Integrating Multidisciplinary Treatment for Advanced Renal Cell Carcinoma

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Prognostic Factors for Localized Renal Cell Carcinoma

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Goran Rac, Hiten D. Patel, and Gopal N. Gupta

Abbreviations

AJCC	American Joint Committee on Cancer
CCP	Cell cycle progression
CRP	C-reactive protein
CSS	Cancer-specific survival
ECOG	Eastern Cooperative Oncology Group
ESR	Erythrocyte sedimentation rate
HIF	Hypoxia-inducible factor
ISUP	International Society of Urologic Pathologists
IVC	Inferior vena cava
LDH	Lactate dehydrogenase
OS	Overall survival
RCC	Renal cell carcinoma
RENAL	Radius, exophytic/endophytic, nearness, anterior/posterior, location
RFS	Recurrence-free survival
TNM	Tumor, node, metastasis
WHO	World Health Organization

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Introduction

The incidence of renal cell carcinoma (RCC) rose over several decades due to an increase in the quality and utilization of cross-sectional imaging with a plateau since 2008 [1]. Globally, there were more than 400,000 new cases of RCC diagnosed with over 175,000 deaths in 2020 [2]. The majority of RCC diagnosed is clinically localized largely because of stage migration toward lower stage disease since the 1980s, though this effect has slowed in recent years [3]. Even among the localized subset, RCC is heterogenous with a variable prognosis in terms of recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS).

A variety of prognostic factors drive these differential outcomes. In general, these can be divided into clinical, anatomic, histopathologic, and molecular factors. Additionally, patient-related factors such as age and comorbid conditions including baseline renal dysfunction will have an impact on OS and should be factored into decision making. A thorough understanding of these factors is critical for physicians taking care of patients with RCC such that they may better counsel them on the risks of recurrence and mortality. Awareness of these factors and the available predictive instruments that incorporate them may also help guide surveillance protocols following treatment and determine patient candidacy for clinical trials and adjuvant therapy. This chapter outlines the current available literature on prognostic considerations for localized RCC.

Clinical

In the current era of widespread cross-sectional imaging, 60% of RCC diagnoses are made incidentally on imaging obtained for unrelated indications in asymptomatic patients [4]. The classic RCC symptom triad of gross hematuria, flank pain, and palpable abdominal mass is now fortunately an uncommon finding, as this is strongly associated with poor prognosis and advanced disease. Other symptoms that may be associated with localized RCC include those related to inferior vena cava (IVC) obstruction such as bilateral lower extremity edema and nonreducing or right-sided varicocele [5]. While the presence of symptoms has been shown to be associated with poorer CSS, this effect is lost when controlling for stage of disease [4]. Additionally, a proportion of clinically diagnosed localized renal masses on imaging are ultimately found to be benign upon pathologic examination [6]. Among baseline patient factors, only male sex has been shown to be associated with risk of malignancy in composite models with inconclusive evidence for age, body mass index, and incidental diagnosis [7].

Several laboratory value derangements have been associated with poor prognosis in RCC. These include anemia, thrombocytosis, hypercalcemia, elevated lactate dehydrogenase (LDH), elevated alkaline phosphatase, elevated erythrocyte sedimentation rate (ESR), and elevated C-reactive protein (CRP). While these are more

common in patients with advanced RCC, Magera et al. showed that hypercalcemia, anemia, and elevated ESR were also independently associated with poor CSS in patients with clinically localized clear cell RCC [8].

Another important factor to consider when evaluating patients with localized RCC is their comorbidity status, which represent potential competing risks of death that should be balanced with oncologic risk. The Charlson comorbidity index is a tool used to predict 10-year OS in patients with multiple comorbidities [9]. Though the index has limitations, modification into a cardiovascular focused index improved stratification of survival among patients with small renal masses [10]. Importantly, older patients at high cardiovascular risk had similar CSS regardless of whether they received surgery while patients at lower cardiovascular risk had two to fourfold benefit in CSS associated with surgery [11]. Comorbidity and patient-reported quality of life measures have also been shown to aid in selection of patients with small renal masses for active surveillance [12]. When feasible, nephron-sparing approaches should be prioritized for amenable masses especially among patients with pre-existing chronic kidney disease [13, 14]. Finally, performance status is another important prognostic clinical factor in RCC, including localized disease, which may capture additional dimensions relative to traditional comorbidity measures. The Eastern Cooperative Oncology Group (ECOG) and Karnofsky scores are the most commonly used performance scales [15, 16].

Anatomic

The most consistent prognostic factor for RCC is the anatomic extent of disease [17]. The American Joint Committee on Cancer (AJCC) has created the Tumor, Node, Metastasis (TNM) staging system that stratifies patients based on the extent of disease and correlates with prognosis (Table 1.1). The TNM system has gone through several iterations to reflect updates in prognostic data since its initial proposal in 2009. At the time of this publication, the AJCC TNM classification system is in its eighth edition and can be assigned based on available clinical and/or pathologic information [18]. The primary tumor factors assessed in the T stage of the system are tumor size and invasion into adjacent structures. Stage I and II RCC is confined to the kidney with specific substage (T1a, T1b, T2a, or T2b) defined by tumor size as outlined in (Table 1.1). Stage III RCC is either locally invasive into the fat/vasculature (T3) or has regional lymph node involvement (N1). Stage IV RCC has spread beyond Gerota fascia into adjacent organs by direct invasion (T4) or have distant metastases (M1). Among stage cT1 renal masses, greater tumor size is the only other consistent predictor of malignancy besides male sex [7].

Overall, organ-confined RCC has a 5-year survival of 70–90% with worsening prognosis as the TNM stage progresses as given in (Table 1.1) [5]. Though venous involvement has historically been viewed as a very poor prognostic indicator, some

Table 1.1 AJCC TNM stage and 5-year survival for RCC

Tumor stage			5-Year survival (%)
Primary tumor (T)	TX	Primary tumor cannot be assessed	–
	T0	No evidence of primary tumor	–
	T1a	Tumor ≤4.0 cm and confined to kidney	90–100
	T1b	Tumor >4.0 cm and ≤7.0 cm and confined to kidney	80–90
	T2a	Tumor >7.0 cm and ≤10.0 cm and confined to kidney	65–80
	T2b	Tumor >10.0 cm and confined to kidney	50–70
	T3a	Tumor grossly extends into renal vein or segmental branches	40–60
		Tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia	50–70
	T3b	Tumor grossly extends into vena cava below diaphragm	30–50
	T3c	Tumor grossly extends into vena cava above diaphragm or invades wall of vena cava	20–40
	T4	Tumor invades beyond Gerota fascia	0–20
		Contiguous extension into ipsilateral adrenal gland	0–30
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed	–
	N0	No regional lymph node metastasis	–
	N1	Metastasis in regional lymph node(s)	0–20
Distant metastases (M)	MX	Distant metastasis cannot be assessed	–
	M0	No distant metastasis	–
	M1	Distant metastasis present	0–10

Modified from [5, 18]
AJCC American Joint Committee on Cancer, *TNM* tumor, node, metastasis, *RCC* renal cell carcinoma

studies have shown that improved outcomes can be achieved with aggressive surgical control. One study found 5-year survival rates of 43.2% with isolated renal vein involvement, 37% with involvement of the IVC below the diaphragm, and 22% with IVC involvement above the diaphragm [19]. Any lymph node involvement or presence of metastatic disease significantly worsens prognosis which may be subclinical or micrometastatic at initial diagnosis. Even in stage III RCC, tumor size remains a significant predictor of prognosis with 10-year survival rates of 77% for tumors ≤4.0 cm, 54% for tumors >4.0 cm and ≤ 7.0 cm, and 46% for tumors >7 cm in size [20].

Though invasion into the urinary collecting system is not a part of the TNM staging system, a recent meta-analysis has shown it to be associated with worse outcomes in stages I and II RCC (HR 2.05, $p < 0.001$) [21]. There was mixed evidence for stage III RCC, but they ultimately concluded that invasion into the urinary collecting system was not predictive of survival in stage III-IV RCC.

Additionally, the presence of sarcopenia, defined as a loss of muscle mass and function which be quantified radiographically, has recently emerged as an important prognostic indicator in a variety of malignancies. It has been shown to be an independent risk factor for all-cause (OS 82.1% vs. 94.0%, HR 2.58, $p < 0.001$)

and cancer-specific mortality (CSS 91.8% vs. 97.5%, HR 3.07, $p < 0.001$) in RCC in a study of 632 patients undergoing radical nephrectomy for organ-confined disease [22].

Though not explicitly an anatomic factor, prognosis can vary with the type of intervention performed for RCC depending on a variety of anatomic factors. For example, as the TNM stage progresses, the appropriateness for intervention with ablative therapy and partial nephrectomy decreases due to the increased risk of residual tumor and local recurrence. Additionally, there is a risk of pT3a upstaging among patients with clinically localized stage cT1-2N0M0 tumors [23]. One tool developed to assist with better prediction of partial nephrectomy postoperative complication outcomes with the goal of optimizing patient selection for the procedure is the radius, exophytic/endophytic, nearness, anterior/posterior, Location (RENAL) nephrometry score [24]. RENAL nephrometry scores of 4–6, 7–9, and 10–12 represent low, intermediate, and high complexity tumors, respectively. High RENAL nephrometry scores have been suggested to be associated with worse oncologic outcomes and predictive of histopathologic tumor grade although findings across studies are not consistent and may largely be due to the tumor size component [7, 25, 26].

Histopathologic

RCC can be divided into various histologic subtypes as defined most recently in 2016 by the World Health Organization (WHO) and International Society of Urologic Pathologists (ISUP) [27]. The most common of these are clear cell RCC (70–90%), papillary RCC (10–15%), and chromophobe RCC (3–5%) [28]. In the nonmetastatic setting, patients with type 1 papillary RCC have a better OS rate compared to clear cell RCC (HR 0.76, $p < 0.001$) [29]. Type 2 papillary RCC is traditionally described as more aggressive than type 1 RCC, likely secondary to its greater propensity for presenting at higher TNM stages [30]. However, several recent studies have shown that the two subtypes have similar survival outcomes in the clinically localized setting [30, 31]. Chromophobe RCC in general carries a more favorable prognosis in the nonmetastatic setting and absence of sarcomatoid differentiation [32]. Additional rarer subtypes have also been identified with varying prognostic implications (Table 1.2).

Nuclear grade also provides valuable prognostic information. Multiple classification systems have been proposed for nuclear grade, with the most widely used one being the Furman grade. Originally described in 1982, four nuclear grades (1 through 4) were defined in order of increasing nuclear size, irregularity, and nucleolar prominence which correlated with 5-year survival rates of 64%, 34%, 31%, and 10% for grades 1 through 4, respectively [33]. Although primarily applied to clear cell RCC, there is evidence that Fuhrman grade can provide valuable prognostic information for papillary RCC as well [34]. However, nuclear grade has been shown

Table 1.2 Prognostic implications of various 2016 WHO-ISUP renal cell carcinoma subtypes in the setting of localized disease

Histologic subtype	Incidence	5-Year survival (%)
Clear cell RCC	70–80	85
Papillary type 1 RCC	5–10	82–95
Papillary type 2 RCC	5–10	80–95
Chromophobe RCC	3–5	90–100
Clear cell papillary RCC	1–4	100
Hereditary leimyomatosis and RCC-associated RCC	<1	30[a]
Collecting duct (Bellini) carcinoma	<1	34–48[a]
Renal medullary carcinoma	<1	0[a]
MiT family translocation RCC	<1	20
Succinate dehydrogenase-deficient RCC	<1	85
Mucinous tubular and spindle cell carcinoma	<1	Rare metastasis[b]
Tubulocystic RCC	<1	Rare metastasis[b]
Acquired cystic disease-associated RCC	<1	95
Multilocular cystic renal neoplasm of low malignant potential	1–3	100
Unclassified	1–3	46

Compiled using data sourced from [5, 30, 31, 63–71]
WHO World Health Organization, *ISUP* International Society of Urologic Pathologists, *RCC* renal cell carcinoma
[a] 5-year overall survival for all stages including metastatic disease provided due to low overall incidence
[b] Limited data available due to low incidence

to have little prognostic value in chromophobe RCC [35]. While renal mass biopsy can often differentiate RCC subtypes, it is important to note that about 16% of patients found to have grade 1–2 on biopsy may upgrade to grade 3–4 on surgical pathology [36].

The presence of sarcomatoid differentiation, characterized by spindle cell histology, is another important prognostic factor seen in about 5% of RCC [37]. Previously considered a separate histologic subtype of RCC, it is no longer categorized as such since it can occur with any of the histologic subtypes and is rarely isolated in the absence of another subtype. Sarcomatoid differentiation confers a poor prognosis following surgery with a 5-year CSS of 77.7%, 67.8%, and 35.4% for patients with stage I, II, and III disease at presentation, respectively [38]. The presence of tumor necrosis is another important prognostic factor that correlates with worse RFS, CSS, and OS in patients with RCC [39].

Postoperative surgical margin status is also closely related to oncologic outcomes. Following standard margin partial nephrectomy, a large meta-analysis found that the presence of a positive surgical margin (PSM) was associated with worse OS (HR 1.3) as well as an increased risk of local recurrence (HR 6.11) and metastasis (HR 3.29) [40]. The presence of a PSM in patients with T3 disease following radical nephrectomy has similarly been shown to be associated with an increased risk of RFS (HR 4.3) [41]. Notably, margin status may be less prognostic among patients receiving a tumor enucleation approach to partial nephrectomy to maximize renal function [42].

Molecular

Multiple molecular markers have been shown to be associated with worse prognosis in various RCC subtypes. These include genomic alterations and epigenetic changes leading to varying levels of RNA expression. A comprehensive study by the Cancer Genome Atlas Research Network found that aggressive clear cell RCC tumors demonstrated downregulation of genes involved in the tricarboxylic acid cycle, decreased AMPK and PTEN protein levels, upregulation of the pentose phosphate pathway and glutamine transporter genes, increased acetyl-CoA carboxylase protein, and altered promoter methylation of miR-21 and GRB10 within the PI3K/AKT pathway [43].

Deletion of chromosome 9p has been shown to independently confer worse RFS in localized clear cell RCC with 5-year RFS rates of 49% and 77% with and without 9p deletion, respectively [44]. Conversely, the deletions of chromosome 3p and mutations of the von Hippel-Lindau tumor suppressor gene involved in the hypoxia-inducible factor (HIF) pathway located at 3p25 are in general associated with less aggressive disease [45, 46]. Other chromosomal deletions that have been associated with a worse prognosis include the loss of chromosomes 4p and 14q, the latter of which is associated with the loss of HIF-1α [46]. Several other factors in the HIF pathways have also been associated with worse prognosis. Specifically, aberrant expression of carbonic anhydrase IX has been shown to be associated with unfavorable tumor phenotype and poor disease course [47]. While most papillary RCC exhibits a complete absence of carbonic anhydrase IX, tumors with worse prognosis were shown to have detectable levels. Conversely, clear cell RCC typically has strong carbonic anhydrase IX positivity, and worse prognosis was associated with decreased carbonic anhydrase IX expression [48].

The exonic single-nucleotide polymorphism rs11762213 located in the MET oncogene has been identified as another prognostic marker for adverse CSS and RFS in clear cell RCC [49]. Activation mutations of the MET gene have also been implicated in both hereditary and less commonly sporadic papillary RCC [5].

Increased expression of proliferation markers such as Ki-67 has been found to be an independent risk factor for worse prognosis in clear cell RCC [50]. Additionally, increased expression of oncofetal RNA-binding protein IMP3 has also been shown to be associated with a 5- to tenfold increased incidence of metastasis in clear cell, papillary, and chromophobe RCC [51, 52]. Increased expression of p53, independent of p53 mutation, has also been shown to confer poor prognosis with a greater than threefold increase in risk of RFS [53].

Alterations in chromatin remodeling genes have also been associated with progression of clear cell RCC. Mutations of tumor suppressor genes in this class such as BAP1 and SETD2 have been associated with poor prognostic outcomes [54]. Conversely, mutations in PBRM1 appear to confer a better prognosis [43].

Interestingly, all 3 genes are tumor suppressor genes located on chromosome 3p21 in close proximity to the VHL gene.

Immune regulation pathways have also been shown to play a significant role in the progression of RCC. Increased B7-H1 expression, a costimulating glycoprotein involved in downregulation of T cell activation, has been shown to be associated with greater risk of disease progression, cancer-specific mortality, and overall mortality in clear cell RCC likely secondary to inhibition of the antitumor immune response [55].

In addition to having the potential to provide valuable prognostic information, these molecular aberrations may serve as potential therapeutic targets in the future. Although these markers have been shown to be associated with worse prognosis in various studies, they continue to have limited clinical applicability and are not commonly utilized in practice at the present due to a lack of extensive validation. Nonetheless, investigation into these markers and their integration into predictive models continues.

Rini et al. developed a 16-gene expression panel based on 11 cancer-related genes strongly associated with RFS in clear cell RCC that was used to develop a recurrence score which they validated and found to be independently associated with an increased risk of tumor recurrence [56]. Brooks et al. developed a 34-gene classifier (ClearCode34) for clear cell RCC which identified two distinct clusters, ccA and ccB, the latter of which was associated with a poor prognosis [57]. The cell cycle progression (CCP) score, a RNA expression assay initially developed for use in prostate cancer that measures the activity of genes involved in cellular proliferation, has recently been utilized for localized RCC with mixed results. One study found that a higher CCP score correlated with a higher 5-year mortality, while a second study was unable to correlate the score with prognostic outcome [58, 59]. While the initial results are promising, further study is warranted to determine the clinical utility of these panels.

Integrated Predictive Tools

Many integrated predictive tools have been developed using a variety of combinations of the aforementioned prognostic factors. The predictive tools can be categorized based on whether they are intended for use in the preoperative or postoperative settings to provide information about recurrence and survival. In general, the tools provide an output of either patient risk strata or a nomogram for prognostication.

Preoperative predictive tools incorporate prognostic factors such as tumor size, TNM stage, symptoms, laboratory findings, imaging findings, age, gender, and race (Table 1.3). Postoperative predictive tools additionally incorporate pathologic information such as histologic subtype and grade as well as various molecular markers (Table 1.4). Several predictive instruments have also been developed for use specifically in the advanced RCC setting and will be further discussed in other chapters.

