far, no robust data is available in nccRCC, but the RAMPART trial of durvalumab ± tremelimumab versus observation in localized RCC will include nccRCC subtypes and will generate valuable data for these patients (NCT03288532).

Prognostic and Predictive Biomarker Developments in Non-Clear Cell Renal Cell Carcinoma

With increased ability for molecular profiling, developments in biomarker-based trials emerged with frequent and targetable mutations such as *MET*, as described previously. The EORTC 90101 CREATE trial suggested that papillary RCC (pRCC) patients with *MET* mutations demonstrated longer disease control and favourable objective responses,[112] before the SAVOIR phase 3 trial showed encouraging efficacy of savolitinib versus sunitinib in a similar setting.[113] Other genomic alterations are now investigated as potential predictors of response to therapy, although those did not yet translate into the clinic. Recent efforts notably showed that 83% (10 of 12) of nccRCC with either *NF2* or *FH* mutations achieved an objective response to the combination treatment of cabozantinib plus nivolumab, which may indicate biology-driven sensitivity to such a combination.[114]

Regarding immune checkpoint inhibitors as a whole, the immunohistochemical staining of PD-L1 has been widely used in clinical practice to assess the immune status in other solid tumours and try to predict treatment

response. For nccRCC, multiple studies have revealed that PD-L1 expression on tumour cells is not associated with survival in patients treated with immune checkpoint inhibitors.[46,115–117] Conflicting data is however available, with a combined positive score (CPS) associated with response to pembrolizumab in patients treated in the KEYNOTE-427 trial; the response rate was 35.3% and 12.1% for patients with PD-L1 CPS ≥1 and CPS <1, respectively.[118] Routine integration of these markers in clinical practice remains however debated and thus far does not accurately guide treatment with immune checkpoint inhibitors.

Other putative biomarkers may be able to provide more insights into nccRCC prognosis. A phase 2 trial found that all 5 papillary nccRCC patients with *ARID1A* mutations achieved a PFS exceeding 6 months while treated with everolimus plus bevacizumab.[119] A post-hoc analysis of phase 2 trial exploring the prognostic role of circulating cytokines and angiogenic factors with sunitinib found that the high levels of baseline soluble tumour necrosis factor (TNF) and angiogenic mediators are significantly correlated with lower overall survival of nccRCC, including TNF receptor 1, IL-8, transforming growth factor-α, and VEGFR-2.[120,121] Other systemic inflammatory markers have been explored such as C-reactive protein (CRP) and neutrophil-to-lymphocytes ratios, but an association with survival has not been confirmed.[122,123] All these studies with limited results ultimately show that further integration of genomic data is needed to bring molecular profiling results into valuable tools for clinical practice.

Conclusion

Non-clear cell RCC is a burgeoning field shaped by advances in molecular biology that further our understanding of the disease, and novel targeted therapies and immune checkpoint inhibitors that raise hopes to improve cure in patients with these hard-to-treat diseases. It is anticipated that novel insights in ccRCC including evaluation of triplets and adaptive strategies may further help developments in nccRCC. Hopefully, these developments will be better tailored to these specific histologic and molecular subtypes in the near future, thanks to broader availability of molecular studies and improved ability to select patients. In the next decade though, the rarity of these subtypes still implies the need for worldwide collaborations and a push to include more patients into clinical trials to help this steady improvement in outcomes that we have the privilege to witness and the duty to be part of.