Table 1.3 Integrated predictive tools for localized RCC in the preoperative setting

Outcome	Study (year)	Format	Patients (source)	Prognostic variables	Accuracy (validation)
Recurrence	Yaycioglu et al. (2001)	Risk groups	862 (single institution)	Tumor size, symptoms	65–66% (external)
	Cindolo et al. (2003)	Risk groups	660 (multi-institution)	Tumor size, symptoms	67–75% (external)
	Brookman-Amissah et al. (2008)	Risk groups	771 (single institution)	Tumor size, platelet count	72% (internal)
	Raj et al. (2008)	Nomogram	2517 (multi-institution)	Tumor size, symptoms, gender, lymphadenopathy, necrosis	80% (internal)
Survival	Karakiewicz et al. (2008)	Nomogram	2474 (multi-institution)	Tumor size, TNM stage, age symptoms, gender	74–88% (external)
	Kanao et al. (2009)	Table	545 (single institution)	TNM stage	69–82% (external)
	Kutikov et al. (2009)	Nomogram	30,801 (population-based)	Tumor size, age, gender, race	70–73% (external)

Summary of data from [72–78], modified from [17]
RCC renal cell carcinoma, *TNM* tumor, node, metastasis

Table 1.4 Integrated predictive tools for localized RCC in the postoperative setting

Outcome	Study (year)	Format	Patients (source)	Prognostic variables	Accuracy (validation)
Recurrence	Kattan et al. (2001)	Nomogram	601 (single institution)	Tumor size, TNM stage, symptoms, histologic subtype	61–84% (external)
	Leibovich et al. (2003)[a]	Risk groups	1671 (single institution)	Tumor size, TNM stage, nuclear grade, necrosis	70–80% (external)
	Sorbellni et al. (2005)[a]	Nomogram	701 (single institution)	Tumor size, TNM stage, symptoms, nuclear grade, necrosis, vascular invasion	78–79% (external)
	Klatte et al. (2009)[a]	Nomogram	170 (single institution)	TNM stage, Ki-67, p53, p21, endothelial VEGFR-1, epithelial VEGFR-1, epithelial VEGFD-D	90% (internal)

(continued)

Table 1.4 (continued)

Outcome	Study (year)	Format	Patients (source)	Prognostic variables	Accuracy (validation)
Survival	Zisman et al. (2001)	Risk groups	661 (single institution)	TNM stage, nuclear grade, performance status	64–86% (external)
	Frank et al. (2002)[a]	Risk groups	1801 (single institution)	Tumor size, TNM stage, nuclear grade, necrosis	75–88% (external)
	Kim et al. (2004)[a]	Nomogram	318 (single institution)	TNM stage, performance status, p53†, vimentin†, carbonic anhydrase IX†, gelsolin†	79% (internal)
	Karakiewicz et al. (2007)	Nomogram	2530 (multi-institution)	Tumor size, TNM stage, symptoms, nuclear grade	75–89% (external)
	Karakiewicz et al. (2007)	Nomogram	313 (multi-institution)	Tumor size, TNM stage, age, symptoms, nuclear grade, histologic subtype, gender, performance status, CRP	84–88% (internal)
	Parker et al. (2009)[a]	Risk groups	634 (single institution)	Bioscore: B7-H1, survivin, Ki-67	75% (internal)
	Klatte et al. (2009)[a]	Nomogram	282 (single institution)	TNM stage, nuclear grade, loss of chromosome 9p	89% (internal)
	Iimura et al. (2009)[a]	Risk groups	249 (multi-institution)	TNM stage, CRP	82% (internal)
	Klatte et al. (2010)[b]	Nomogram	258 (multi-institution)	TNM stage, symptoms, necrosis, vascular invasion	94% (external)
	Leibovich et al. (2018)	Nomogram	3633 (single institution)	Tumor size, TNM stage, symptoms, necrosis, sarcomatoid differentiation	83–86% (internal)
	Mattila et al. (2021)	Nomogram	194 (single institution	Tumor size, nuclear grade, vascular invasion	84% (external)

Summary of data from [46, 79–92], modified from [17]
RCC renal cell carcinoma, *TNM* tumor, node, metastasis, *CRP* C-reactive protein
[a] Study applies to clear cell RCC only
[b] Study applies to papillary RCC only; †Variable applies only in metastatic setting

Conclusion

It has been well-demonstrated that patients diagnosed with localized RCC may exhibit a wide spectrum of outcomes depending on the clinical, anatomic, histopathologic, and molecular factors discussed in this chapter. All the aforementioned factors should be taken into consideration when counseling patients with

localized RCC and making decisions regarding the optimal management strategy in both the preoperative and postoperative settings [60]. The ability to risk stratify patients provides valuable information that can be used to direct treatment and surveillance plans following surgery. By some models, patients with high-risk RCC have a greater than 40% 5-year risk of recurrence after surgery [61]. These patients, if properly identified, may benefit from adjuvant therapy. Currently, the only approved adjuvant therapies for high-risk localized RCC are sunitinib and more recently pembrolizumab based on the S-TRAC and KEYNOTE-564 trials, respectively. There are several other ongoing trials the in localized RCC setting investigating the adjuvant use of checkpoint inhibitors such as atezolizumab (IMmotion010, NCT03024996), nivolumab (PROSPER RCC, NCT03055013), combined nivolumab and ipilimumab (CheckMate 914, NCT03138512), and durvalumab (RAMPART, NCT03288532) [62]. Optimal patient selection to identify those that stand to gain the most potential benefit from these and future trials is imperative. The means with which this will be done are ever evolving, highlighting the importance of continued research into prognostic factors and tools for localized RCC.

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2 Active Surveillance of Patients with Clinically Localized Small Renal Masses

Muammer Altok and Eric C. Kauffman

Abbreviations

DI	Delayed intervention
PCI	Progression criteria for intervention
RCC	Renal cell carcinoma
RMB	Renal mass biopsy
SRM	Small renal masses

Introduction

Small renal masses (SRM) are defined as renal cortical tumors that are less than 4 cm. SRM include both benign neoplasms and renal cell carcinomas (RCC), the latter of which have only rare metastatic potential [1]. Historically, surgery was the main and only curative management option for these tumors. With the contemporary over-utilization of cross-sectional imaging, there has been a significant shift from diagnosis of symptomatic advanced disease with large primary tumors towards incidental detection of asymptomatic clinically localized SRM [2, 3]. While radical nephrectomy was the gold standard management option for decades, the treatment for localized renal tumors, especially for SRM, has more recently shifted towards less aggressive treatments such as partial nephrectomy and thermal ablation due to growing appreciation of treatment morbidity [4, 5] and the value of renal preservation [6]. The additional realization of low SRM metastatic potential and high (20%–40%) rates of benign resection in surgical series [7–10] have together driven the field to consider even more

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conservative management with an initial expectant approach, aided by the clinical success of active surveillance for low-risk prostate cancer that established a precedent for a successful "less is more" approach. Thus, the concept of non-interventional monitoring of an SRM patient was born 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 [11–14]. With active surveillance of SRM patients, unnecessary treatment can be delayed or avoided, minimizing the impact of associated treatment side effects and with low-to-negligible oncologic risk. This chapter describes the definitions, biology, patient factors, tumor factors, practice patterns, and reported oncologic outcomes that altogether underlie active surveillance management of SRM patients, as well as a detailed description and comparison of current consensus guidelines on SRM patient management from national and international urology and medical oncology committees.

Active Surveillance Definition

Active surveillance is one of two types of expectant management for SRM patients, the other being observation (i.e., watchful waiting). Active surveillance is distinct from observation due to its intent for curative delayed intervention (DI) in patients who demonstrate local progression during follow-up. In contrast, observation is reserved for patients whose comorbidities or otherwise shortened life expectancy contraindicate any curative intent treatment. Avoidance of cancer-specific mortality is a primary goal with either active surveillance or observation. However, whereas metastasis avoidance is paramount during active surveillance, metastasis may be conceded during observation when the likelihood of death from other causes predominates [15]. The European Association of Urology (EAU) [15] and The American Urological Association (AUA) [11] explicitly endorse distinction between active surveillance and observation, however, much of the "active surveillance" literature is contaminated with observation patients, particularly studies published more than a decade ago that still heavily drive current consensus guidelines.

Small Renal Mass (SRM) Indolence

SRM tumors are heterogenous and include both benign and malignant histologic subtypes. Benign tumors including renal angiomyolipomas or oncocytomas represent 20–40% of SRM [7, 16–18]. When malignant, SRM are usually low grade ($\leq$2) and low stage (T1a) RCC, with high-grade (3–4) and/or pT3 tumors comprising only 15–25% of surgical cases [19–23]. Yet regardless of histology, SRM rarely metastasize, and risk of death from other causes is generally higher independent of age, comorbidity, and tumor size [24]. Compared to large (>7 cm) RCCs, SRM RCCs have much less genomic complexity and fewer subclonal events [25]. As tumors grow and evolve, acquisition of late subclonal chromosomal changes leads to divergence of gene expression [25]. Cooperative genomic initiatives such as that

from TRACERx support low mutational diversity in SRM tumors [5, 26, 27]. This biology is referred to the "VHL mono driver" evolutionary subtype because other (i.e., non-VHL) driver mutations are uniquely lacking, and it is largely specific to SRM tumors. The VHL mono driver subtype is characterized by limited genetic evolutionary branching and often requires decades to acquire mutations conducive to metastatic potential, yielding excellent long-term survival outcomes [26, 27].

Trends in Active Surveillance Utilization

Utilization of active surveillance across urology practices has gradually increased over the past two decades. While international studies are lacking, analysis of U.S. population registries (SEER, NCDB) suggests that active surveillance rates, once <5%, have increased to ~17–18%, although perhaps static over the most recent decade [28, 29]. During this time, there have been even greater increases in either partial nephrectomy or percutaneous thermal ablation, even among the elderly [30]. Recently, particularly high rates of active surveillance utilization have been described by certain Urology practices, suggestive of evolving comfort among both physicians and patients. In a recent study from Roswell Park Cancer Center, >95% of all SRM patients seen over 5 years by a single urologic oncologist underwent active surveillance management, regardless of patient age or health, representing the first report in which the vast majority of SRM patients deferred immediate treatment [22]. Substantial variation in active surveillance utilization was observed across a variety of academic and private practices in Michigan [31]. These two studies underscore that factors related to the provider and healthcare setting may be more important than tumor factors in driving current active surveillance utilization. Provider-related differences may in turn reflect variable awareness or comfort/certainty regarding active surveillance management regimens and/or oncologic safety, perhaps reflecting a lack of standardization among different consensus group guidelines (see later in the chapter).

Selection of Patients for Active Surveillance

There is strong general agreement, including among different consensus guidelines groups, to select active surveillance patients based on a combination of tumor size, comorbidities, and life expectancy [11, 14, 15, 32–34]. Patient selection criteria can be divided into specific **tumor factors** and **patient factors**, as described below.

Tumor Factors

- *Tumor Size (a.k.a., Longest Tumor Diameter, LTD)*. The strong association between LTD and metastasis is well established from the surgical literature. Rates of metachronous metastasis approach 0% for SRM <2 cm, and are <1% for SRM <3 cm, and 2–3% for SRM of 3–4 cm, increasing exponentially once a

tumor surpasses 4 cm [24, 35–38]. Surgical series outcomes are consistent with size-specific rates of metastasis reported in active surveillance studies. In a systematic review of early active surveillance series, metastasis never occurred below a primary tumor LTD of 3 cm, and ~90% of all metastases occurred after the primary tumor surpassed 4 cm [39, 40]. More contemporary active surveillance series similarly support a negligible metastatic rate for LTD of <3 cm, and a very low metastatic rate for LTD of 3–4 cm, with the vast majority of reported metastases occurring after the LTD has passed 4 cm (Table 2.1). Accordingly, patients with SRM <2 cm can be considered ideal patients for active surveillance, but accumulating research (see *Reported Active Surveillance Outcomes*, below) also supports the oncologic safety of active surveillance for patients with SRM up to 4 cm. At present, consensus guidelines panels of the American Urological Association (AUA), National Comprehensive Cancer Network (NCCN), and Canadian Urological Association (CUA) recommend consideration (AUA, NCCN) if not preferential selection (CUA) of active surveillance for all patients with a SRM <2 cm regardless of age or health. The American Society of Clinical Oncologists (ASCO) and European Society of Medical Oncologists (ESMO) both support active surveillance for an SRM up to 4 cm if patients have significant comorbidities and/or short life expectancy. The European Association of Urologists (EAU) guidelines do not currently endorse any specific size threshold for active surveillance patient selection.

- *Cystic vs. Solid*. Compared to solid tumors, predominantly cystic tumors (Bosniak III-IV) tend to have more favorable pathology and prognosis, with only rare occurrence of metastasis [51, 52]. Accordingly, Bosniak III-IV SRM are ideal masses for active surveillance. Consensus guidelines panels of the AUA, CUA, and NCCN all support active surveillance as a first line option for SRM up to 4 cm if predominantly cystic, regardless of health or age.
- *Renal Mass Biopsy (RMB) Histology*. No imaging modality reliably distinguishes malignant and benign SRMs, and tumor growth rate also is unreliable [12]. RMB can be used to differentiate benign vs. malignant SRM, and also to help detect unfavorable malignant histology (nuclear grade ≥ 3, papillary type 2 RCC, translocation RCC, unclassified/indeterminable RCC subtypes) that may worsen active surveillance candidacy. RMB is thus increasingly used to guide SRM patient management, with general consensus that it is helpful but not required in this setting. RMB accuracy for benign vs. malignant distinction is excellent, with a recent large meta-analysis reporting the diagnostic sensitivity and specificity of core biopsies for malignancy to be 99.1% and 97.7%, respectively [53]. Non-diagnostic biopsies can occur in 5–15% of cases, which should trigger either a second biopsy attempt or histology-agnostic management. Richard et al. showed that, conservatively, 10% of patients could have avoided treatment of tumors with confirmed benign histology [54]. Similarly, high-volume active surveillance centers including Roswell Park Cancer Center and the Canadian RCC Consortium have successfully avoided benign SRM resection using routine RMB [12, 22, 55]. In addition to benign tumor histology identification, RMB provides prognostic information to guide malignant

Table 2.1 Summary of patients with SRM (≤4 cm at presentation) who developed metastasis during active surveillance

Studies	Cohort type	Patients, *n*	Metastases during AS, Overall[a] *n* (%)	Size of metastatic SRM at AS initiation, cm	Size of metastatic SRM at metastasis, cm	GR of metastatic SRM, mm/year	Time to SRM metastasis, months	SRM metastasis site(s)
Wong 2007 [41]	SRM	1	1 (100)	3.5	5.9	1.9	15	LN
Siu 2007 [42]	RM	41	1 (2.4)	3.0	6.0	0.5	72	LN
Abou Youssif 2007 [43]	SRM	35	2 (5.7)	2.7 2.7	5.8 4.5	0.95 0.9	40 26	Spine Lung
Crispen 2009 [39, 44]	RM	154	2 (1.3)	3.0 3.2	8.0 4.8	1.1 0.3	54 63	Lung LN
Rosales 2010 [45]	RM	212	4 (1.9)	2.6 3.1	4.1 3.8	2.1 0.4	NR	NR
Jewett 2011 [12]	SRM	178	2 (1.1)	2.4 2.7	NR	NR	5 12	Bone Lung
Mason 2011 [46]	RM	84	1 (1.2)	2.9	7.2	2.9	18	NR
Dorin 2014 [47]	RM	114	1 (0.9)	3.6	5.1	1.5	12	Lung
Zhang 2015 [48]	RM (biopsied ccRCC)	60	6 (10)	1.6 1.9 0.1 3.6	4.4 2.8 8.0 7.0	0.2 0.6 4.7 1.3	155 32 32 98	Lung Lung Brain Pancreas
Paterson 2017 [49]	SRM	158	7 (4.4)	3.7 2.8 4.0 1.3 4.0 1.7 3.0	8.1 5.7 – 4.6 10.0 3.6 4.0	2.1 0.8 – 0.6 1.1 0.6[b] 0.7	41 25 50 64 63 64 18	Lung/liver Liver Bone Lung LN Lung/liver Lung/bone
McIntosh 2018 [19]	RM	457	8 (1.8)	2.2[c]	NR	0.7[c]	NR	NR
Whelan 2019 [50]	RM	103	2 (1.9)	3.7 4.6	4.8 8.5	0.4 0.6	30 35	Adrenal Lung

AS active surveillance, *ccRCC* clear cell renal carcinoma, *GR* growth rate, *LN* lymph nodes, *NR* not reported, *RM* renal mass(es) of any size, *SRM* small renal mass(es) ≤4 cm

[a] Overall metastases include both SRM (≤4 cm at initial presentation) and non-SRM (>4 cm at initial presentation)

[b] GR calculated based on the 3-year period prior to metastasis (prior to this period the renal mass did not grow)

[c] Median value for the eight patients with metastases (values for individual renal masses were not reported)

SRM patient management, with high specificity albeit low sensitivity for unfavorable RCC histology (i.e., high nuclear grade and/or papillary non-type 1, unclassified RCC/non-specified subtype or translocation RCC). Unfavorable pathology is infrequent among SRMs, but its occasional presence suggests a higher oncologic risk that may warrant intervention. The prognostic impact in SRM patients of different favorable RCC histologies (low grade clear cell vs. papillary type 1 vs. chromophobe) is more controversial, although the clear cell subtype appears to have faster growth and higher progression/metastasis/intervention rates [22, 55]. Current consensus guidelines generally provide histologic subtype-agnostic recommendations but also commonly support RMB at the discretion of the provider, whenever management may be influenced by the result.

Patient Factors

- *Comorbidities and Age/Life Expectancy*. SRM patients are more likely to die of other causes than of kidney cancer, and this is most evident among the elderly or patients with significant comorbidities [56–59]. Therefore, all major guidelines [11, 14, 15, 32–34] favor active surveillance in patients with short life expectancy, although the precise definition of short is often not provided [11, 32, 34]. AUA guidelines [11] favor active surveillance in elderly patients with life expectancy <5 years, while ASCO guidelines [14] consider an absolute indication for patients with life expectancy <5 years; and relative indication for patients with life expectancy <10 years. In young and healthy patients, the role of active surveillance remains more controversial, particularly for SRM of >2 cm. Recently, DISSRM investigators published a subgroup analysis focused on young patients [60]. This study included 224 SRM patients with age ≤60, including 68 (30%) patients electing active surveillance. Tumor sizes in the active surveillance cohort were typically quite small (median 1.5 cm), and the median growth rate was only 0.09 cm/year, with 27% experiencing zero growth. Twenty (29%) active surveillance patients experienced a clinical progression event defined as an elevated growth rate or elective crossover to DI with objective tumor progression, and 13 (19.1%) total patients ultimately crossed over to DI. Local progression-free survival in these young active surveillance patients was 67% at 5 years, and without any metastases [60]. Similarly, a 72% rate of active continuation beyond 5 years was reported in Roswell Park Cancer Center's recently updated experience of active surveillance recommended to over 200 consecutive progression-free SRM patients without age-related or health-related selection bias, which yielded a relatively young and healthy active surveillance cohort [61]. Thus, active surveillance may be a safe option in young and healthy patients, and also durable in a substantial portion, but further investigation is needed.
- *Renal Function*. Renal function is another important factor during consideration of treatment for SRM patients. An estimated loss 10–20% in glomerular filtration rate is expected with conventional nephron-sparing surgery, however, lower

losses might be achievable with an enucleation surgical approach [30]. Patients with chronic kidney disease who are at high risk for end-stage renal disease (and associated cardiac/other morbidity) with treatment are ideal candidates for active surveillance.

- *Disease Uncertainty*. Disease uncertainty in either the patient or physician can generate anxiety that may swing the risk/benefit balance towards definitive treatment. Historically, this factor has had a predominant role in the management of SRM patients. The impact of the provider and healthcare is supported by the highly variable rates of active surveillance management across different providers. The Michigan Urological Surgery Improvement Collaborative (MUSIC) initiative recently observed widely variable rates of active surveillance management among 13 urology practices, ranging from 0% to 68% [31]. At Roswell Park Cancer Center, nearly all SRM patients seen over a 5-year period were recommended active surveillance. Intriguingly, despite the highly conservative nature of this approach, almost all of these patients agreed to active surveillance after initial informed counseling (95% vs. 1% immediate treatment vs. 4% unknown), including a 100% rate of active surveillance election among patients following up at Roswell Park [22]. These findings underscore the close interconnection between the healthcare provider/setting, anxiety and informed counseling, which altogether continues to have a significant impact on SRM patient management decisions.

Active Surveillance Imaging and Monitoring

The foundation of active surveillance monitoring is periodic renal mass imaging and staging for metastatic progression, with or without adjunct use of RMB [62]. Many prospective active surveillance pathways report the use of multiphasic cross-sectional imaging initially, but transition in the long-term to ultrasound of more indolent masses in order to minimize risks related to radiation and contrast exposure [22, 55, 63]. Short-term interval reimaging of the tumor (typically within 3–6 months) is uniformly endorsed to rule out rapid growth, followed by progressively longer intervals of 6–12 months [12, 19, 22, 63]. The Roswell Park Cancer Center pathway incorporates size-based interval for initial reimaging, with an initial 3-month vs. 6-month scan recommended for tumors >3 cm vs. ≤3 cm, respectively, given the higher metastatic potential of the former [22]. Baseline chest imaging to rule out pulmonary metastasis is universally recommended [36]. However, the utility of subsequent chest monitoring is more controversial, since the metastatic risk approaches 0% in the absence of significant SRM growth [39]; and there are well established psychologic, medical, and financial harms to incidental pulmonary findings. Some active surveillance centers therefore condone omission of repeat chest imaging unless there is (1) an abnormality on baseline imaging, (2) significant SRM growth, or (3) plans for DI, particularly since 20% of chest imaging tests reveal other abnormalities that are typically non-actionable [62, 64].

Role of Renal Mass Biopsy (RMB) in Active Surveillance

RMB is increasingly used to aid SRM patient management by identifying occasional benign or unfavorable histology, with a general consensus that RMB is helpful but not required. Complications from RMB are uncommon and limited primarily to a 1% incidence of clinically significant bleeding, with historical concerns of tumor seeding being largely dismissed due to rarity. RMB usage has grown recently due to growing consensus of a high diagnostic rate and excellent safety profile [53, 65], with some contemporary active surveillance cohorts such as those of Roswell Park and the Canadian RCC Consortium reporting RMB utilization rates of >50% [12, 22, 66]. RMB is often deferred until LTD reaches >2 cm, given the negligible oncologic risk and lower technical success rates of biopsy at smaller sizes [11, 18, 22]. However, some programs, such as at Roswell Park and Bologna (Italy), also utilize RMB in smaller SRM (i.e., <2 cm) with a rapid growth rate (>5 mm/year) to rule out benign tumor histology prior to committing to DI conversion [20, 22]. The DISSRM consortium did not historically utilize RMB, but has evolved to selectively recommend RMB to active surveillance patients with rapid tumor growth or patient-specific LTD sizes (e.g., >2, >3 or >4 cm) [67].

Triggers for Delayed Intervention (DI) During Active Surveillance

An increase in oncologic risk during active surveillance that surpasses the treatment risk is an absolute indication for conversion to DI. The oncologic-treatment risk balance is assessed largely by the same tumor factors and patient factors that drive initial selection of active surveillance patients, with the important exception that tumor growth kinetics revealed during active surveillance can be additionally utilized to improve risk assessment [22]. Historically, the assessment of this risk balance has been largely subjective, which has challenged standardization efforts [21, 63]. In some series, specific objective thresholds are mentioned, but rates of patient's meeting these thresholds are not reported [12, 63], while many patients who meet these thresholds are not converted to DI, perhaps due to common contamination of active surveillance cohorts with unhealthy patients more suited to watchful waiting [39, 40]. While disease uncertainty and patient anxiety continue to drive high variability in contemporary DI rates (11–50%) [22, 27, 35, 36, 68–70]; DI is increasingly triggered by objective tumor factors rather than subjective patient factors, reflecting increased present-day comfort with the concept of treatment deferral for SRMs [12, 19, 21, 46, 47, 49, 50, 55, 68, 74, 76].

Tumor Factors

Despite patient-related factors greatly impact the DI rates even in the contemporary studies, tumor related factors are the main referred factors for progression

criteria for intervention (PCI), aka DI triggers. PCI standardization has been challenged by inconsistent usage of and variability in proposed thresholds [21, 22, 27, 35, 47, 49, 61, 70–74], yielding substantial variability in reported PCI rates (9–30%) [22, 27, 69]. Roswell Park Cancer Center has proposed tumor PCI to fall within 5 categories under the acronym "**GLASS**": **1- Growth rate; 2- Longest tumor diameter; 3- Adverse (i.e., unfavorable) biopsy histology; 4-Stage (i.e., radiographic infiltration); 5-Symptoms**. Based on both incidence and likely impact, growth rate and longest tumor diameter can be considered major PCI, whereas other categories can be considered minor PCI. Roswell Park Cancer Center excludes patients with benign RMB histology from meeting PCI, avoiding unnecessary DI in approximately 15% of SRM patients on active surveillance [22].

Major "GLASS" PCI

- *Growth rate*. Numerous retrospective studies support a significant association of tumor growth rate with RCC grade [22, 48, 68, 76] and metastatic potential [20, 39, 46–50, 69]. Faster growing tumors also appear to be more likely to have clear cell histology [55]. The systematic review by Smaldone et al. of >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 non-metastatic patients [39]. Rapid primary tumor growth is the most common predefined PCI used in contemporary active surveillance series [21, 22, 35, 46, 55, 70–72]. Of the approximately 3 dozen reported cases to date of metastasis during active surveillance for which the primary tumor growth rate is also provided (Table 2.1) [19, 39, 41–43, 45–50, 75], the vast majority had a rapid primary tumor growth rate >5 mm/year, suggesting this otherwise uncommon feature (only ~15% of all SRMs) to be useful for predicting metastasis. Furthermore, *there has not yet been a reported metastasis on active surveillance for a SRM that remains <4 cm in size with a growth rate ≤3 mm/year* (Table 2.1), suggesting that this majority subset of SRM patients may have negligible metastatic risk as long as they remain in this category. Despite limitations of these data, which include common retrospective study designs introducing potential bias in retrospective growth rate measurement, growth rate may still be the best readily measurable indicator of metastatic risk, in addition to tumor LTD. Current AUA, ASCO, and CUA guidelines recommend a linear growth rate of >5 mm/year as a PCI threshold, which is most commonly studied threshold in the active surveillance literature and met by ~13–18% of active surveillance patients [21, 22, 45, 52, 68, 76]. The Roswell Park team [22] has proposed size-stratified growth rate PCI: for SRMs <3 cm, a growth rate threshold of 5 mm/year is used; however, for SRMs with LTD ≥3 cm, they endorse a more conservative growth rate threshold of only >3 mm/year to trigger DI, due to a 2–3% rate of metastasis at this size and multiple reports of metastasis for LTD of 3–4 cm with a growth rate of 4–5 mm/year but not ≤3 mm/year (see Table 2.1); as well as the high likelihood that SRMs with LTD >3 cm and confirmed GR >3 mm/year will ultimately meet a size-based PCI threshold (i.e., LTD >4 cm) within only 1–3 years anyway.

- *Longest Tumor Diameter*. The association between LTD and metastasis in both surgical and active surveillance series was described earlier (see above: Selection of Patients For Active Surveillance / Tumor Factors) including a negligible metastatic rate below 3 cm, and infrequent metastasis between 3 and 4 cm (Table 2.1) [46, 47, 49, 50, 55, 67]. At present, 4 cm is accordingly the most commonly used PCI threshold size for triggering DI in reported active surveillance series. In the Roswell Park cohort [22], 9% of patients developed LTD >4 cm, including 30% of PCI cases and 50% of DI cases; whereas only 25% of DI cases in the Canadian RCC Consortium cohort were triggered by LTD >4 cm [12]. In contrast, the AUA guidelines [11] endorse an LTD threshold of >3 cm to trigger DI in non-hereditary active surveillance patients. One rationale for this lower size threshold is that patients with LTD surpassing 3 cm have high risk to progress to LTD >4 cm shortly thereafter, as Menon et al. [22] observed that only half of patients surpassing 3 cm LTD remained PCI-free 3 years later. However, use of >3 cm as a predefined PCI in active surveillance series is rarely reported, and likely overtreats many patients, particularly those with slow growth (<3 mm/year) for which metastasis rates appear to be negligible.

Minor "GLASS" PCI

Very few series have utilized minor PCI to date, so their value as DI triggers remains unclear. Roswell Park observed that only <3% vs. 30% of SRM patients met minor PCI vs. major PCI, respectively, during active surveillance.

- *Adverse (Unfavorable) Histology*: As described above (see Selection of Patients For Active Surveillance/Tumor Factors/Renal Mass Biopsy), RMB has low sensitivity but high specificity for adverse/unfavorable RCC histology, defined as grade ≥3, papillary non-type 1 RCC, translocation RCC, or unclassified/indeterminable RCC subtypes. Given the higher metastatic risk of unfavorable histology in surgical series [23], patient with unfavorable histology on RMB should be considered for discontinuation of active surveillance.
- *Stage (Invasion/Infiltration)*: Upstaging from cT1a to cT3a is rarely observed in active surveillance series but is known independent prognostic variable for metastasis in surgical series. Therefore, active surveillance patients with new radiologic findings of tumor infiltration sufficient for cT3a upstaging should be considered for DI given the potentially higher metastatic risk. In the Roswell Park cohort only one patient (1%) developed cT3 disease who also progressed by both growth rate and LTD. [22] Similarly, the Canadian Consortium reported only one (1%) patient with DI triggered by tumor thrombus [12].
- *Symptoms*: SRM appear to be almost always asymptomatic. Symptoms that are classically related to RCC tumors, such as gross hematuria, retroperitoneal bleeding/pain, and paraneoplastic syndrome, appear to be rarely if ever observed in SRM patients. To date, the DISSRM Registry [21, 63] had identified no cases of gross hematuria during active surveillance, while the Roswell Park cohort [22] reported one case and the Canadian RCC Registry [12] identified three cases, although bleeding was not clearly related to the SRMs. It is important that other reasons for new symptoms be ruled out before considering DI in SRM patients on active surveillance.

Patient Factors

Although conversion to DI is increasingly triggered by tumor factors (i.e., tumor PCI), only a few contemporary active surveillance centers such as at Roswell Park Cancer Center or University of Bologna have reported tumor PCI development as the most common reason for treatment [20, 22]. Instead, most DI cases in the contemporary active surveillance reports are still performed due to patient factors without PCI development [12, 18, 44, 46, 68, 76]. In the multicenter prospective registries of DISSRM and Canadian RCC Consortium, around 50% or more of patients who crossover to DI do so without tumor PCI development [12, 63].

- *Patient Preference/Anxiety*. At present, patient preference due to anxiety remains the most common patient factor triggering DI, underscoring the persistence of disease uncertainty in contemporary SRM management [12, 21, 44, 46, 68]. The DISSRM team has strived to quantify the impact of anxiety on SRM patients and the durability of active surveillance, demonstrating statistical associations with general quality of life, cancer-specific quality of life, and distress [69]. However, in a structured active surveillance program, mental health scores appear to improve over time, as patient comfort may increase with demonstration of tumor indolence during surveillance (e.g., slow/no growth) [70]. As discussed above, the provider and health care setting likely have a major role in patient acceptance and tolerance of active surveillance, as reflected by very low rates of DI due to anxiety reported by some active surveillance centers (e.g., Roswell Park—1%; University of Bologna—4%) [20, 22]. To minimize unnecessary conversion to DI, in depth discussions from the provider may be necessary to empower the patient with knowledge regarding details such as planned PCI thresholds and expected outcomes, such as slow or potentially zero growth, negligible metastatic risk in the absence of PCI development, and excellent likelihood for freedom from treatment for at least 5 years (see below, *Reported Active Surveillance Outcomes*). Additionally, the provider should emphasize the ability to intervene with DI well in advance of missing a window for cure.
- *Life Expectancy*. Whereas PCI development should be an absolute indication for DI in young/healthy patients, continued active surveillance using modified (less stringent) PCI or conversion to observation may be appropriate in elderly/comorbid patients with limited life expectancy. Future metastasis will be clinically insignificant when life expectancy is limited (e.g., <5 years) [71]. On the other hand, improved patient health during active surveillance (e.g., resolution of an acute health issue such as stented coronary artery disease) may increase life expectancy and swing the risk-benefit balance towards treatment [46]. The Roswell Park active surveillance program recently described an algorithm that integrates PCI triggers with life expectancy estimations to guide decision making regarding DI conversion [22].
- *Other Patient Factors*. Although an uncommon scenario, patients with end-stage renal disease may require resection to be eligible for renal transplantation [49, 62]. Risk for patient non-compliance is rarely reported for DI conversion, but is perhaps under-utilized since many reported metastases during active surveillance

have been ascribed to lost patient follow-up that resulted in large primary tumor sizes [39, 49]. Unrelated additional surgery has also been reported as a DI trigger [72], but this reason is generally not endorsed. Similarly, concern for losing a window to perform nephron-sparing treatment should not trigger early DI, since active surveillance does not appear to compromise the ability for nephron-sparing treatment [20–22, 44, 47, 49, 55, 68, 76].

Research Support for Active Surveillance

Early research in active surveillance was guided by pioneering studies from the National Cancer Institute on hereditary RCC (particularly VHL syndrome), which accounts for ~5% of all RCC cases. The long-term dialysis risk of these patients due to bilateral/multifocal tumor intervention(s) necessitated more conservative management such as active surveillance. Moreover, prior surgical series indicated the metastatic potential of VHL syndrome-related RCC to be closely related to primary tumor size, with metastasis never observed with tumors <3 cm [38]. Therefore, a threshold tumor size of 3 cm was adopted as a trigger for intervention, and active surveillance thus grew into routine practice for renal tumors <3 cm in patients with VHL syndrome and certain other hereditary RCC syndromes [38, 73]. This pioneering work revealed the oncologic safety of active surveillance in treatment risk-adverse SRM patients, and set the stage for extrapolation of this management into sporadic (non-hereditary) RCC patients, as described below.

Systematic Reviews

Early research into active surveillance management for sporadic renal tumors included predominantly patients who were unfit for surgery, at a time when thermal ablation was not yet widely available as a less invasive option. Many of these patients were, by current definitions, “observation” patients rather than “active surveillance” patients, since curative DI was never intended due to significant comorbidity and/or limited life expectancy. Nevertheless, this early work was pivotal in revealing clinically indolent behaviors of SRM, namely their generally slow (and frequently zero) growth, and their very low metastatic potential including a near-zero incidence with tumor sizes <3 cm, paralleling the hereditary RCC patient active surveillance literature. These early series were excellently summarized in a comprehensive systemic review and pooled subset analysis by Smaldone et al. in 2012, which included active surveillance studies published between 1966 and 2010 [39]. In total these investigators identified 18 retrospective active surveillance series comprising 880 patients with 936 “small renal masses” (median size 2 cm), although many masses were in fact >4 cm at active surveillance initiation (range up to 12 cm); and ~1 in 4 patients were likely “observation” patients, given reportedly an unacceptable operative/renal risk with treatment that negated elective treatment; and tiny lesions of necessarily indeterminate nature (e.g., 0.2 cm) appear to have been

included. With median follow-up of 27.5 months, the median linear growth rate was 0.25 cm/year (range −1.4 to +2.5 cm/year), and ~1 in 4 tumors showed zero net growth. Six studies comprising 259 patients (284 masses, median age 69 years) provided adequate individualized data for pooled analysis, in which 45% of tumors progressed to DI after a median of 24 months. Patient factors unrelated to tumor growth (e.g., anxiety) were responsible for most (64%) DI conversions, while tumor growth accounted for only a minority (36%). Of all 880 patients, only 18 (2%) progressed to metastasis, and in most of these cases the patients were not candidates for surgery due to health risks, consistent with "observation" status, and with large tumor sizes (commonly >6 cm) at the time of metastasis. As expected, patients who progressed to metastasis had significantly older age (median 78 vs. 69), larger initial tumor size (median 3.1 vs. 2.0 cm), larger final tumor size (median 5.9 vs. 2.7 cm), and faster tumor growth (median 0.65 vs. 0.25 cm/year). *Only 2 metastatic patients had a primary tumor size <4 cm at the time of metastasis, and no tumor metastasized when it remained <4 cm with a growth rate of ≤3 mm/year*. This large systematic review thus guided more contemporary active surveillance protocols regarding tumor thresholds for conversion to DI related tumor size and growth rate, setting the stage for contemporary active surveillance management in progressively healthier patients with SRM [22].

A more recent systematic review by Mir et al. [40] in 2018 analyzed 28 active surveillance studies (cT1-cT2) published from 2000 to 2017, although only 10 of these studies included exclusively cT1a patients (median tumor size 2 cm). The median age for the cT1a cohort was 72 years, reflecting selection bias for elderly patients. The median follow-up, at 43 months, was longer than that of the Smaldone et al. review [39] and similar to or longer than most reported surgical series. DI rates for these cT1a patients varied widely (1–26%), likely reflecting the predominant influence of patient factors rather than tumor factors. Similar to the Smaldone review, the median tumor growth rate was 0.37 cm/year overall and 0.22 cm/year for cT1a tumors, while faster among patients electing DI (overall 0.73 cm/year, cT1a 0.62 cm/year). Metastasis rates were low (1.4% for cT1a, 2.5% overall) and cancer-specific mortality was 1%. This review substantiated slow tumor growth and low metastasis and cancer-specific mortality, supporting the oncologic safety of active surveillance for patients with SRMs.

Active Surveillance Series with Prospective Management Pathways

A comprehensive summary of published contemporary active surveillance series (>50 patients, minimum) is provided in Table 2.2. Conclusions are limited by the commonly retrospective study designs and heterogeneous active surveillance management strategies even within a single active surveillance center. A major challenge to interpreting this literature has been the scarcity of prospectively applied active surveillance approaches, particularly with regard to imaging approaches (modality/intensity/frequency) and objective tumor PCI thresholds for triggering

Table 2.2 Summary of progression and DI outcomes of contemporary active surveillance (>50 patients)

Studies	Center	Patients (SRM)	Age (years)	Tumor selection	Biopsy rate (%)	Progression criteria for DI	Initial LTD (cm)	FU (years)	Growth rate (cm/yr)	No growth (%)	PCI-Free rates (%)	DI rates (%)	Met rates (%)
Crispen 2009 [44]	Single center Retrospective	154 (172)	71	Localized RM (cT1–2)	–	Not defined	2.0	2.0	0.15	26	–	39	1.3
Rosales 2010 [45]	Single center Retrospective	173 (178)	–	SRM subgroup	19	Not defined	1.9	–	0.27	–	–	5.7	1.9
Jewett 2011 [12]	Multicenter, prospective (RCC Consortium of Canada)	178 (209)	74	SRM	55.6	– LTD ≥4 cm – Volume DT ≤1 year – Metastases	2.1	2.4	0.13	36	Overall 85%	5.1	1.1
Finelli 2020 [55]	Multicenter, mixed prospective retrospective (RCC Consortium of Canada)	134 (136)	70	SRM Proven RCC	100	– LTD ≥4 cm – Volume DT <1 year	2.3	5.8	0.28	–	5-year 46%	38.9	4.5
Mason 2011 [46]	Single center Prospective	82 (84)	74	RM ≤7 cm (cT1)	8.5	Not reported	–	3.0	0.25 (mean)	15.5	–	14.6	1.2
Dorin 2014 [47]	Single center Retrospective	114 (131)	69	All RM that enrolled to AS (no info on size or stage)	–	Significant growth, no predefined metrics, maybe >3 cm	2.1	4.2 (mean)	0.72 (mean)	37.4	–	11.5	0.9
Schiavina 2015 [20]	Single center Retrospective	70 (74)	77	SRM	40	Fast growth No predefined metrics	2.1	5.1	0.6	–	–	–	2.9

Paterson 2017 [49]	Single center Retrospective	158[a]	71.5	SRM	15.6	– Solid >4 cm – Increase in size	2.2	1.6	0.1	35.6	–	26.9	4.4
McIntosh 2018 [19]	Single center Retrospective	457 (544)	70	Localized RM (cT1–2)	–	Not reported	2.1	5.6	0.19	38	–	34	1.8
Gupta 2019 [21]	Multicenter prospective (DISSRM registry)	371	71	SRM	11.4	– LTD ≥4 cm – GR >0.5 cm/yr	1.8	1.96	0.09	–	–	12.4	0
Whelan 2019 [50]	Prospective Single center	103 (107)	75	RM <6 cm	10.7	Not reported	2.1	4.6	0.21 (mean)	–	–	16.5	1.9
Menon 2021 [22] Updated Altok 2022 [61]	Retrospective Single center	201 (226)	65	SRM	59.7	– LTD ≥4 cm – GR >0.5 or 0.3 cm/yr	2.2	3.3	0.2	35.3	5-year 60%	21	0
Ajami 2021 [76]	Retrospective Single center	73 (73)	75	RM T1a-b	8.2	– GR >0.5 cm/yr	2.1	2.8 (mean)	0.2	48	–	21	0
Bertelli 2021 [68]	Retrospective Single center	158	–	SRM	–	– GR >0.5 cm/yr	1.6	2.1	0.4	52	90%	27.2	0

AS active surveillance, *DI* delayed intervention, *FU* follow-up, *GR* growth rate, *LTD* longest tumor diameter, *Met* metastases, *PCI* progression criteria for intervention, *RM* renal masses, *SRM* enhancing small renal masses (≤4 cm)

[a] Only solid SRM cohort included. Study separated cystic SRM with Solid SRM

DI. Recently, several centers have described the use of prospectively applied active surveillance pathways, with or without required protocol enrollment. These series differ in nuances of their prospective pathways, but collectively provide strong support for the durable safety of active surveillance.