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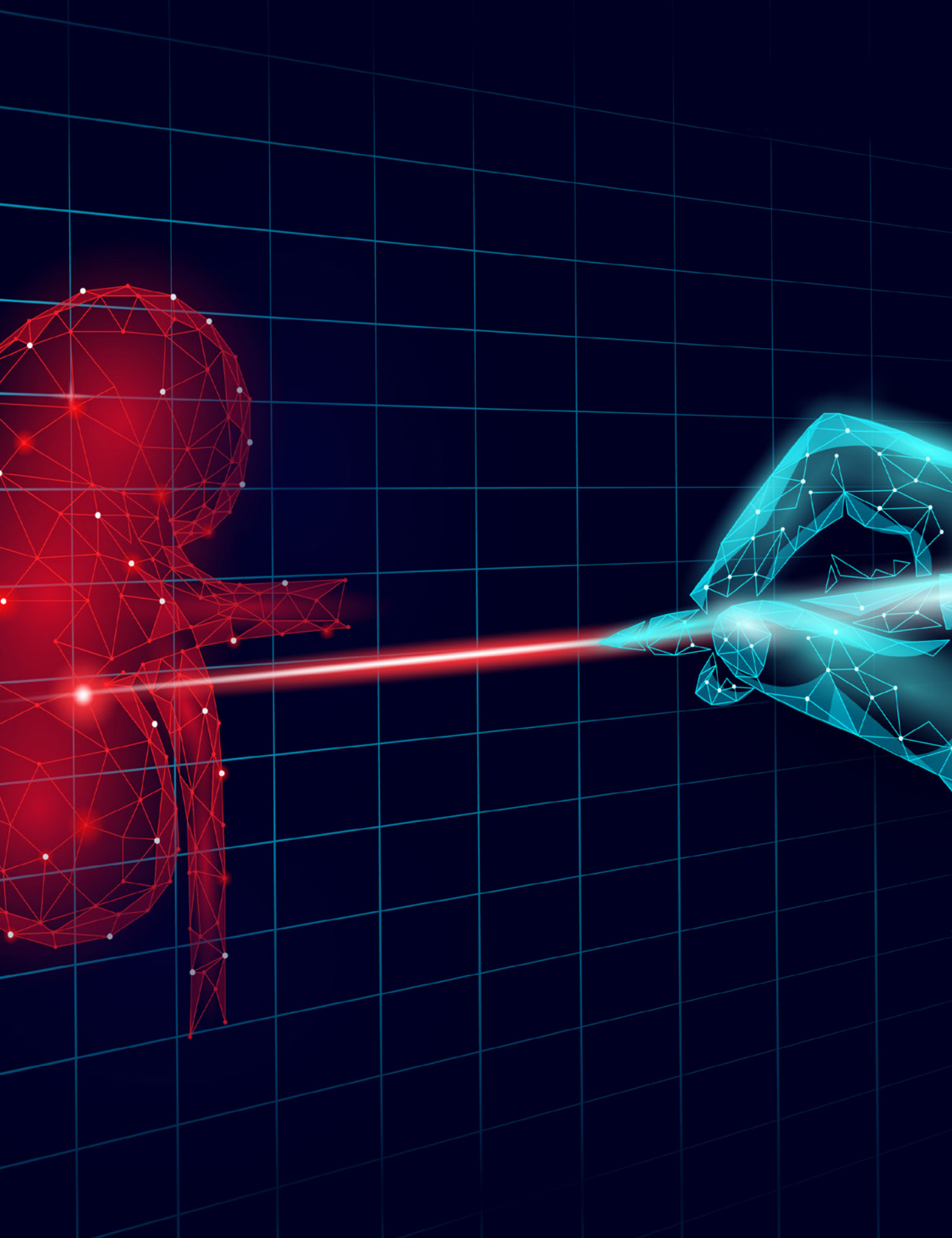
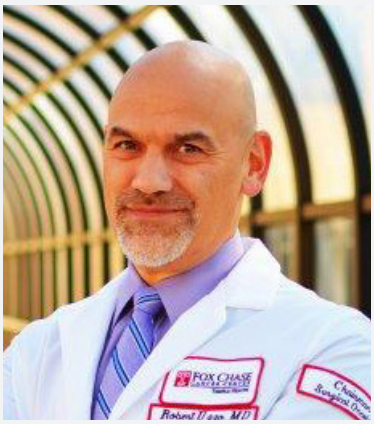