- *The Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry* described by Pierorazio et al. in 2015 [63] and updated by Gupta et al. in 2019 [21] includes a large cohort of non-randomized SRM patients who were prospectively enrolled with the primary outcome measure of oncologic outcome between active surveillance vs. surgery. DI was recommended for renal masses with growth rate >0.5 cm/year or size >4 cm. Per most recent update, a total of 727 SRM patients were enrolled, including 371 (51%) electing active surveillance with median follow-up of 23.6 months, during which 46 (12.4%) crossed over to DI. Median tumor size in the active surveillance cohort was only 1.7 cm and median age was 71 years, reflecting expected selection biases. Compared to the surgical cohort, active surveillance patients were significantly older, unhealthier, and more likely to have smaller and multiple tumors. No progression to metastasis or cancer-specific deaths occurred in active surveillance patients, whereas two deaths occurred in the surgery group ($p = 0.8$); and 33 (8.9%) patients died secondary to other causes. Although the median follow-up interval for surveillance patients was only 23.6 months, 25% of this cohort had at least 5-year follow-up, and the 5-year DI-free survival rate was 78%. Hence, *most active surveillance patients had durable avoidance of treatment and without any apparent compromise in oncologic outcome.* While overall rates of PCI were not reported, half of DI cases were ascribed to PCI while around half were due to patient preference, underscoring the persistent role for anxiety in truncating surveillance and perpetuating overtreatment.
- The prospective registry of the *Renal Cell Cancer Consortium of Canada* includes active surveillance patients from eight centers, the initial outcomes of which were detailed by Jewett et al. in 2011 [12]. From 2004 to 2009, 178 patients with 209 incidentally detected SRMs who unfit for surgery due to advanced age, comorbidities, or treatment refusal were enrolled (median age 74 years, median size 2.1 cm). Patients were excluded if they had less than a 2-year life expectancy, SRM diagnosis >12 months prior to enrollment, systemic therapy for other malignancies, or a known hereditary RCC syndrome. Tumor progression was prospectively defined as size ≥4 cm, doubling of volume in ≤12 months, or metastasis. With a median follow-up of 29 months, 27 (15%) patients progressed, including 13 (48%) due to size, 12 (44%) due to doubling rate, and 2 (7%) due to metastases. Only 9 of 25 (36%) patients who progressed locally underwent DI, suggesting likely "observation" status at the time of progression. Median tumor growth was only 0.13 cm/year, and ~1 in 3 tumors did not grow. More recently, this consortium described outcomes of active surveillance (2004–2015) for a 134 SRM patient subgroup with biopsy-proven RCC (median age 70 years, median size 2.3 cm) [55]. This report is significant because it focused exclusively on malignant SRM, exploiting this

consortium's common if not routine use of renal mass biopsy, in contrast to other high-volume active surveillance centers in the U.S. or Europe (other than Roswell Park Cancer Center, see below). The 5-year PCI rate was 54%, with the majority of PCI cases having clear cell histology (73%). The median growth rate was 0.17 cm/year in the first year and 0.19 cm/year over the first 3 year, although a mathematically predicted 12-year growth rate was 0.28 cm/year. The growth rate with clear cell history was significantly higher than with other RCC subtypes, which commonly had no growth (median 2.5 vs. 0.2 mm/year, respectively). Moreover, metastases occurred in 6 (4%) patients, all with clear cell histology, and most of which had local progression. Importantly, 2 patients had metastasis without "significant" local progression, although the specific sizes and growth rates were not reported for these 2 cases. Overall, 29 patients died, including 3 due to metastases, 23 due to other causes, and 3 due to unknown causes.

- More recently, *Roswell Park Comprehensive Center* has described a unique clinical practice of a single urologic oncologist, in which ***active surveillance was recommended universally over ~5 consecutive years to all SRM patients lacking evidence of local progression at the time of presentation***, a practice which resulted in >95% of all newly presenting SRM patients undergoing active surveillance [22]. Thus there was no health- or age-related selection bias, which is novel among reported active surveillance series. This cohort is the first reported consecutive patient series in which the vast majority of SRM patients deferred immediate treatment. Per their prospective management pathway, DI was recommended only if tumor PCI developed during active surveillance. PCI thresholds were prospectively defined using the GLASS criteria described above. However, for the growth rate threshold, the researchers utilized a size-stratified cut-off, including growth rate >5 mm/year for SRM size ≤3 cm, but >3 mm/year for SRM size >3 cm. Similarly, initial repeat cross-sectional imaging (CT or MRI) and staging chest X-ray (CXR) were recommended after 6 months for SRM size <3 cm, but after 3 months for SRM size >3 cm. Additional serial imaging was then obtained every 6 months until tumor stability was observed (<3 mm/year over a 2–3-year period). Patients with low oncologic risk (tumor stability or benign histology on biopsy) and/or high treatment risk were switched to annual ultrasound monitoring after at least 3 years of cross-sectional imaging. Patients who met >1 progression criteria were offered treatment if life expectancy was >15 years or were converted to observation if life expectancy was <5 years. Overall, of the 128 patients electing active surveillance, 75% remained DI-free at 3 years and none metastasized. In their recently updated report of 201 patients with median follow-up of 40 months [61], the 5-year PCI-free and DI-free survival rates were 60% and 71%, respectively. Worse PCI-free and DI-free survival was associated with the initial tumor size and clear cell RCC biopsy histology, supporting the importance of histologic subtype as also reported by the Canadian RCC Consortium (see above). DI resections were enriched for pT3 and/or nuclear grade 3–4 malignant pathology (55% of DI cases), including no benign resections, suggesting that their prospectively applied PCI thresholds may be

effective at identifying more aggressive SRM cases for treatment, given that only 15–25% of SRM generally harbor adverse pathology. Importantly, only 1 active surveillance patient had crossed over to DI without PCI development, indicating excellent overall tolerance of the "universal" active surveillance approach at their cancer center. No patient developed metastasis, supporting the oncologic safety of this unique approach.

- *The Michigan Urological Surgery Improvement Collaborative (MUSIC)* recently initiated a prospective kidney mass registry for all patients with newly presenting cT1 renal masses, with a goal to assess initial management decisions across a diverse range of urology practices [31]. From September 2017 to April 2019, patients with cT1a or cT1b renal masses were studied from 13 practices. The terminology of observation was used in this study instead of active surveillance. Out of 965 patients, an initial observation period was employed in 48% (n = 459), with individual practice rates ranging widely from 0% to 68%. As expected, patients managed with observation (vs. immediate treatment) were significantly older (71.2 vs. 62.8 year) and had smaller tumors (2.3 vs. 3.4 cm). Observation was used for 53.5% of cT1a renal masses, 29.9% of cT1b renal masses, and 42.5%, 53.7%, and 63.9% of radiographically solid, Bosniak III–IV cystic, and indeterminate cT1RMs, respectively. Factors significantly associated with observation in multivariable analysis included lesion type (Bosniak III–IV vs. solid), tumor stage (cT1a vs. cT1b), and higher age. DI was performed in only 3.1% (14 patients) of the observation patients in a median follow-up of 24.6 months. In univariate analyses, physicians were more likely to observe a cT1 renal mass if they practiced in a non-academic setting (52.9% vs. 42.8%, $p = 0.002$) and if RMB was not performed (49.2% vs. 39.5%, $p = 0.022$); however, these associations were not maintained in multivariable analyses. This early work is informative to capture the current large variation in active surveillance utilization among contemporary academic and private practices.

Summary of Consensus Guidelines

Commonly used guidelines for the management of SRM include those from the American Urological Association (AUA), European Association of Urology (EAU), Canadian Urology Association (CUA), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and European Society of Medical Oncology (ESMO). Summaries of these guidelines are provided below and in Table 2.3. Other national Urological societies including those from England, Japan, Saudi Arabia, and Argentina have published guidelines on the management of RCC, however, these guidelines have not been updated for more than 5 years and are not discussed here.

Table 2.3 Summary of the guidelines' recommendations on active surveillance

Guidelines	Recommendations
AUA	• Active surveillance appropriate initial management for all SRM patients with a tumor that is either <2 cm or predominantly cystic • Progression criteria: Absolute size >3 cm, median growth rate in excess of 5 mm/year, clinical stage migration, infiltrative appearance, or aggressive histology on RMB • RMB is recommended for further oncologic risk stratification in patients with a solid or Bosniak 3/4 complex cystic renal mass in whom the risk/benefit analysis for treatment is equivocal and who prefer active surveillance • Imaging: Initial scan should be contrast-enhanced cross-sectional imaging, while subsequent imaging may include the same or an abdominal ultrasound. Chest XR annually or if intervention triggers are encountered or symptoms arise (initial chest imaging XR or CT)
EAU	• Weak recommendation of active surveillance in frail or comorbid patients • No recommendation about size or follow-up period • Weak recommendation for RMB in patients for whom active surveillance is under consideration
NCCN	• Endorse active surveillance as an option for the initial management of patients with SRM <2 cm and in patients with T1a tumors (≤4 cm) that have a predominantly cystic component • For larger cT1 masses up to 7 cm, active surveillance recommended in case of competing risks of death or morbidity for intervention • RMB is recommended at initiation of active surveillance or at follow-up, as clinically indicated • Imaging: Contrast-enhanced CT or MRI is recommended at initiation and every 6 months for the first 2 years, subsequent imaging may be performed annually thereafter with either cross-sectional imaging or ultrasound. Chest X-ray or chest CT is recommended at baseline, and annually as clinically indicated
ASCO	• Active surveillance is recommended as an initial management option for patients with SRMs who have significant comorbidities and limited life expectancy – Absolute indication: High risk for anesthesia and intervention or life expectancy <5 years – Relative indication: Significant risk of end-stage renal disease if treated, SRM <1 cm, or life expectancy <10 years • RMB should be considered in all SRM when the results may alter management • Chest X-ray and axial abdominal imaging (or ultrasonography) was recommended every 3 months in the first year, twice in the second and third years, and yearly thereafter • Treatment during active surveillance was recommended when tumor grows >0.5 cm per year or reaches >4 cm in size, depending on the patient's comorbidities and life expectancy
ESMO	• Very limited discussion on active surveillance • Active surveillance is recommended for SRM as an option in elderly patients with significant comorbidities or those with a short life expectancy • RMB is recommended to select patients with SRM for active surveillance • No recommendation on follow-up, progression, or treatment for patients elected for active surveillance

(continued)

Table 2.3 (continued)

Guidelines	Recommendations
CUA	• Active surveillance is recommended as the preferred strategy for SRM <2 cm • For SRM 2–4 cm, either active surveillance or definitive treatment (partial nephrectomy or thermal ablation) are endorsed • For patients with a SRM and significant comorbidities and/or limited life expectancy, watchful waiting (observation) is recommended as the preferred strategy • RMB is recommended whenever the result may alter management • DI during active surveillance is recommended as growth of the longest tumor diameter to >4 cm and/or growth rate > 0.5 cm/year • Imaging: Cross-sectional imaging (CT or MRI) and chest X-ray at baseline (chest CT if suspicious lesion on chest X-ray). During follow-up, ultrasound was recommended once every 3–6 months for the first year and then once every 6–12 months if the lesion remains stable. If tumor growth suspected cross-sectional imaging should be performed for confirmation. Chest X-ray was recommended from for-cause to once a year. Stop imaging if definitive treatment is no longer considered

American Urological Association (AUA) Guidelines

The AUA updated their guidelines on SRM active surveillance in 2021 [11]. The current guidelines make a conditional recommendation (Evidence Level: Grade C) for active surveillance with potential DI as an appropriate initial management for all SRM patients with a tumor that is either <2 cm or predominantly cystic. For larger SRM, the AUA recommends prioritizing active surveillance/expectant management whenever the anticipated risk of intervention or competing risks of death outweigh the potential oncologic risks of the tumor. Tumor radiographic or histologic features that favor active surveillance/expectant management per the AUA include size <3 cm, growth rate <5 mm per year, non-infiltrative appearance, predominantly cystic nature, intralesional fat suggestive for an AML, or favorable histology by renal mass biopsy (RMB). Regarding patient factors, the guidelines favor active surveillance/expectant management in elderly patients with life expectancy <5 years, high comorbidities, excessive perioperative risk, poor functional status, marginal renal function. The AUA guideline also emphasizes the importance of informing patients regarding the possibility of benign rather than malignant tumor.

The AUA guidelines endorse a role for RMB in assessing active surveillance candidacy in patients with a solid or complex cystic renal mass (if adequate solid component) in whom the risk/benefit analysis for treatment is equivocal. For those with predominantly cystic lesions, RMB should be avoided. Regarding imaging modality, the AUA guidelines recommend that the initial scan consist of contrast-enhanced cross-sectional imaging, while subsequent imaging may include the same or an abdominal ultrasound. For imaging interval, the AUA guidelines recommend an initial 3–6-month period to assess interval growth, after which the subsequent imaging interval should be individualized to the patient based on growth rate, tumor biology, risk calculations and shared decision making focusing on goals, risks and triggers for intervention. Regardless of the surveillance intensity, surveillance chest

imaging with plain radiography is recommended annually or whenever intervention triggers or symptoms arise. Acknowledging a lack of level 1 supporting evidence, the AUA guidelines recommend that triggers for DI should generally be driven by changes in risk based on a combination of these tumor factors (absolute size >3 cm, median growth rate in excess of 5 mm/year, clinical stage migration, infiltrative appearance, or aggressive histology on RMB) and patient factors (life expectancy, comorbidities), with continual objective reassessments that may include the use of RMB when appropriate. More specifically, DI should be recommended per AUA guidelines whenever substantial interval growth is observed or other clinical/imaging findings suggest that the risk/benefit analysis is no longer equivocal or favorable for AS continuation, although it is not explicitly stated in the guideline what constitutes equivocal or favorable risks, permitting some subjectivity in evaluation.

European Association of Urology (EAU) Guidelines

The EAU guidelines (2022 updated annually) [15] make a weak recommendation to offer active surveillance to frail or comorbid patient with SRM considering the slow tumor growth in most cases and low progression rate to metastatic disease (1–2%). The guideline does not mention any specific size or period for follow-up. The EAU guidelines make a weak recommendation for RMB when active surveillance is under consideration and acknowledge that characterization of histological grade and subtype by is useful to select SRM patients at lower risk of progression that can be managed safely with active surveillance. The EAU guidelines explicitly distinguish the concept of active surveillance from that of watchful waiting, and do not require follow-up imaging for the latter.

Canadian Urology Association (CUA) Guidelines

Recently published guidelines from CUA [34] for managing a patient with an SRM(s) acknowledge that there is no "one-size-fits-all" strategy and emphasize the consideration of shared decision making based on the tumor characteristics, competing medical risks and patient's values and preferences. As with AUA and EAU guidelines, CUA guidelines differentiate active surveillance from watchful waiting (observation). For SRM <2 cm, these guidelines endorse active surveillance as the preferred strategy over immediate intervention (Conditional recommendation). For SRM 2–4 cm, either active surveillance or definitive treatment (partial nephrectomy or thermal ablation) is endorsed (Conditional recommendation). RMB is recommended whenever the result may alter management, but not for patients who will undergo surgical removal regardless of histology or watchful waiting patients who will not undergo treatment regardless of the RMB result. The panel defines indications for conversion to DI as growth >4 cm and/or consecutive growth rates of >0.5 cm/year (clinical principle). In case of suspected tumor growth on ultrasound, cross-sectional imaging should be performed to confirm growth prior to

intervention. The guidelines recommend contrast-enhanced CT or MRI at baseline like other guidelines. Different than other guidelines, acknowledging that the sensitivity for metastasis is low with chest X-ray compared to a chest CT, the guidelines suggest a chest X-ray at the initial imaging of choice, given the low incidence of metastasis and lower harms and cost. If any abnormalities are detected on the chest X-ray, a chest CT should be performed. For patient on follow-up during AS, the panel recommended routine abdominal ultrasound until definitive treatments are no longer considered. Chest X-ray imaging was recommended during follow-up for metastatic staging. The panel was unable to achieve a consensus as to the frequency of abdominal imaging. Similarly, no consensus was reached for the interval of metastatic staging, which varied from for-cause to once a year.

National Comprehensive Cancer Network (NCCN) Guidelines

Similar to AUA guidelines, NCCN guidelines (2022) [32] endorse active surveillance as an option for the initial management of patients with SRM <2 cm or with a predominantly cystic component. For the cT1 masses up to 7 cm, they recommend active surveillance as the primary consideration if there is decreased life expectancy or significant competing risks of death/morbidity from intervention. Unlike AUA and EAU guidelines, the current NCCN guidelines do not differentiate active surveillance from watchful waiting. NCCN guidelines recommend RMB at initiation of active surveillance or at follow-up, as clinically indicated. In order to determine the tumor growth rate, abdominal imaging with contrast-enhanced CT or MRI is recommended within 6 months of active surveillance initiation and every 6 months for the first 2 years; subsequent imaging may be performed annually thereafter with either cross-sectional imaging or ultrasound. The NCCN guidelines state that all three imaging modalities (US, CT, and MRI) accurately predict pathologic tumor size, therefore, best clinical judgment should be used in choosing the imaging modality. For metastatic staging, NCCN guidelines recommend chest x-ray or chest CT at baseline, annually "as clinically indicated," and whenever intervention is under consideration. However, these guidelines also allow follow-up to be individualized based on "surgical status," treatment schedules, side effects, comorbidities, and symptoms.

American Society of Clinical Oncology (ASCO) Guidelines

ASCO guidelines [14] (2017) recommend that active surveillance for SRM should be an initial management option for patients who have significant comorbidities and limited life expectancy. They note an absolute indication for patients at high risk for anesthesia/intervention or life expectancy <5 years; and relative indication for patients with significant risk of end-stage renal disease if treated, SRM <1 cm, or life expectancy <10 years. The guideline recommends that a RMB biopsy should be considered for all patients with an SRM when the results may alter management. The

guideline recommends a staging chest x-ray and axial abdominal imaging (or ultrasonography) every 3 months in the first year of active surveillance and twice in the second and third years (yearly thereafter), which is notably more frequent than other guidelines endorse. DI triggers supported by ASCO include tumor growth >0.5 cm/year or size >4 cm, depending on the patient's comorbidities and life expectancy.

European Society of Medical Oncology (ESMO) Guidelines

ESMO guidelines [33] (2019) are mainly focused on metastatic RCC and provide very limited recommendations and discussion on active surveillance. The guidelines recommend active surveillance as an option in elderly patients with significant comorbidities or those with a short life expectancy and SRM measuring <4 cm. RMB is recommended to select patients with SRM for active surveillance, because of the incidence of non-malignant tumors in this setting. The guidelines do not mention any recommendation on follow-up, progression or treatment for patients elected for active surveillance.

Conclusion

Despite limitations of the current literature, accumulating evidence indicates that active surveillance is a safe initial management strategy for many SRM patients. Future research should focus on standardization of objective PCI definitions and characterization of long-term active surveillance outcomes, including rates of DI, metastasis, and cancer-specific survival. Additionally, more investigation is needed to define the role of active surveillance in young healthy patients, as well as impacts on quality of life and health care finance.

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Partial Nephrectomy in the Treatment of RCC

3

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Historical Background

The first partial nephrectomy (PN) was performed in 1867 when part of a kidney was accidentally removed during an operation for liver cysts. In 1869, the first successful radical nephrectomy (RN) was performed for a urinary fistula proving that people could survive with only one kidney. This may have been one of the reasons for the delayed rise in the popularity of PN.

In the late 1800s, numerous trials focused on PN for localized kidney diseases. However, PNs quickly fell out of favor due to the high complication rates and poor outcomes. Radical nephrectomy became the treatment of choice, especially for cancer operations, due to good oncologic control and substantially lower complication rates. In the early 1900s, RN was the treatment of choice for kidney cancer, while PN was performed only out of necessity and was, in fact, contraindicated if the contralateral kidney was believed to be healthy [1].

In the 1950s, Vermooten began promoting PN as data from that time demonstrated that small renal tumors are frequently well-encapsulated leading to low rates of recurrence and metastasis [2]. Since that time, PN has been gaining in popularity with the development of numerous advances leading to improved surgical and oncologic outcomes.

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Controversies

The controversies of adopting PNs have not only originated from technical challenges. Several other observations and studies definitively demonstrated excellent safety, longevity and long-term outcomes of RN. While historic observations found that patients could survive with only one kidney, studies from transplant literature demonstrated that donor nephrectomy patients did well, with minimal complications and no significant renal dysfunction. Additionally, several meta-analyses demonstrated a low absolute risk of end-stage renal disease (ESRD) in donor transplant nephrectomy patients [3, 4]. Finally, living kidney donors did not have an increased risk for other major chronic diseases [4].

With time, however, it was appreciated that donors or patients with excellent performance status and renal function may not necessarily be reflective of the population that presented with renal cell carcinoma (RCC). For example, Huang et al. demonstrated that many cancer patients had some degree of pre-existing chronic kidney disease (CKD) and RN was a significant risk factor, compared to PN, for the development or progression of CKD [5]. This key study demonstrated that patients with kidney cancer were not equivalent to highly selected renal donors.

In addition, the concept of medical and surgical kidney disease evolved further, demonstrating major differences between transplant donor patients and cancer patients. Medical kidney disease is caused by chronic health conditions, such as diabetes and hypertension, leading to gradual bilateral kidney deterioration. Surgical kidney disease, on the other hand, is due to procedures that either decrease or damage the number of nephrons. Generally, patients with medically-induced kidney disease are older with more medical comorbidities, have higher rates of functional decline and have worse survival outcomes than patients with surgically-induced kidney disease [6]. Compared to patients with medical renal disease, surgically-induced chronic kidney disease is associated with a relatively low risk of progressive renal decline [7]. Over time, the dogma that RN was the treatment of choice for RCC began to shift towards more individualized approaches.

Adding to the above controversies is the appropriate selection for small renal tumors. The European Organization for Research and Treatment of Cancer (EORTC) randomized trial 30,904 compared PN with RN for the treatment of small, solitary renal masses [8]. This study demonstrated an overall survival (OS) advantage for patients treated with RN compared to those treated with PN. While being the only randomized study, it was underpowered and had a significant crossover between treatment arms. Adopting the findings of this trial has been challenging in light of numerous retrospective studies revealing superior outcomes with PN.

With a plethora of retrospective studies, it is quite important to recognize numerous biases that affect results and subsequent conclusions and decisions. Addressing the issue of biases and patient selection, in a SEER-Medicare study, Shuch et al. found that PN patients had better outcomes than RN in pT1a tumors [9]. Interestingly, the authors also found that patients undergoing PN had improved survival outcomes compared to non-cancer control patients. These findings may reflect a strong selection bias in choosing patients to undergo PN.

Indication for Partial Nephrectomy

PN remains an accepted treatment for small renal masses less than 4 cm, while its use for larger tumors is more controversial. Despite this, there are several absolute indications for PN [10], such as a solitary kidney, bilateral renal masses, or cases where the loss of the normal parenchyma could subject the patient to dialysis. Relative indications for PN include patients with pre-existing renal disease in the contralateral kidney (chronic pyelonephritis, renal artery stenosis, vesicoureteral reflux, chronic renal obstruction, or systemic diseases such as diabetes, hypertension or nephrosclerosis), hereditary diseases (von Hippel-Lindau disease (VHL), Birt-Hogg-Dubé syndrome (BHD), hereditary leiomyomatosis and renal cell cancer (HLRCC), hereditary papillary renal cancer (HPRC)), or those with multifocal tumors [10]. Many argue that hereditary multifocal RCC may belong in the category of absolute indications, but that is also decided based on the size and location of the mass, as well as the specific syndrome [11]. However, the approach for each hereditary RCC subtype is different and will be further discussed in section "Partial Nephrectomy in Management of Hereditary RCC Syndromes".

Patient Selection

In choosing whether to proceed with PN, patient selection is critical and several host factors have been shown to impact surgical and functional outcomes following PN. In a meta-analysis, complex tumors (R.E.N.A.L. score 7 or greater, or PADUA score 7 or greater), size greater than 4 cm and hilar tumors were associated with significantly longer operative times, higher estimated blood loss, longer ischemia time, and higher rates of postoperative complications [12]. Similarly, patients with abnormal body mass index tended to have longer operative times, estimated blood loss, and postoperative complications, and those with baseline chronic kidney disease had increased postoperative complications [12]. In a retrospective study, Zaid et al. showed that male sex, solitary kidney, chronic kidney disease, Charlson score ≥ 3, and tumor size were associated with increased risk of 30-day complication rates, regardless of surgical approach [13].

Describing the Surgical Complexity of Tumors

Since not all PN are the same in complexity and with efforts to assess and compare outcomes across studies, it became obvious that a standardized method of describing the tumor complexity was needed. With this in mind, several scoring systems to standardize and quantify tumor characteristics were published. In 2009, the first nephrometry scoring system was created to quantify the anatomical characteristics of renal masses (Table 3.1) [14]. The R.E.N.A.L. Nephrometry Score consists of (R) adius (tumor size as maximal diameter), (E)xophytic/endophytic properties of the

Table 3.1 Nephrometry scoring systems

R.E.N.A.L.			
Radius (max diameter in cm)	≤4 (1 pt)	>4 but <7 (2 pt)	≥7 (3 pt)
Exophyitic/ endophytic	≥50% exophytic (1 pt)	<50% endophytic (2 pt)	Entirely endophytic (3 pt)
Nearness to sinus or collecting system (mm)	≥7 (1 pt)	>4 but <7 (2 pt)	≤4 (3 pt)
Anterior/posterior	Assigned suffix a (anterior), p (posterior), × (unable to determine), h (hilar)		
Location relative to polar lines	Entirely above upper or below lower polar line (1 pt)	Lesion crosses polar line (2 pt)	>50% of the mass crosses polar line or the mass is located entirely between polar lines (3 pt)
PADUA			
Longitudinal (polar) location	Superior/inferior (1 pt)	Middle (2 pt)	
Exophyitic/ endophytic	≥50% exophytic (1 pt)	<50% endophytic (2 pt)	Entirely endophytic (3 pt)
Renal rim	Lateral (1 pt)	Medial (2 pt)	
Renal sinus	Not involved (1 pt)	Involved (2 pt)	
Urinary collecting system	Not involved (1 pt)	Dislocated/ infiltrated (2 pt)	
Tumor size (cm)	≤4 (1 pt)	>4 but <7 (2 pt)	≥7 (3 pt)
Simplified PADUA (SPARE)			
Tumor size (cm)	≤4 (1 pt)	>4 but <7 (2 pt)	≥7 (3 pt)
Exophytic rate	≥50% exophytic (1 pt)	<50% endophytic (2 pt)	Entirely endophytic (3 pt)
Renal sinus involvement	Absent (0 pt)	Present (3 pt)	
Rim location	Lateral (0 pt)	Medial (2 pt)	
C-index			
C-index = (distance between the center of hilum to center of tumor)/(radius of tumor)			
Contact surface area (CSA)			
CSA = 2*(π)*(radius of tumor)*(distance of tumor invasion into kidney)			

tumor, (N)earness of tumor deepest portion to the collecting system or sinus, (A) nterior (a)/posterior (p) descriptor and the (L)ocation relative to the polar line. The suffix h (hilar) is assigned to tumors that abut the main renal artery or vein. The R.E.N.A.L. nephrometry scoring system was able to predict both nephron-sparing surgery and minimally invasive techniques based on the objective complexity of the tumor characteristics [15], and was further validated in numerous independent articles from a multitude of institutions.

The Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification was then designed to standardize patients who are candidates for nephron-sparing surgery (Table 3.1) [16]. This classification system scores tumors based on polar location (superior/inferior vs. middle), exophytic properties of the tumor, renal rim (lateral vs. medial), renal sinus involvement, urinary collecting system involvement and tumor size. Similar to RENAL scoring, higher PADUA scores were independent predictors of complication rates [16, 17] and were significantly correlated with the complexity of PN [17]. The PADUA scoring system was then updated to the Simplified PADUA REnal (SPARE) nephrometry score that removed polar location and urinary collecting system involvement from the scoring [18]. There was no difference in its accuracy to predict overall complications compared to the original PADUA classification [18].

Several imaging parameters have been designed as adjuncts to R.E.N.A.L. and PADUA/SPARE scores. The centrality index (c-index) scoring was devised to quantify the proximity of kidney tumors to the central renal sinus [19]. The c-index is calculated by dividing the distance between the center of the tumor to the center of the kidney by the tumor radius and was able to predict technical complexity. The contact surface area (CSA) score is a measure of the tumor with adjacent renal parenchyma [20]. Higher CSA values were predictive of adverse tumor characteristics, perioperative outcomes, and postoperative renal function [20, 21].

While numerous studies have been performed to compare the above-described nephrometry scores in predicting perioperative outcomes, tumor complexity, and postoperative renal function, the results are mixed as to which model or scoring system is superior [22–25]. Regardless of superiority, these nephrometry scores proved to be reproducible and allowed for improved communication between physicians, as well as enhanced the quality of the published literature on PN outcomes.

Surgical Techniques

While initially only performed via an open approach, over the past few decades, there has been a consistent rise in the use of minimally invasive surgery for PN. Numerous studies have compared surgical outcomes between open, laparoscopic, and robotic PN. Robotic PN has been shown to have fewer complications, estimated blood loss, and hospital stay but longer operative time and warm ischemia time [26, 27]. However, there appears to be an inherent learning curve for robotic-assisted PN, after which perioperative outcomes favor performing the surgery robotically, even for more complex tumors [27, 28]. Similar studies demonstrated improved outcomes when the surgery was performed robotically rather than laparoscopically, with decreased rates of procedural conversion [29]. Nevertheless, due to the significant learning curve in performing any PN, surgeons must perform the right operation, whether it be open or laparoscopic or robotic, to maximize the chances of the best outcome for the patient [30].

Transperitoneal Vs. Retroperitoneal

Since the development of minimally invasive surgery, laparoscopic and robotic PN can be performed using the transperitoneal or retroperitoneal approach. While the transperitoneal approach allows for more working space and familiar anatomic landmarks in the abdominal cavity, it can be more challenging in accessing posterior or lateral masses, and may not be the preferred approach in a hostile abdomen after prior complex abdominal surgeries, carrying a risk of significant complications. Therefore, in some cases the retroperitoneal approach may be preferred. Studies regarding outcomes between the transperitoneal and retroperitoneal PN are mixed. In one study, the approach predominantly varied based on tumor location and surgeon experience [31]. There did not appear to be a substantial difference in outcomes between the transperitoneal or retroperitoneal approaches, however, some studies quoted shorter operative times, reduced blood loss, shorter length of stay, and decreased ischemia time in the retroperitoneal groups [32–34].

Ischemia

The role and type of ischemia have been a subject of long-term discussions, debates, and controversies. Traditionally, in patients with multifocal renal carcinomas, many tumors were removed without occluding blood supply to the kidney. Resection of the tumors without vascular clamping was performed as standard management of patients with hereditary renal syndromes. Building on their open experience, in 2009, the NCI team published their initial experience with robotic partial nephrectomy for multiple tumors, documenting that the last 3 of their first 10 patients with multiple tumors had tumor removal without any ischemia [35]. Later, in 2011, this technique was further popularized as “zero-ischemia” or “off-clamp” PN. [36]. This was also feasible using a robotic approach.

In 2011 Shao et al. first described the segmental artery clamping with a laparoscopic approach where they documented a series of 75 patients with segmental renal artery clamping, concluding that it was safe and feasible in clinical practice while minimizing intraoperative warm ischemia injury and providing better early postoperative renal function compared with main renal artery clamping [37]. Subsequently, Gill et al. also reported their experience with vascular microdissection of the renal hilum and selectively clamping vessels feeding the tumor, while retaining perfusion to the remainder of the kidney [38]. Some investigators documented the utility of intraoperative indocyanine green (ICG) as a useful tool to assess vascular anatomy that assisted in super-selective dissection during robotic PN [39]. The initial excitement of super-selective clamping has been tempered with some studies demonstrating no advantage to this technique. For example, some reported that while super-selective clamping was associated with slightly increased blood loss, it preserved kidney function and offered comparable oncologic outcomes without an increase in perioperative complication rates [40, 41].

Several studies have also examined the effect of cold versus warm ischemia during PN. The purported mechanisms for ischemic renal failure are believed to be due to persistent vasoconstriction, abnormal endothelial cell response, tubular obstruction due to sloughed tubular epithelial cells, membrane debris leading to leakage of glomerular filtrate into capillaries, and ischemic reperfusion injury following the restoration of blood flow. Transplant literature demonstrates that cold ischemia preserves organ function significantly longer than warm ischemia. A similar approach was examined in PN as prolonged warm ischemia was thought to cause long-term renal dysfunction, however, results appear to be mixed and the effect of ischemia on functional outcomes will be further discussed below [42–46].

Additionally, mannitol has been hypothesized to decrease reperfusion injury following renal ischemia. It is thought that, in low doses, mannitol can help increase renal blood flow and urine output and, if given shortly prior to arterial clamping during PN, can be renoprotective [47, 48]. The use of mannitol was initially extrapolated from transplant literature that found a decrease in acute renal failure and delayed graft function [49]. However, this was not able to be replicated in PN. A randomized clinical trial comparing the administration of 12.5 g mannitol vs. placebo found no significant clinical benefit at 6 months or 3 years, even when examining subgroups of patients comparing preoperative eGFR, comorbidities, ischemia time and tumor size on post-hoc analysis [50, 51]. In addition, mannitol is not harmless. The volume expansion increases cardiac preload, which can exacerbate heart failure, and diuresis can mask hypovolemia and cause electrolyte abnormalities [52].

Standard Partial Vs. Enucleation

There are two main surgical approaches to the excision of the renal mass, standard PN and tumor enucleation. Previously, standard PN involved wide excision with at least a 1 cm margin to ensure negative margins and reduce tumor recurrence. More recently, studies have shown that minimal margin and even tumor enucleation, which involves blunt dissection of the renal tumor along the plane of the tumor capsule and normal renal tissue, offered similar oncologic outcomes [53–57]. The fibrous connective tissue separating the tumor and the adjacent renal parenchyma is known as the tumor pseudocapsule. Various histologic subtypes have been shown to have predictable pseudocapsule characteristics, with papillary histology (30%) more commonly invading beyond the pseudocapsule than the clear cell (8%) and chromophobe (0%) histologic subtypes [58]. Although some studies have shown that tumor enucleation may increase rates of positive surgical margins, local tumor recurrences were comparable to standard PN [59]. In addition, due to a smaller resection and sparing more normal renal parenchyma, tumor enucleation offers improved preservation of renal function and decreased operative times compared to the standard resection technique [53, 54, 57, 59, 60].

Renorrhaphy

Following resection of the renal mass, renorrhaphy, or repair of the kidney, is performed to achieve hemostasis and close any collecting system defects. Several approaches have been developed to optimize operating time, reduce perioperative complications, and preserve long-term renal function. Single-layer renorrhaphy, while omitting the cortical renorrhaphy, appears to improve postoperative renal function with similar complication rates [61–63]. A randomized, controlled trial demonstrated higher creatinine and volume loss in the cortical renorrhaphy group and suggested that omitting cortical renorrhaphy may result in the preservation of renal volume and function [64]. Authors hypothesized that cortical renorrhaphy can damage and compress normal renal parenchyma and lead to volume loss and pseudoaneurysms. Other studies demonstrated no significant difference in operative time, ischemia time, or kidney function between the single-layer versus cortical renorrhaphy, while showing a higher incidence of minor complications with single-layer renorrhaphy [65]. In addition, several surgical renorrhaphy adaptations have been designed. Sliding-clip renorrhaphy involves placing surgical clips on both ends of the renorrhaphy stitch which can be adjusted to provide optimal tension and reduce operative and warm ischemia times [66, 67]. The use of barbed sutures compared to traditional sutures has also been shown to decrease warm ischemia times and postoperative complications [68–70].

Hemostatic Agents

In addition to renorrhaphy to minimize postoperative bleeding risk, it has become common place to use hemostatic agents to reduce intracorporeal suturing, warm ischemia time, and postoperative hemorrhage. However, the type of hemostatic agent and whether or not to even use a hemostatic agent remains a debate. There are numerous hemostatic agents available on the market, including Surgicel (oxidized regenerated cellulose), Floseal (gelatin granules and human thrombin), Spongostan (porcine gelatin), Hemopatch (absorbable collagen), Tisseel (fibrant sealant), Gelfoam (porcine gelatin), as well as many others. One study found that Floseal decreased estimated blood loss compared to Spongostan and Surgicel [71]. Other studies found no difference in bleeding complications between hemostatic agents nor the number of hemostatic agents used, especially in cases without substantial intraoperative blood loss [72–74]. Hemostatic agents have also been used to substitute sutures in suture-less renorrhaphy techniques, which have been described in patients wherein the collecting system/ renal sinus was not entered [75]. Additionally, since the initial description of renorrhaphy without bolsters by Weight et al., the use of surgical bolsters has largely been abandoned as it affects the appearance of the renal bed in postoperative imaging, potentially mimicking recurrence during follow-up [76].

Functional Outcomes: Preserving Renal Parenchyma and Renal Function

One of the main reasons to pursue PN is nephron preservation in order to optimize renal function, and there are several factors that contribute to functional outcomes [77, 78]. Baseline renal function is an important factor in consideration of whether to pursue PN vs. RN in many cases, with partial preferred in those with baseline CKD. In a comparison of CKD upstaging in patients in the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry, PN was equivalent to surveillance for CKD upstaging while RN was associated with worse renal function outcomes [79]. In patients with stage 2 CKD, PN should be prioritized due to increased risk of GFR <45 following RN [80]. Similarly, in a cohort of veterans, RN led to a greater proportion of patients ultimately having GFR <60 over 6 months postoperatively and correlated with higher mortality risk proportional to the decrease in GFR [81]. In patients with normal baseline renal function, hypertension and diabetes were not found to significantly associated with postoperative renal function [82].

Preservation of renal function, in addition to oncologic and surgical outcomes, has become an important assessment of the success of PN. The concept of trifecta following PN was described by Hung et al. as functional preservation, negative surgical margin, and complication-free recovery [83]. However, this was further modified by Brassetti et al. who used more objective cutoffs. They defined Trifecta following PN as the coexistence of negative margins, no Clavien-Dindo ≥3 complications and ≤30% postoperative estimated GFR reduction. Patients who achieved trifecta had a 65% reduced risk of developing stage IIIb-V CKD and a 55% reduced risk of overall mortality [84]. In another series of 74 patients with a solitary kidney, Trifecta has been described as negative surgical margins, warm ischemia time of less than 20 mins and low operative/perioperative morbidity, however, the major limitation of this study was the absence of comparator arm to validate this metric [85].

Many factors contribute to long-term effects on renal function following PN. Within the first week postoperatively up to 20% of patients experience AKI, and those who developed an AKI were more likely to have CKD upstaging and less likely to recover 90% of their baseline renal function [86]. This suggests identifying and mitigating this effect is important to long-term functional outcomes. Various nephrometry scores were found to be predictors for early postoperative renal function, with RENAL and preoperative assessment of volume preservation (PAVP) also predictive for later renal functional outcomes [87]. In one retrospective study, proportional eGFR (calculated as a product of percent function on renal scan total eGFR) was suggestive to be a more sensitive marker of renal function after PN as compared to total eGFR as it was more strongly associated with factors related to dysfunction including clamp time and tumor size [88]. In a propensity score matched analysis of patients with no pre-existing hypertension, RN was associated with a higher risk of new-onset hypertension compared to PN, which may in turn affect long-term renal function [89, 90]. Finally, even in young patients less than 40 years

of age, a SEER database study found PN was associated with improved survival, although attributing it to the preservation of renal function is difficult [91].

One of the most important factors for the postoperative function is the degree of spared parenchyma. Estimation of preserved renal volume intraoperatively has been shown to be the most accurate predictor of postoperative unilateral renal function [92, 93]. The percentage of preserved parenchymal mass, as measured using postoperative and preoperative CT scans, strongly correlated with preserved global and ipsilateral GFR whereas excised parenchymal mass (measured from pathology specimens) did not correlate with functional outcome [94]. The devascularized parenchymal mass, defined as the difference between that lost and that excised, however, was found to have a larger impact on functional outcomes [95]. In the evaluation of renal volume, it was shown that both surgeon assessment of volume preservation (SAVP) intraoperatively and preoperative assessment of volume preservation (PAVP) based on preoperative imaging significantly and similarly predicted postoperative GFR in multivariate analysis [96]. Also, several measurement methods to estimate the preserved parenchymal mass were effective at predicting final renal function [97]. Lower preserved parenchymal mass was associated with larger tumors, greater tumor complexity, and prolonged ischemia, whereas preserved mass was greater in solitary kidneys [98].

As mentioned above, ischemia is another factor that can affect functional outcomes. While volume loss is the major determinant of ipsilateral renal function, ischemia time affected early GFR reduction and had a smaller effect as ipsilateral function improved [93, 99]. In multiple studies and systematic reviews, zero-ischemia or off-clamp techniques were associated with smaller decreases in ipsilateral GFR than both warm and cold ischemia [100–102]. Overall, hypothermia vs. warm ischemia does not appear to make a large contribution [42, 43]. Longer intervals of warm ischemia did associate with decreased functional recovery [46, 103–106], but the changes were modest and likely not clinically significant in the more recent retrospective analysis [104]. Parekh et al. studied 40 patients prospectively, evaluating if the duration of ischemia time affected the renal function and found that there was no correlation of ischemia duration with renal injury [107]. Additionally, a recent randomized controlled trial suggested that renal hypothermia during planned open partial did not preserve renal function in those patients with normal or mildly impaired function [108].

Other factors can also influence or help predict renal function following PN. As mentioned above, renorrhaphy may impact function and limited literature suggests that a single-layer renorrhaphy and omitting cortical renorrhaphy may be associated with improved renal function outcomes [109]. This was being investigated in a randomized trial but the study was terminated due to slow accrual and no statistical significance on interim analysis (clinicaltrials.gov, NCT02131376). Utilization of intraoperative hyperspectral imaging to measure tissue oxygenation demonstrated higher baseline renal oxygenation was associated with improved functional outcomes and patients with lower baseline oxygenation had a greater decline in GFR [110]. Several nomograms and quantitative tools have been developed to help predict functional outcomes to aid in clinical decision making [111, 112].

Oncologic Outcomes

While renal function preservation is one of the important factors to proceed with PN for appropriately selected renal masses, it must not come at the expense of oncologic control. For the management of cT1 renal masses, no significant difference in cancer-specific or all-cause mortality has been seen in the comparison of PN and RN [113]. Similarly, equivalent oncologic outcomes are seen for robotic PN as compared to laparoscopic or open techniques [114–117]. The surgical approach was not associated with oncologic outcomes in one analysis with a minimum of 10 years of follow-up [118]. PN has been shown to have good oncologic outcomes with 5-year OS and cancer-specific survival (CSS) of 91.1% and 97.8% in over 100 consecutive patients undergoing robotic PN at a single institution [119]. The only factor associated with a higher risk of overall mortality was the age-adjusted Charlson comorbidity index [119]. Overall, 5-year CSS was 90.1–97.9% across multiple studies of robotic PN [117]. Simple enucleation has also been seen to have equivalent oncologic outcomes compared to standard PN [120].