COMMITTEE 18

Future Directions in Renal Cell Carcinoma



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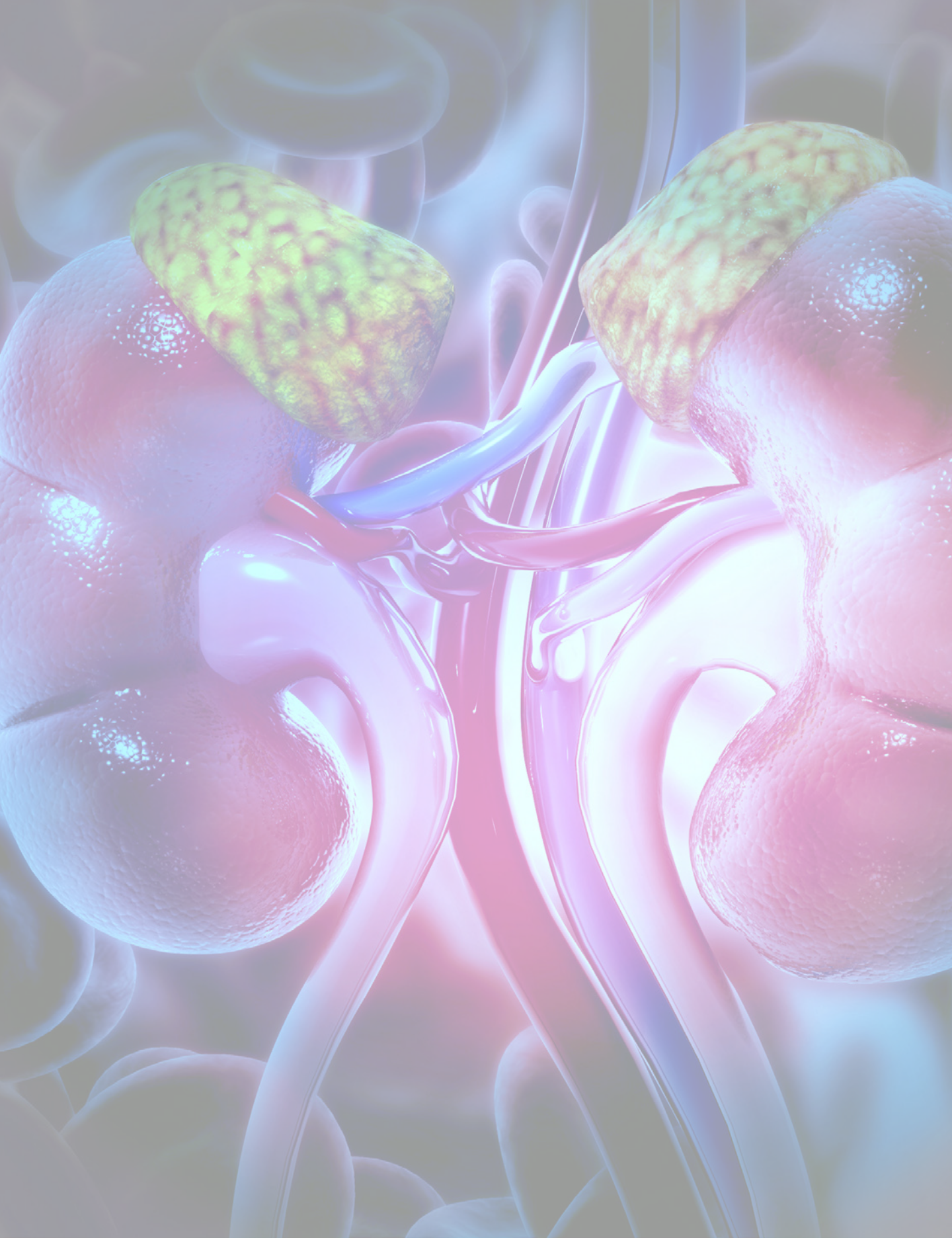
Basic and translational research led by investigators unraveling the genetics of hereditary kidney cancer over the past three decades have clarified aberrant proliferative, angiogenic, and metabolic pathways inherent to most kidney cancers. These data have led to a realization of the extreme genomic, biological, and ultimately clinical heterogeneity of renal cancers. For this reason, renal cancer is now considered a collection of multiple diseases, each with its own biology and host interactions. Simultaneously, improvements in imaging, staging, biomarker and risk stratification, perioperative management, minimally invasive techniques, ablative techniques, and a growing recognition that not all renal masses are equally lethal have led to massive refinements in the care of patients with localized and locally advanced renal cell carcinoma (RCC).

Sequential or combination systemic antiangiogenics and immunotherapies will continue to dominate the next several years of systemic therapies in RCC. Nevertheless, novel targets, and agents that impair them, are now emerging to manage promiscuous and escape pathways including transcriptional factors targeting hypoxia-induced and metabolic proteins. Furthermore, based on the successes of antibodies targeting the programmed cell death 1 receptor (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) immune checkpoints, innovative immunotherapies are now in clinical development, including modified cytokines, checkpoint inhibitors with novel targets, co-stimulatory agonists, as well as cell therapies and personalized vaccines. The interplay of these agents, together with surgical and ablative techniques as multimodal treatments, will also need to be studied. Together with research around prevention and early detection, these strategies will be needed to enhance cure rates for initially localized disease. All these treatments will eventually need to be integrated into the clinical armamentarium through our rich clinical trial networks. Additionally, a deeper understanding of non-clear cell RCC must remain a priority.



2nd WUOF/SIU ICUD on Kidney Cancer

This book comprising 18 chapters presents expert opinion on the management of kidney cancers from a variety of perspectives to help guide physicians and inform their treatment decisions. This is an exciting time for the field of kidney cancer, and the next several years will incorporate new therapeutics with state-of-the-art technologies such as artificial intelligence. These advances will facilitate the emergence of novel, personalized treatment paradigms that will profoundly change the management of this disease. The aim is to evolve toward the development of individualized therapies, which will enhance treatment efficacy and safety. The results of new clinical trials and advances in the molecular biology and genetics of kidney cancer are thoroughly summarized in this book.

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