Indications for PN have also expanded to larger tumors, and meta-analyses looking at cT1b and cT2 tumors demonstrated PN to have equivalent cancer control to RN in this cohort with acceptable surgical morbidity and better functional outcomes [121, 122]. It was, however, noted that for T2 tumors, use of PN needed to be more selective [121]. In another retrospective analysis of PN in 298 patients with cT2 tumors, 25 developed recurrence or metastasis in a median follow-up of 1 year and a higher pT stage was predictive of recurrence/metastasis [123].

Many factors contribute to oncologic outcomes and influence recurrence following PN. Higher complexity tumors (as assessed by higher PADUA scores) have similar oncologic outcomes although positive surgical margins were associated with increased PADUA score [124]. Positive surgical margin rate differs across literature and there is disagreement among studies with regards to whether positive margins are associated with worse recurrence free survival or OS [125, 126]. Positive surgical margins were associated with aggressive disease and low surgeon experience in one study [127]. Pathologic upstaging to pT3a and advanced clinical stage were also associated with worse recurrence free survival following PN, suggesting attentive surveillance is needed in this cohort [126, 128].

Surveillance Following Partial Nephrectomy

Following PN, patients do need to continue to undergo surveillance with repeat follow-up imaging. Various guidelines differ in their follow-up schedules and stratification is based on staging (Table 3.2) [129–134]. In general, chest and abdominal imaging is obtained 3–6 months following surgery and every 6–12 months for 3–5 years depending on the stage and guideline followed. In one large retrospective analysis, it was seen that local recurrence generally emerged earlier than distant metastasis and recurrence rates were higher in patients with adverse pathologic and anatomic characteristics including pT1b or higher, high-grade tumors, positive

Table 3.2 Comparison of major guidelines for recommendation of partial nephrectomy and imaging follow-up

Guideline	Indications for partial	Follow-up imaging recommendations		
		Risk category or stage	First 3 years	>3 years
AUA	Prioritize partial: • cT1a masses, • Solitary kidney, • Bilateral tumors, • Known familial RCC, • Pre-existing CKD, • Proteinuria, Consider partial: • Young, • Multifocal, • Comorbities likely to affect renal function in future	Low (pT1 and grade 1/2)	Chest (CXR) and abdominal (CT or MRI) imaging at 12 and 24 months	Image at 4 and 5 years (may use abd US), longer per shared decision making
		Intermediate (pT1 and grade 3/4 or pT2)	Chest (CXR) and abdominal (CT or MRI) imaging at 6, 12, 24, and 36 months	Image at 4 and 5 years (may use abd US), longer per shared decision making
		High (pT3a)	Chest (CT) and abdominal (CT or MRI) imaging every 6 months for 3 years	Image at 4 and 5 years, longer per shared decision making; can use CXR annually after 5 years
		Very high (pT4 or N1, sarcomatoid/ rhabdoid, macroscopic + margin)	Chest (CT) and abdominal (CT or MRI) imaging every 3 months for 1 year, every 6 months until 3 years	Image at 4 and 5 years, longer per shared decision making; can use CXR annually after 5 years
EAU	Offer partial to patients with T1 tumors.	Low	US at 6 months and 2 years CT at 1 year and 3 years	CT every 2 years, counsel about recurrence risk of 10%
		Intermediate/high	CT at 6 months, 1, 2, and 3 years	CT every 2 years
NCCN	cT1a—Partial preferred cT1b, stage II—Partial is an option	Stage I (pT1a and pT1b)	Baseline CT or MRI preferred or US within 3–12 months and annually for 3 years CXR or CT annually for 5 years	Continue abdominal and chest imaging as indicated
		Stage II or III	Baseline abdominal CT or MRI and chest CT within 3–6 months, then CT or MRI preferred or US every 3–6 months for 3 years	Abdominal CT or MRI and chest CT annually to 5 years, longer if indicated

surgical margins, and moderate or high RENAL scores [135]. Early recurrence was most common in higher stage disease whereas many recurrences for T1 tumors have been seen late, beyond the standard surveillance period [136].

Surveillance is complicated, as early postoperative imaging often has "abnormal" findings following PN in about a third of cases [137]. There are multiple

findings commonly seen including parenchymal defects, perinephric fat stranding, high attenuation objects including hemostatic agents, and fluid collections [138]. Subsequent imaging is generally considered normal though this leads to shorter intervals and more imaging [137]. In appropriately selected patients, initial imaging may be able to be pushed out to 1 year to avoid this complication [137]. In one retrospective analysis of over 1400 patients with pT1 disease, there was low yield of surveillance imaging in the first 3 years postoperatively with nearly 1000 imaging studies performed to detect one relapse that required treatment [139]. Mass-like lesions could also be seen on postoperative MRIs in the renal parenchymal defect, and one study examining these lesions found that there was no significant association with the use of hemostatic agents [140]. Ipsilateral recurrence has been shown to most commonly occur due to incomplete initial resection though in some cases is secondary to spread by microvascular embolization or true multifocality [141]. Multifocal disease and other unique circumstances including tumors in solitary kidneys and renal masses associated with genetic syndromes are unique cohorts in the discussion of PN.

Additional Considerations: Hereditary, Multifocal, and Advanced Disease

Partial Nephrectomy on a Solitary Kidney

As RN would leave patients with renal masses in a solitary kidney anephric, this is one population where PN has a key advantage and is used to avoid progression to dialysis dependence. In analysis of 5- and 10-year follow-up following open PN in patients with solitary kidneys, 89.7% had CKD stage 3 or higher and 6% ultimately required permanent dialysis or renal transplant, though they had significantly lower baseline renal function [142]. Five-year OS was 78.5% and age at the time of surgery and malignant pathology were significantly related to OS on multivariate analysis [142]. Furthermore, repeat PN in a solitary kidney had no significant differences in outcomes compared to initial PN in one analysis [143]. Another study of repeat PNs in solitary kidneys from the NCI experience had a high complication rate but no significant difference in GFR at 1 year follow-up and metastasis-free survival of 95% at 57 months [144]. Additionally, in patients with a solitary kidney, PN for at least 3 tumors was shown to have similar complication rates as well as functional and oncologic outcomes as standard PN for one to two tumors in a solitary kidney [145].

Multifocal and Repeat Partial Nephrectomy

Multifocal disease, whether unilateral or bilateral, poses additional challenges and considerations for PN. In retrospective analysis, those with unilateral, synchronous, multifocal tumors with favorable characteristics were successfully managed with

PN with low recurrence rates [146]. Five-year OS was 96% and RFS was 98% (n = 78 treated with PN) [146]. In those who present with bilateral tumors, comparing bilateral open and laparoscopic PN demonstrated equivalent oncologic outcomes [147].

Repeat and salvage PN after local recurrence, while challenging, has been shown to maintain good functional and oncologic outcomes in selected groups [148]. Most patients were able to avoid dialysis after repeat PN and while many required re-operation for local recurrence or de novo tumor formation median time to subsequent surgery was 50 months in one cohort [149]. PN, including the robotic approach, can also be used in the salvage setting following local recurrence after either PN or ablation with a reasonable safety profile in select patients [150–153].

Partial Nephrectomy in Management of Hereditary RCC Syndromes

Generally, PN should be undertaken in patients with genetic predisposition syndromes when the largest tumor reaches 3 cm, with the exception of HLRCC or succinate dehydrogenase mutated (SDH) tumors, where any solid lesion should be removed early due to the aggressiveness [11, 154]. As described by Shuch et al., this is a complex decision making process in the setting of bilateral disease as to how to stage these procedures [11]. Attempts should be made for nephron-sparing wherever possible. Early experience with robotic PN for multiple tumors suggested that patient selection was key and the transition was made to attempt to do these cases without hilar clamping in anticipation of patients with hereditary syndromes requiring multiple ipsilateral procedures [35]. Robotic PN for multiple tumors in a cohort of patients with hereditary syndromes with a mean of 8.63 tumors removed (range 3–52) demonstrated no significant changes to renal function at 3-month follow-up, suggesting this is a feasible option to preserve renal function in this challenging scenario [155]. PN for multifocal disease, including in those with the largest lesion over 4 cm, had similar overall and metastasis-free survival as that for T1b tumors in the sporadic population, suggesting that PN is still a reasonable option in these patients [156]. Additionally, aggressive PN in an NCI cohort of patients with at least 20 tumors removed during a single operation (median 26.5 tumors) demonstrated that it is technically feasible [157]. Although renal functional decline was seen, the authors demonstrated that at least 80% of preoperative function was preserved in 29/30 patients and oncologic outcomes were encouraging at intermediate follow-up [157].

While PN has been the mainstay in the management of these patients, advances in the understanding of the biology of the disease and the development of new targeted agents may change this in the future. Recent FDA approval of belzutifan, a novel HIF2α inhibitor, for treatment of patients with VHL came following a 49% objective response rate after a median follow-up of 21.8 months [158]. Prolonged treatment with belzutifan may reduce the surgical burden in this disease and provide

an adjunct to assist with local control, decreasing the number of needed PNs and associated functional loss [158].

Partial Nephrectomy in pT3a RCC

Though currently PN is not routinely performed in cT3a RCC, there are many reports of upgrading to pT3a following PN. Shvero et al. reported that there was no difference in oncologic outcomes between patients undergoing PN vs. RN for a pT3a tumor [159]. However, it is important to note that these were not classified as cT3a tumors preoperatively and were instead upgraded to pT3a by the pathologist. Based on these observations the authors suggested that PN can be considered for cT3a tumors as well [159]. Additionally, one meta-analysis examining PN versus RN for pT3a tumors found comparable oncologic outcomes with improved renal function after PN [160].

In both the above-described studies, PN was performed in patients who were staged as clinical T1/2 preoperatively but had pathological T3a in final pathology, which suggest a bias towards those tumors that are surgically amenable to PN and these findings are not generalizable to all pT3a tumors. Liu et al. compared 4 groups of patients namely pT3a ≤4 cm with perinephric fat extension, pT3a 4–7 cm with perinephric fat extension, pT3a ≤4 cm with sinus/perisinus extension, and pT3a 4–7 cm with sinus/perisinus extension. They concluded that PN was associated with significantly improved OS in the pT3a ≤4 cm with perinephric fat extension subgroup. There was no difference in OS in the remaining three groups or CSS in all the four groups [161]. Some experts have recommended using tumor size as separate criteria in predicting the outcome of pT3a RCC and urged AJCC to revise their pT3a classification [162, 163].

Partial Nephrectomy in Metastatic Disease

Small retrospective series have also concluded that PN is feasible, safe, and better than RN in metastatic renal cell cancer (mRCC) [164–166]. Hockman et al. analyzed a cohort of 18,433 men with mRCC from the SEER database of which 7598 had a radical nephrectomy, 208 had PN and 78 had ablative therapy. The PN subset had significantly better OS and CSS compared to the other two groups. Preserving renal function may have helped these patients to tolerate systemic therapy or allowed them to participate in further clinical trials [90, 167].

Conclusions and Future Directions

PN is now the standard of care for many cT1 and some cT2 tumors. When the patient is appropriately selected, one should aspire to achieve Trifecta following PN. Renal parenchymal preservation and good oncologic technique are vital.

Baseline renal function is critical in determining outcomes following PN. PN should be performed by experienced surgeons in high-volume centers for patients with complex or multiple tumors. With the increased use of renal mass biopsy and the increased availability of genetic markers for renal cancers, we may be able to better risk stratify these tumors. In the future, this may help us in selecting optimal treatment for patients, in our aims of improving OS without compromise in the CSS.

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Ablative Options for Renal Cell Carcinoma

4

Hal D. Kominsky and Jeffrey A. Cadeddu

Introduction

The incidence of renal cell carcinoma (RCC) has risen over the past three decades largely because of the increased use of cross-sectional imaging [1, 2]. Within that timeframe, disease management modalities have evolved with an emphasis on preserving renal function and minimizing treatment associated morbidity. Guideline panels recommend prioritizing minimally invasive and nephron-sparing treatment options, when possible, particularly for cT1a tumors [3, 4].

Minimally invasive kidney surgery began with the laparoscopic radical nephrectomy in the 1990s [5]. Since then, partial nephrectomy has become the most common approach for the treatment of small renal masses [6]. This treatment offers patients improved renal function, better cardiac outcomes, and similar overall survival compared to radical nephrectomy. Additionally, minimally invasive partial nephrectomy techniques are accompanied by improved blood loss, length of hospitalization, and excellent oncologic efficacy [7]. For these reasons, partial nephrectomy is typically considered to be the "gold standard" treatment for early stage, localized renal cell carcinoma.

Focal ablation (FA) for the small renal mass also had its origins in the 1990s. This collection of treatments offered a less technically demanding and less morbid management option compared to extirpative surgery. While all renal surgery, be it open, laparoscopic, or robotic assisted, requires at least some degree of hilar dissection and renorrhaphy, FA modalities require none of these maneuvers. Moreover, renal function recovery after FA is comparable to and even in some cases, better than, partial nephrectomy with similar oncologic efficacy [8–12]. With these advantages in mind, indications for FA include small tumors (<3 cm), poor risk

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surgical candidates or those at risk for renal insufficiency, bilateral renal tumors, and those with hereditary RCC syndromes such as von Hippel-Lindau. And as long-term treatment data demonstrates excellent rates of metastasis free survival, the status of FA techniques has been elevated to a widely accepted treatment for sporadic tumors.

Focal ablation is not one treatment modality, but rather a group of individual technologies all with the unified goal of ablating tissue with minimal invasiveness and morbidity. This chapter will focus on the most common FA techniques for RCC, namely cryoablation (CA) and radiofrequency ablation (RFA) in addition to microwave ablation (WMA), all together referred to as thermal ablation (TA). There will also be a discussion of radiotherapy ablation (RA).

Technique Considerations

TA procedures (CA, RFA, and MWA) can be carried out with either a laparoscopic or percutaneous approach. An in-depth technical description of how to perform these ablation procedures is beyond the scope of this text. The percutaneous approach for TA treatments is more commonly employed over laparoscopy in the current era [3, 6]. A percutaneous technique is well tolerated by patients, associated with less anesthesia requirements, has shorter hospitalization and recovery times while providing equivalent oncologic efficacy to TA using laparoscopy [13].

In a percutaneous approach one or more probes are inserted through the skin into the tumor under image guidance (typically CT or ultrasound). Patients are typically placed in the prone position, but descriptions of procedures in the semiprone and lateral decubitus positions also exist [14]. General anesthesia and deep sedation are both available options, and specific decisions about anesthesia level are institutionally and provider dependent [13, 14]. Further technical details associated with each ablative procedure are to follow in this chapter.

Cryoablation

CA is the practice of using extreme cold temperatures to treat a pathologic lesion. The extreme drop in temperature initiates a process of coagulative necrosis, cellular apoptosis, and eventual tissue fibrosis with scaring. Freezing the lesion forms an "iceball" which causes tissue destruction. Rapid freezing in the area of the probe forms ice crystals within the intracellular space, causing mechanical trauma to plasma membranes, ultimately leading to cell death and tissue ischemia [15, 16]. A cooling process follows rapid freezing, which is responsible for formation of extracellular ice crystals that deplete extracellular water and lead to further cellular membrane disruption by osmosis. As the tissue thaws, extracellular osmolarity decreases with crystal melting, leading to decreased extracellular osmolality, followed by

rapid infusion of water into cells causing cellular edema and destruction. Additionally, freezing of endothelium causes platelet activation, vascular thrombosis, and tissue ischemia [17]. The freezing mechanism can be compromised by the "heat sink" phenomenon wherein larger blood vessels that are adjacent to the tumor may counteract the formation of ice crystals.

The initial problem with early CA technology was that there was no way for the operator to visualize the extent of the iceball, and if there was any collateral damage in the areas adjacent to the lesion. Cryotherapy treatment zones were first monitored by physical exam and then later, ultrasound equipment [18–20].

An important development in CA technology was the transition to argon gas which provided more precise temperature control compared to nitrogen gas [21]. Different target tissues require specific temperature thresholds to ensure complete destruction using cryoablation. Cancerous tissue is more fibrous compared to normal parenchyma, so temperatures as low as −50 °C may be required to ensure complete tissue destruction [22].

Tissues at the center of the iceball are at the lowest temperature and moving radially outward, the tissue temperature increases. Therefore, the temperature of the tissue throughout the ablation zone is not necessarily uniform. This was demonstrated by Campbell and colleagues who measured intrarenal temperatures during CA and demonstrated that the center of the iceball had temperatures around −20 °C to within 3 mm of the normal tissue interface where temperature was closer to 0 °C [23]. Based on this work, common practice is to create a treatment zone 5–10 mm beyond the target lesion. An alternative set-up employs multiple small probes around the target lesion which is useful for complex tumors or challenging anatomy [24].

Initially, one freeze-thaw cycle was performed, and this was based on early animal model experiments. Further in vivo animal models demonstrated that multiple freeze-thaw cycles promoted larger and more effective tissue necrosis [25]. Many authors advocate for two repetitions of freezing-thawing. The thawing can be a passive process—in which the iceball melts without any intervention once the argon gas is no longer flowing through the probe. The thawing can be an active process in which gas is pushed through the probe which creates a local warming effect; this is faster than passive thawing. While there is not a practice pattern consensus between active and passive thawing, some promote passive thaw between cycles and active thaw at the end of treatment make addressing post-treatment bleeding easier.

The precise time for cell death from CA in humans is unclear. Auge and colleagues studied cell death times in a pig model by performing cryoablation for 5, 10, and 15 min [26]. Complete tissue necrosis was seen within 5 mm of the probe for all animals but only those treated for 10 or 15 min had necrosis zones extending 10 mm more from the probes. Shorter treatment time directly increased bleeding risk, while longer treatment time increased the risk of tumor fracture – also a risk for bleeding. Some authors advocate for a freeze cycle duration of 8–10 min [27, 28].

Radiofrequency Ablation

RFA energy heats tissue, causing cell death. Monopolar alternating electric current delivered at 450 to 1200 kHz makes ions vibrate within the tissue leading to molecular friction and heat production. Heat produced during RFA causes cellular protein denaturation and cell membrane disintegration [29]. The probes themselves do not get hot, but the heat is a direct product of the ionic vibration in the tissue. Modern RFA probe technology was pioneered by two separate groups in the early 1990s [30, 31]. Probes have an exposed metal tip and the rest of the length of the probe is insulated to allow safe percutaneous access to the lesion. The amount of tissue destruction achieved can be adjusted by changing the length of exposed probe. The RFA probe placement can be visualized with ultrasonography, MRI, and most commonly, CT guidance.

There are two types of equally effective systems for RFA. A temperature-based system uses a sensor at the tip of the electrode with the goal of achieving a specific temperature threshold during treatment cycles. An impedance-based system has a sensor at the electrode that measures impedance or resistance to alternating current at the electrode tip with the goal of achieving specific impedance level.

Early probe designs had maximum treatment zones of 2 cm, and larger tumors required multiple cycles with overlapping treatment zones. Eventually a probe was developed with 12 deployable tines that allowed for wider zones of current delivery in a spherical shape [32].

Contemporary devices with different numbers of deployable tines and shapes such as a starburst pattern are also available. Multi-tine electrodes provide more complete and precise necrosis and superior treatment outcomes [33, 34]. Bipolar electrodes are another system design which deliver higher energy and heat compared to monopolar electrodes [35]. This design produces an elliptical treatment zone which is less practical for renal cancers which are mostly spherical. Outcomes data have revealed that target sizing is less accurate and highly variable, so this technology has not been widely adopted [36].

Radiofrequency ablation probes can be further stratified into “dry” or “wet.” In a dry RFA system, tissue desiccation leads to charring which increases impedance which then limits size of ablation zone. This system can be thought of as internally cooled. The so-called “wet” RFA probes deliver saline to cool the temperature of the tissue at the probe tip and lower the impedance – this widens the ablation zone and uses less total energy [37, 38]. Importantly, there is less precise control over treatment zone size with wet RFA, so overtreatment is a concern [39].

There are three elements of RFA that lead to efficient treatment: power delivered to the probe, maximum temperature obtained, and total ablation time [40].

During RFA treatments, tissue temperatures are kept below 105 °C to prevent tissue charring. The minimum temperature goal to produce irreversible cell injury and cell death is 70 °C [41]. Corresponding impedance-based systems should be set to 40–80 W and increased at 10 W/min to max 130–200 W; total impedance should

be 200–500 ohms. When the target treatment zone is highly vascular or adjacent to large blood vessels, thermal energy is dispersed to the blood vessels creating a "heat sink." Heat sink may prevent complete treatment of tumor tissue that is adjacent to blood vessels. Temperature and or impedance can be actively monitored and manipulated during treatment. Two cycles separated by 30-second cool down period is typically recommended [42, 43].

Microwave Ablation

An early, and very successful, application of microwave ablation (MWA) was for the treatment of liver lesions. This technology works by the delivery of energy through semiflexible probes inserted directly into the lesion, similar to the technique of RFA. The energy of MWA operates in the 900 MHz to 2.45 GHz range of the electromagnetic spectrum. As with RFA, MWA energy creates rapid water ion oscillation and frictional heat in the target tissue [44]. The heat produced is dependent on the water content of the tissue, which can be challenging in the kidney due to its heterogeneous tissue structure [34, 45]. An advantage over RFA is that MWA probes can achieve treatment temperatures above 60 °C quicker than RFA probes without tissue charring [46]. In addition, MWA has been shown to potentially be immune to the "heat sink" effect observed in RFA [47].

Individual microwave ablation antennas can generate a target ablation zone up to a radial distance of 2 cm [46, 48, 49]. When multiple antennae are used together, they synergistically create an expanded area of ablation that can be six times the size of that created by a single antenna [49]. It has been demonstrated that MWA can create a larger target ablation zone than in RFA [46].

An early report of ten patients undergoing MWA for renal lesions showed complete tissue necrosis of the target zone, with the largest tumor being 5.7 cm in diameter [50]. Larger, more recent series have demonstrated greater than 90% success rates for T1a and T1b lesions [51, 52]. In a series of 119 T1a renal tumors, technical success was achieved in 100% of patients, complete response was achieved in 95.3% of patients with a 90.6% recurrence free survival rate at 3 years of follow-up [53].

When microwave ablation was directly compared to nephron-sparing surgery in a prospective fashion for patients with small renal tumors, Guan and colleagues found recurrence free survival rates of 91% and 96% for MWA and surgery, respectively, at mean follow-up of 3 years [54]. The authors also reported the MWA patients experienced decreased estimated blood loss, a lower complication rate, and a smaller reduction in renal function. Similar results have been published by other groups [55, 56]. According to meta-analysis prepared by Choi et al. representing 616 malignant renal tumors, MWA had a local tumor recurrence rate of 2.1% and a cancer-specific survival rate of 96.9% [57]. Complication rates for MWA are in the range of 1.8–5.7% [53, 57]. Larger prospective studies and longer follow-up data are necessary to understand how MWA techniques compare to other TA procedures and extirpative surgery.

Evaluation of Post-Ablation Treatment Success and Surveillance

Evaluating the success of an ablation treatment comes with its own distinct challenges, namely the lack of surgical margins. Cross-sectional imaging is heavily relied upon in the post-treatment period to identify any signs of persistent or recurrent disease.

Complete loss of contrast enhancement on CT and MRI is a reliable indication for treatment success [58]. Typically, the first imaging study obtained following an ablation should be in the timeframe of 6–12 weeks. The American Urologic Association guideline panel recommends imaging within the 6 month window [59]. Contrast enhancement in the ablation zone at this point would suggest incomplete treatment, and a repeat ablation is scheduled. If a study that was previously non-enhancing becomes enhancing on subsequent scans, recurrence is suspected, and another ablation is scheduled. Cryoablation zones can be expected to reduce up to 50% in size 1 year out from treatment [60, 61]. Heat-based treatment zones (RFA and MWA) do not typically contract, rather there is a distinctive fibrotic halo or circular demarcation which is indicative of fibrotic scarring. This halo is a benign finding and is visible on studies even several years following a successful ablation [62].

Role of Biopsy

A discussion on the sensitivity and accuracy of renal biopsy is outside the scope of this chapter, however, results from large institutional experience series show acceptable and reliable results [63]. Association guideline panels do recommend renal mass biopsy prior to performing ablation, rather than during the ablation procedure itself [3, 4]. The role of post-ablation biopsy is not clearly defined, with questions surrounding histologic accuracy and the ability to correlate with long-term oncologic outcomes [64].

Oncologic Outcomes and Surveillance Regimens

Providing a direct comparison of oncologic outcomes between ablation and extirpative surgery is challenging due to numerous patient and tumor specific factors as well as surgeon selection biases. Progression free survival and disease-specific survival for ablation and surgery, at least in the intermediate term, both exceed 90% for those respective outcomes [3, 59]. When evaluating TA compared to partial nephrectomy in the context of sporadic, unilateral cT1a RCC, 5-year local recurrence free survival and overall disease free survival, and progression free survival were similar [65]. The Mayo Clinic experience of 1422 cT1a (≤3 cm) patients found similar results at median clinical follow-up of 9.4, 7.5, and 6.3 years for partial nephrectomy, RFA, and CA, respectively [66].

Local recurrence can be thought of as any disease remaining in the kidney after a primary procedure. Several studies have demonstrated similar local recurrence free rates between CA and RFA [67, 68]. In a comparison of 10 CA studies and 10 RFA studies, average recurrence free survival for CA was 90.6% (83.8 to 94.7%) and RFA was 87% (83.2 to 90%) [3]. Similarly, El Dib and colleagues compared 20 cryoablation series to 11 radiofrequency ablation series and found clinical efficacy (no recurrence detected on post-treatment imaging) of 89% and 90%, respectively [69]. In a meta-analysis of 147 studies on management of localized renal masses, at mean 60 months and 48 months of follow up for partial nephrectomy and TA, respectively, the local recurrence free survival was 98.9% and 93%, respectively [6]. It should also be noted that performing a salvage TA in cases of persistent or recurrent disease increased the local recurrence free survival to 97–100%. To that end, surveillance, epidemiology, and end results program data only showed a 1.7% survival advantage increase of partial nephrectomy over TA [70]. Tumor size has proven to be a significant indicator of ablation outcomes. In patients undergoing RFA, the 5-year overall local recurrence free survival in 108 biopsy-proven RCCs was 95% for those with tumors smaller than 3 cm but only 78% for those with tumors 3 cm or larger [65]. Psutka and colleagues demonstrated that 5-year local recurrence free survival and overall disease free survival after RFA of 96.1% and 91.5% with tumors smaller than 4 cm compared with 91.9% and 74.5% in tumors larger than 4 cm [71]. In an analysis of CA data with mean follow up of 6 years, tumor size above 2.6 cm was the only predictor of oncologic failure on multivariate analysis [72].

Metastatic recurrence is disease anywhere in the body other than the previously treated kidney or ipsilateral renal fossa after primary ablation. Long-term outcomes following TA appear to be durable beyond 5 and 10 years. Meta-analyses have failed to find a difference in metastases free survival between TA and extirpative surgery [6, 73]. No significant difference in cancer-specific survival (CSS) has been identified when comparing CA and RFA. Cancer-specific survival for CA is 95.2% (89.2% to 97.9%) and RFA is 98.1% (95.2–99.2%) according to American Urologic Association meta-analysis data [3]. Furthermore, there is no significant difference in CSS when comparing extirpation and TA [6, 74].

Atwell et al. compared 189 percutaneous CA and 256 percutaneous RFA cases, finding no significant difference in recurrence free survival, a CA local recurrence rate of 2.8% (mean 0.9 years), and an RFA local recurrence rate of 3.2% (mean 2.8 years) [75]. In an analysis of 275 LCA and 137 PCA, there was similar 5 year recurrence free survival 79 vs. 80% at 4.4 and 3.1 years, respectively, with an incomplete treatment rate of 6.9 and 6.6%, respectively [76]. Hegarty and colleagues compared 164 laparoscopic CA and 82 percutaneous RFA, with no significant difference in impact on long-term renal function [77]. Meta-analyses data comparing nephron-sparing surgery and TA reveal similar long-term renal function outcomes as well [78].

It is well understood that patients electing for TA tend to have more comorbidities and are older compared to patients undergoing surgery for treatment of a localized renal mass [79]. Mean overall survival after TA is 75% to 85% at 5 years and 54% to 64% at 10 years [29, 71].

Because there is no compelling data to separate CA and RFA in terms of local tumor recurrence, disease progression/metastases, CSS, and OS these treatment modalities are often combined in guidelines and other series that compare TA to extirpative surgery. Guideline panels recommend TA with the choice of RFA or CA left up to institutional and individual preference [3, 4].

The authors recommend post-treatment surveillance following TA with multiphase CT or MRI within 6 months. Using a risk adapted approach, subsequent cross-sectional imaging will be performed every 6 months or annually, similar to guideline recommendations for the management of small renal tumors [3].

Complications of TA

Meta-analysis data comparing urologic and non-urologic complications after TA and surgery show comparable risk profiles between these treatment modalities. Major urologic complications for TA and surgery were 4.9% (3.3 to 7.4%) and 6% (4.3 to 8.2%), respectively [3, 59]. Furthermore, there was no difference in rates of major urologic complications between CA and RFA. Non-urologic complication rates were 5% (3.5 to 7.2%) for CA and 5.4% (3.2 to 6.2%) for RFA. In a retrospective comparison of risk of major and overall complications, TA and surgery carry risks of 7.4 vs. 11.1 and 2.3 vs. 5%, respectively [73]. While laparoscopic TA is performed less frequently than the percutaneous approach in the current practice landscape, previous analyses have demonstrated higher complication rates in the former, mostly related to the aspect of laparoscopic surgery and not the actual tumor ablation itself [80]. European Registry for Renal Cryoablation (EuRECA) looked at 808 patients undergoing laparoscopic CA at 8 European centers and noticed an increased risk of complications with an American Society of Anesthesiology (ASA) score above 3 [81].

The risk of complications following TA has been linked to specific tumor characteristics. RENAL Nephrometry score, a nomogram that captures tumor complexity, and has been validated to predict postoperative complications [82, 83]. Okhunov and colleagues reported complication rates based on low (4–6) moderate (7–9) or high (10–12) RENAL Nephrometry for 77 laparoscopic CAs at three high volume centers [84]. The overall complication rate was 19.5% with a 9.5% major complication rate. There was a significant association between tumor complexity and complication rate. There were no complications with a low score, 35% with a moderate score, and 100% with a high score [84]. Similarly, Schmit examined 679 percutaneous TA cases (both CA and RFA), stratified by RENAL score [85]. They declared a major complication rate of 5.6% (7.8% CA and 2.7% RFA). The mean score for those developing complications was 8.1 compared to 6.8 in the individuals without a complication. High complexity tumors (score at or above 10) had 14.3% risk of major complications [85]. Interestingly, a comparison of patients undergoing either a laparoscopic or percutaneous RFA did not reveal a correlation between tumor complexity and complications in 199 total cases [86].

The most common perioperative complication from percutaneous TA is hemorrhage [75] (Fig. 4.1). Contemporary hemorrhage rates for percutaneous TA are between 4–6% but historically have been as high as 11–27% of cases [67, 87]. Transfusion rates for TA have been reported as 3.2% (2 to 4.9%) with CA and 2.4% (1.4 to 4%) with RFA [3]. Increased institutional experience has demonstrated the ability to lower that risk to under 2% [81, 84]. When multiple probes are used, typically a strategy for treating larger masses, bleeding risk increases [84]. Tumors can also fracture and bleed during cryoablation when the probe is removed prior to complete tissue thawing. If bleeding occurs from placement of an RFA needle, one need only to begin the ablation since the heat generated from the thermal energy will provide a coagulative effect. Should bleeding occur during a laparoscopic thermal ablation, hemostatic agents and direct pressure can be utilized similar to maneuvers during other laparoscopic surgical procedures.

Percutaneous procedures carry risk of damage to abdominal wall vasculature and in even rarer cases, intercostal arteries. These injuries become apparent during the procedure as images are obtained. Most cases can be treated with serial

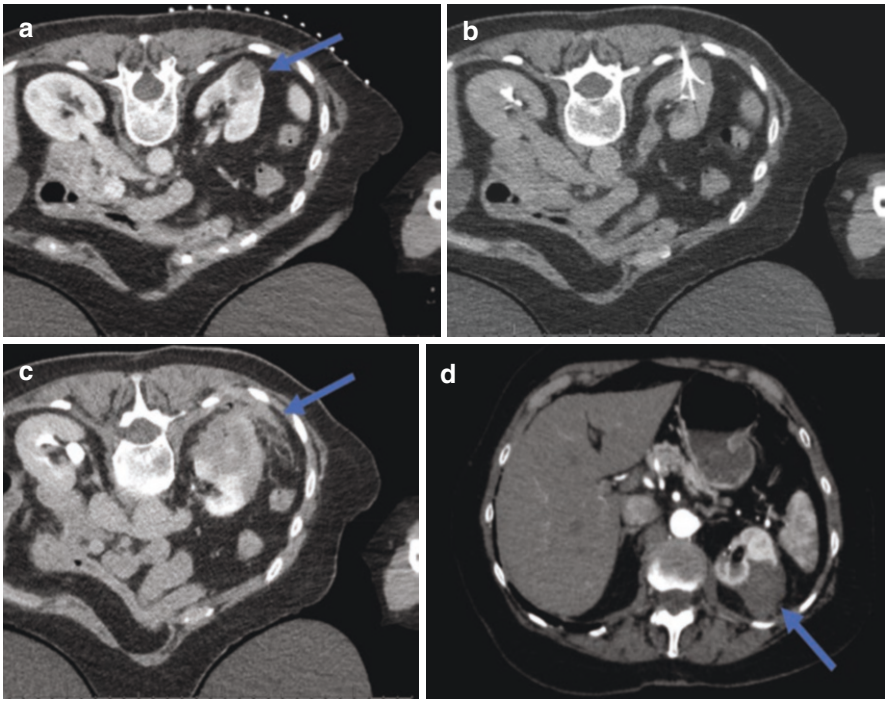

Fig. 4.1 Hemorrhage after percutaneous radiofrequency ablation and subsequent retreatment for persistent disease. (**a**) Patient presented with solitary, enhancing left renal mass (blue arrow) and elected to proceed with percutaneous radiofrequency ablation. (**b**) RFA probe positioned into renal mass and tines deployed. (**c**) Spiral CT immediately after ablation shows evolving perinephric hematoma (blue arrow). (**d**) 5 months after procedure imaging showing ablation zone (blue arrow)

imaging and blood count evaluation. In severe cases of an expanding hematoma, angiographic embolization may be required. Visceral organ injuries are rare with ablation procedures and can be minimized further by appropriate patient selection, preprocedural planning, and good technique. Cross-sectional imaging, which all patients should have prior to undergoing a procedure, is instrumental for planning purposes and give critical anatomical detail such as associated bowel, liver or spleen positioning. Furthermore, tumors with adjacent organ proximity concerns can have cross-sectional imaging obtained in different positions to determine if alternate needle path is necessary. Patients with increased anatomical complexity include anterior tumors, those tumors in close relation to the urinary collecting system, or no clear window to access the tumor of interest percutaneously. In these situations, a partial nephrectomy or ablative laparoscopic approach becomes a more attractive alternative than the percutaneous technique. One can also consider performing hydrodissection to create separation between the tumor and other viscera. The ideal patient for a percutaneous TA has a posterior or lateral tumor, 0.5 cm from ureteropelvic junction or renal pelvis, and those with tumors at least 1 cm from surrounding bowel.

Urothelial injury following an ablation is identified by hematuria, ranging from minor urine discoloration to major bleeding with clots, possibly leading to urinary tract obstruction. Minor hematuria can be safely observed. Major hematuria can be managed safest with angioembolization [88]. Ureteral obstruction or urinary leakage should be managed with observation or an indwelling ureteral stent. Significant perinephric urinoma requires percutaneous perinephric drain placement. There are rare instances of fistula formation following TA [89, 90].

Pneumothorax or hemothorax is possible if the probe placed above the 12th rib to treat an upper pole lesion. Changes in ventilation during the case should raise suspicion to the anesthesiologist and surgery team of a possible pneumothorax. Simple pneumothoraxes can be treated with needle decompression in the standard method once the case is concluded. Chest tubes are reserved for large and severe pneumothoraxes. There should be a low index of suspicion for the patient with chest pain and shortness of breath following the procedure, and expeditiously obtaining upright chest X-ray is recommended.

Colon injury during thermal ablation is rare, especially as the quality of preoperative cross-sectional imaging continues to improve. Tumors in close proximity to the colon can be hydrodissected to create separation between bowel and the kidney [91]. Colon that cannot be pushed away by this method may necessitate a laparoscopic procedure. Colon injury should prompt a General Surgery consultation; look for perforation on imaging and peritonitis in the perioperative period. Controlled colon-nephric fistula should initially be managed with a ureteral stent. Persistent fistula may require fecal diversion and a period of total peripheral nutrition.

Flank pain following percutaneous thermal ablation can occur in 4–8% of cases [67]. One of the more significant causes of flank pain following percutaneous treatments can be neuropraxia, or injury nerves of the posterior abdominal wall. This is often a self-limiting phenomenon [92–94]. Hydrodissection of the tumor away from the abdominal wall can help prevent this complication. If there is not a clear

window for percutaneous access or the tumor is positioned directly against posterior body wall, one can consider performing a laparoscopic procedure to reposition kidney.

Post-ablation infections are rare but can be fatal in complex patients [85]. Chronic colonization of the urinary tract increases risk for infection, such as those with indwelling catheters or urinary diversions [89]. Infections may present as chronic drainage from the puncture site or retroperitoneal abscess detected on cross-sectional imaging. It is good practice to obtain a urine culture and treat appropriately prior to the procedure. It is the author's practice to give perioperative prophylactic antibiotics at the time of procedure while others recommend a longer treatment duration from 2 days prior to 2 weeks following the procedure in high-risk patients [95].

Radiation Therapy

Historically, radiation-based therapy was not thought to be an effective treatment modality for renal cancer. It was posited that the kidney parenchyma surrounding malignant lesions had limited radiation tolerance, and that significant scatter may impact tissue adjacent to treatment target zones. Additionally, target localization for delivery of radiation treatment was thought to be too difficult due to intra-fraction respiratory induced motion of the kidney [96].

RCC was initially assumed to be radioresistant based on early in vitro studies [97]. However, it was discovered that RCC tissues actually have a low α/β-ratio, meaning higher treatment doses - the kind delivered in hypofractionated radiotherapy - may be able to overcome the inherent radioresistance of RCC [98]. By using higher doses of radiation, alternative cell death pathways can be recruited for the destruction of tumor cells [99]. Stereotactic body radiation therapy (SBRT) is the practice of delivering high dose radiation to the target either with a single dose or small number of fractions to a very precise body target. Modern radiation delivery techniques can account for three dimensional coordinates of the target tissue. By adjusting for respiratory induced kidney movement, radiation scatter is reduced, and the patient does not need repositioning during the procedure.

Initial in vivo studies of SBRT using a porcine kidney model and the Cyberknife radiotherapy system were carried out by Ponsky et al. They found that administration of 24–40 Gy resulted in complete necrosis of the target tissue without any adjacent tissue damage [100].

There were three patients entered into a phase I study of SBRT on renal masses with mean tumor size of 2 cm. Patients received 16 Gy to their lesions followed by partial nephrectomy 8 weeks later. Two patients had residual RCC, and one patient had no viable tumor in the specimen. There were no adverse events or radiation toxicity noted [101]. A phase II prospective trial of SBRT for inoperable or metastatic RCC reported on 30 patients with 82 lesions demonstrated at a mean follow-up of 52 months; 21% experienced a complete response and 58% of patients had a partial or stable response [102]. Of note, patients in the trial were treated with varied

radiation doses and fractionation schedules. Siva and colleagues reviewed ten studies (three prospective and seven retrospective) representing a total of 126 patients undergoing SBRT for primary RCC [103]. Local control rates were between 84% and 100% after treatment, and SBRT-related toxicity was relatively low with a grade III and higher toxicity rate of 3.8% [103].

Response to single fraction radiotherapy for renal tumors was prospectively studied by Staehler and colleagues [104]. In a cohort of 40 patients with 45 tumors all under 4 cm, delivery of 25 Gy produced a local control rate of 98% 9 months following treatment. There was no statistically significant change in renal function after the single radiotherapy dose. In 2018, International Radiosurgery Oncology Consortium for Kidney (IROCK) published a pooled, multi-institutional analysis of 223 RCC patients across 9 institutions after either single fraction (median dose of 25 Gy) or multi-fraction SBRT (median dose of 40 Gy in 2–10 fractions) [105]. At mean follow-up of 4 years, local control rate, cancer-specific survival, and overall survival were 97.8%, 91.9%, and 70.7%, respectively [105]. Only 1.3% of patients experienced a major complication (grade III or higher).

The safety profile of SBRT for patients with pre-existing renal disease or those with solitary kidneys has been investigated [102, 106, 107]. Lo et al. reviewed three patients with stage 3 or 4 chronic kidney disease and a T1a renal mass, receiving 40 Gy in 5 fractions. All the patients experienced good local control, and none required dialysis following treatment [106]. Another study comprised of seven patients each with a solitary functioning kidney and a renal mass, and the authors reported that five patients had no change in renal function following SBRT [102]. One patient saw their creatinine rise by 30% at follow-up of 52 months and another patient had a 20% creatinine rise 6 years following treatment.

The IROCK published a multicenter analysis examining SBRT for RCC in 81 patients with a solitary functioning kidney [107]. The oncologic outcomes were deemed to be excellent in terms of local control, progression-free, cancer-specific, and overall survival (98.0%, 77.5%, 98.2% and 81.5%, respectively) after 2 years. Mean glomerular filtration rate dropped from 64.6 ± 21.7 to 59.2 ± 23.9 mL/min/1.73 m^2 at a median of 20 months. Importantly, no patient required dialysis following treatment.

While the early results of SBRT treatment investigations are promising, it is still very much considered an investigational treatment modality. Currently, there are no guidelines supporting this therapy as first line for primary RCC [4, 59]. Additionally, there is no consensus opinion on radiation dose or fractional schedule. There are no established criteria for follow-up and surveillance after treatment. To this later point, Sun and colleagues demonstrated the difficulty with post-SBRT imaging interpretation [108]. The authors noted that the treatment zone does not change enhancement characteristics as it does after TA. Looking at 41 renal tumors treated with SBRT they demonstrated that 75% of the lesions did not change size, 20% demonstrated a partial response and CR occurred only in one patient [39].

Conclusions

Non-surgical focal therapy for the treatment of primary RCC has been gaining traction for several decades. While thermal ablation (CA and RFA) has been elevated to first-line therapy by multiple guidelines, the enthusiasm for other ablation options continues to grow. In fact, there is emerging evidence to show that SBRT combined with short courses of either tyrosine kinase inhibitors or immunotherapy agents may promote increased survival advantage and excellent cancer control rates [109, 110]. Across multiple modalities, focal ablation can provide comparable oncologic outcomes with similar or even better preservation of renal function compared to nephron-sparing surgery. Additionally, non-surgical focal ablation requires less technical skill than extirpative surgery. No longer is focal ablation specifically designated for patients with significant comorbidities or limited surgical options. The authors recommend a multidisciplinary team approach to care which may combine the expertise of Urologists, Interventional Radiologists, and possibly even Radiation Oncologists. While the responsibility of post-treatment surveillance has traditionally fallen upon Urologists, that role can be altered as more specialists participate in a patient's treatment. Before embarking on an ablative treatment plan for a patient with RCC, the practitioner needs to weigh the characteristics of the tumor and the patient before arriving at a treatment decision.

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Radical Nephrectomy for Renal Cell Carcinoma

5

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Introduction

Kidney cancer is one of the most significant contributors to the worldwide cancer burden accounting for 3.5% of all adult malignancies. In 2022 alone the American Cancer Society estimates there will be approximately 79,000 new cases and 14,000 deaths from kidney cancer in the USA [1]. About 80–90% of renal malignancies are renal cell carcinomas (RCCs) which account for approximately 2.2% of all cancers and 1.8% of all cancer-related deaths making RCC the most fatal of urologic cancers. It is estimated that up to 30% of patients have metastatic disease at the time of presentation and in patients with localized renal masses up to 40% will eventually develop metastatic disease [2]. Guidelines from entities such as the American Urology Association, European Association of Urology, and Canadian Urological Association shape the treatment of RCC and each one emphasizes the importance of a multidisciplinary approach for the diagnosis, staging, and treatment of RCC [3–5].

Over the past two decades, the widespread adoption of non-invasive radiological imaging techniques such as computed tomography (CT) and ultrasonography has led to an increase in the detection of early-stage and small-size renal neoplasms with approximately more than 60% of all RCCs now being incidentally detected on imaging [6]. As a result, a large portion of patients undergoing surgery tend to have

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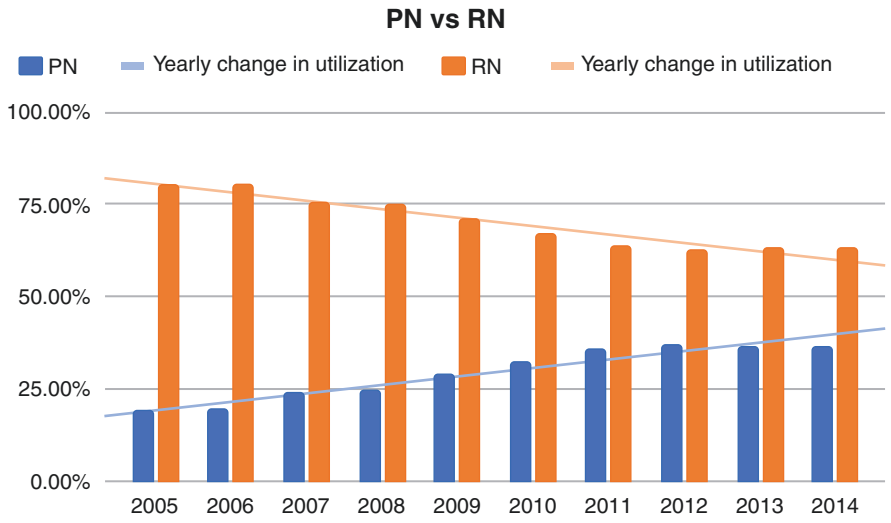

Fig. 5.1 Change in utilization of partial nephrectomy (PN) vs radical nephrectomy (RN) from 2005–2014 (Data from National Inpatient Sample)

small, low stage RCC thus leading to an increase in the utilization of alternative treatment strategies such as active surveillance and nephron-sparing approaches to renal surgery [6]. This has raised questions about overtreatment leading to a decrease in the utilization of radical nephrectomy (RN) [7] (Fig. 5.1). However, RN remains an important component in the management of RCC especially in the treatment of renal masses greater than >4 cm.

Radical nephrectomy has long been considered the gold standard for the surgical management of RCC. The technique of radical nephrectomy was first described by Robson in 1963 and then in 1969 along with his colleagues from the University of Toronto, he would go on to describe the outcomes of 88 patients treated with RN from 1949 to 1964 [8]. RN was historically described as the resection of the kidney with the enveloping Gerota's fascia with the ipsilateral adrenal gland along with the removal of the proximal half of the ureter and complete removal of the regional lymph nodes from the aortic bifurcation to the diaphragm. Since then, the surgical approach for RN has evolved and now encompasses a multitude of techniques with the key surgical principles such as controlling the renal hilum and accessory vasculature and maintaining a plane of dissection external to Gerota's fascia remaining unchanged. Now both extensive lymphadenectomy and adrenalectomy are no longer as common for reasons that will be discussed later. This chapter will review and discuss the role of radical nephrectomy in the management of renal cell carcinoma as well as review common approaches, variations, and considerations when choosing this approach.

Techniques

Open Surgical Approaches: Radical Nephrectomy

In recent years there has been a sharp uptrend in the utilization of minimally invasive techniques in renal surgeries; however, despite this open RN still has a vital role in the management of RCC [9]. While laparoscopic RN (LRN)) certainly has its advantages the fact remains that endoscopic mobilization remains challenging especially in cases with large tumor size and complexity. As such it remains reasonable to consider open RN for cases involving large complex tumors. Open nephrectomy usually involves making a single incision that allows adequate access to the kidney and renal hilum. A multitude of surgical approaches have been described for open RN such as anterior and flank approaches and further classified as retroperitoneal, transperitoneal, or thoracoabdominal (Table 5.1). In addition, several types of incisions can be utilized depending on the approach. Each of these approaches has benefits and drawbacks which makes selection an independent decision of the surgeon.

When choosing the surgical approach necessary for individualized treatment, the surgeon must acknowledge numerous factors, including any known anatomic anomalies, patient's body habitus, prior surgical history, and most importantly, the disease process. These factors will guide the surgeon when deciding which primary open surgical approach to the kidney, either anterior or flank, will be most appropriate.

Anterior Approaches

In the anterior approach, there are numerous incisions, each with its indication, benefit, and limitation. The most common anterior approaches have been listed below. Other incisions include the transverse abdominal incision primarily used for pediatric Wilms tumor, which allows for easy access to both the renal pedicle and retroperitoneal nodes. The paramedian incision when avoiding another structure such as a colostomy. And lastly, the modified thoracoabdominal when approaching a radical nephrectomy that may require suprahepatic or supradiaphragmatic vascular control.

Midline Transperitoneal Incision

The midline transperitoneal incision is indicated for trauma victims, patients with inferior vena cava (IVC) thrombus, bilateral renal or ureteral disease, and horseshoe kidney [10–12]. It is straightforward, non-muscle-splitting incision with rapid opening and closing. This approach allows access to both kidneys and is less painful than muscle-splitting transverse abdominal or flank incisions. It also provides superior exposure to the great vessels optimizing vascular control and locoregional lymphadenectomy. Unfortunately, it has somewhat limited exposure to the upper poles of

Table 5.1 Open surgical approaches for RN

Approach	Incision type	Benefit	Limitation
Anterior		Used when wide exposure to the kidney is needed, such as for cases involving large tumors or tumor thrombus	Midline transperitoneal incisions and subcostal incisions carry the risk of bowel injury with the midline transperitoneal incision also being noted to have a higher incidence of wound dehiscence. The chevron incision carries an increased risk of damage to surrounding organs such as the liver, pancreas, and spleen
	Midline transperitoneal	Non-muscle-splitting, excellent access to great vessels	Limited access to bilateral upper quadrant
	Chevron incision	Excellent access to bilateral upper quadrants	Divides bilateral rectus abdominis
	Subcostal incision	Excellent access to unilateral upper quadrant	Divides unilateral rectus abdominis
	Modified thoracoabdominal	Excellent exposure to suprahepatic vena cava, supradiaphragmatic vena cava and right atrium	Prolonged recovery due to diaphragm incision and rib detachment, significant and severe pain with respiration postoperatively
	Transverse	Excellent exposure to midline and upper quadrant	Muscle-splitting of rectus abdominis
	Paramedian	Non-muscle-splitting, avoids midline, low hernia rate	Reduced access to midline structures such as great vessels
Flank		The flank approach allows for easy access to the kidney and renal hilum while avoiding the peritoneal cavity thus reducing the risk of bowel injury	Supracostal and transcostal flank approaches carry the risk of pleural injury additionally due to the need to divide muscle flank approach are associated with increased postoperative pain and increased risk of incisional hernia
	12th rib supracostal	Excellent exposure to retroperitoneum, avoids peritoneal entry. Direct access to renal artery	Somewhat limited access to upper pole and renal vein
	11th rib supracostal	Excellent exposure to retroperitoneum, avoids peritoneal entry. Direct access to renal artery	Slightly better access to upper pole than 12th rib supracostal incision
	Thoracoabdominal	Excellent exposure to suprahepatic vena cava, supradiaphragmatic vena cava and right atrium	Very morbid recovery due to splitting of diaphragm and division of ribs
Posterior	Dorsal lumbotomy	Avoids peritoneal entry	Limited working space and difficulty extracting larger lesions

the kidney and occasionally to the renal hilum when the kidney is displaced superiorly by a large lower pole tumor.

Chevron Incision

The chevron incision is often used for tumors requiring full liver mobilization, patients with bilateral renal tumors, or polycystic bilateral nephrectomies. This bilateral subcostal incision allows access to both sides of the retroperitoneum, excellent access to both upper quadrants as well as prime exposure of the liver, pancreas, and spleen and provides central vascular control [13]. With this exposure, there is an increased risk of injury to these organs and will be further discussed throughout the chapter.

Subcostal Incision

The subcostal incision is for unilateral radical nephrectomies or ureteropelvic junction obstructions [14]. On the left, the *extraperitoneal approach* is more efficient due to the mobility of the spleen and peritoneal contents. On the right, the liver limits this mobility making the *transperitoneal* approach more practical than the extraperitoneal.

Flank Approaches

The classical flank position involves lateral positioning with the tip of the 12th rib lying directly above the kidney rest [15]. The lower half of the table is flexed, originally the kidney rest would be maximally deployed but more recently this is no longer done. To prevent brachial plexus injury, an axillary roll is placed sitting above the nipple line. Ankles and knees are padded with a pillow is placed between the patient's legs. Finally, before the first incision, the patient should be secured with broad tape at the shoulder and the hip level. The most common flank approaches are listed below.

Eleventh or Twelfth Rib Supracostal and Transcostal Incision

The 11th or 12th rib supracostal approach is mostly utilized for partial nephrectomies, simple nephrectomies, and simple adrenalectomies. These surgical incisions allow for adequate renal and retroperitoneal exposure. This incision provides equal exposure to the eleventh rib and twelfth ribs. Flank approaches are limited by the possibility of diaphragmatic and pleural injury. It is also important to note that while incisional hernias are rare with these incisions there may be a noticeable flank bulge after the procedure.

Thoracoabdominal Incision

The thoracoabdominal incision is commonly used for large renal masses with thrombus extension into the intrahepatic vena cava or direct invasion of the vena cava, liver or surrounding structures [16]. A tumor that has invaded the IVC via a thrombus and has extended into the hepatic veins can be made visible with the thoracoabdominal incision taken through the right seventh or eighth rib. This incision can also be approached extraperitoneally via the modified thoracoabdominal hockey-stick incision.

Laparoscopic and Robotic Approaches: Radical Nephrectomy

For a wide variety of renal conditions, laparoscopy has become widely regarded as an accepted surgical technique. In most technologically advanced settings, LRN has become the gold standard surgical treatment for many disease indications that would have previously resulted in open radical nephrectomy (ORN)) [17]. LRN has been performed successfully on patients with RCC that present with IVC tumor thrombus, larger tumors (>7 cm and up to 25 cm), and patients with metastatic disease who have undergone cytoreductive nephrectomy [18].

For LRN, triangulation of trocar placement is key for this operation as it is for most laparoscopic procedures. Patients are positioned in the lateral decubitus position with the affected side up. The patient is positioned over the flex point of the OR table and the table is flexed to open the space between the costal margin and the anterior superior iliac crest. Generally, a periumbilical 12 mm trocar is placed as is a 5 mm trocar in the midline approximately a handsbreadth cephalad to the umbilicus. A third trocar is placed in the midclavicular line approximately a handsbreadth lateral and 2 cm or so cephalad to the umbilicus. If the tumor is on the right side, a liver retractor may be needed requiring a fourth trocar placed in the sub-xiphoid position (Fig. 5.2).

While LRN and ORN have similar postoperative results, laparoscopic techniques have the advantage of fewer analgesic requirements and shorter recovery periods [19]. It is worth noting that varying levels of expertise amongst surgeons can also impact surgical outcomes, with less experienced surgeons more likely to have longer operative times and more technical complications. Ultimately, it is up to the surgeon conducting the procedure on whether the tumor at hand is most manageable with a laparoscopic or open approach. In the subsequent paragraphs, we will highlight different approaches used in LRN and ORN.

Transperitoneal Approach to LRN

The transperitoneal approach offers the advantage of a large working space and access to all pelvic structures with easy identification of anatomic landmarks. A transperitoneal procedure for LRN follows a similar procedure as a laparoscopic

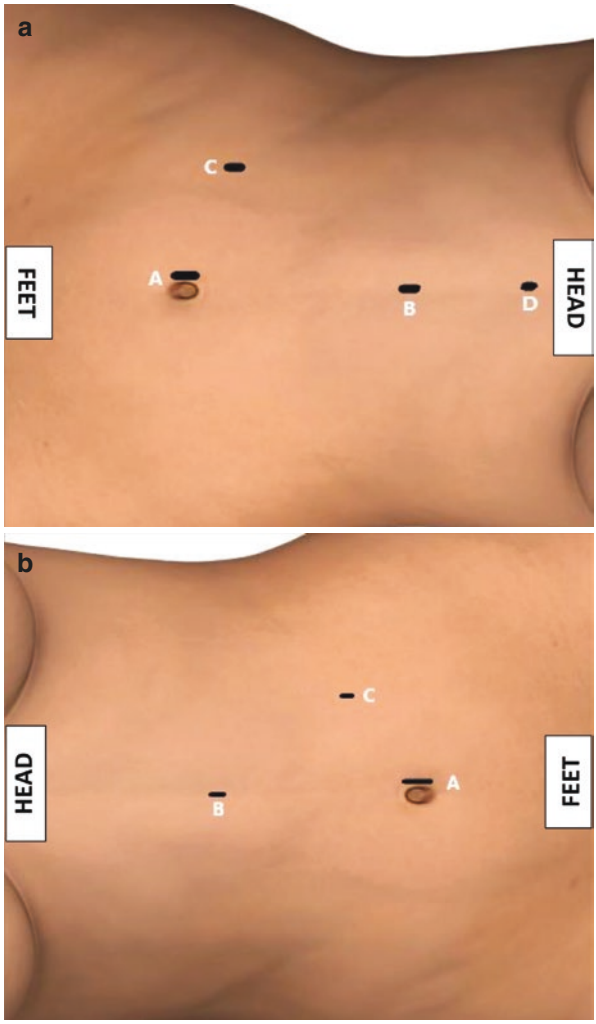

Fig. 5.2 Standard trocar placement for laparoscopic radical nephrectomy (LRN). (**a**) Right LRN trocar placement. (**b**) Left LRN trocar placement. A—periumbilical trocar, usually 12 mm or 15 mm. B—5 mm midline trocar. C—5 mm midclavicular trocar. D—5 mm sub-xiphoid trocar for liver retraction. Extraction of specimen usually performed by extending periumbilical trocar incision in the midline

simple nephrectomy aside from the preservation during dissection of Gerota's fascia and fat [20]. The adrenal glands, lymph nodes, adjacent organs, and adjacent muscles may be removed if indicated. One drawback of accessing the renal structures through the transperitoneal approach includes direct or thermal damage to the bowel during mobilization.

Retroperitoneal Approach to LRN

Access through the retroperitoneal space may be utilized in cases where there are suspected or previously encountered extensive adhesions of the peritoneal cavity

from previous surgeries [18]. Retroperitoneal access is achieved using balloon dilators to expand the avascular plane between the posterior Gerota's fascia and anterior psoas fascia. Benefits of retroperitoneal access include quick access to the renal artery and a decreased risk of trocar site hernias. The retroperitoneal approach is an alternative for the patient with a known kidney infection to avoid peritoneal contamination or in a patient with a history of multiple prior transabdominal surgeries, however, there are some limitations.

Limitations of the retroperitoneal approach include limited working space and lack of standard anatomic landmarks. This approach may be contraindicated in patients with a history of previous open retroperitoneal surgery or chronic kidney inflammation, which may result in perirenal fibrosis that prevents development of the retroperitoneal space. In those situations, balloon dilation can result in tearing of important structures such as the vena cava, renal vein or bowel. During retroperitoneal procedures, anatomic relationships should be continuously reoriented appropriately to prevent misidentification of the inferior vena cava as the renal vein.

Both retroperitoneal and transperitoneal LRN have similar blood loss rates, recovery period, complication rates, hospital stay lengths, analgesic requirements, the number of trocars sites and oncologic outcomes [18, 21, 22]. While one study has noted that retroperitoneal LRN tended to have a shorter operative period than transperitoneal LRN by about an hour, other studies have indicated there was no statistical difference in operative time.

Hand-assisted LRN

Hand-assisted LRN can be viewed as an adaptation or bridge between open surgery and laparoscopy. A hand-assisted laparoscopic nephrectomy uses the surgeon's non-dominant hand through a transabdominal access such as a Gel Port (Applied Medical, Rancho Santa Margarita, CA) to provide retraction and exposure. The dominant hand uses laparoscopic access to dissect with endoscopic scissors. Fingers may be used to palpate arterial pulses as well as guide staples and clips to the artery. An advantage of this approach is being able to manually apply pressure should significant bleeding be encountered [23].

Robotic Radical Nephrectomy (RRN)

For a straightforward nephrectomy not involving lymphadenectomy or tumor thrombectomy, utilization of the surgical robot is probably not necessary in most cases. Given the added expense of using the robot and the well-documented longer operative times with identical surgical outcomes, LRN or ORN would be preferred for these cases over RRN [24]. RRN is often employed in resident training to familiarize trainees with the robot on a simpler case, but typically RRN is not necessary for most straightforward radical nephrectomies. However, the added magnification and the increased dexterity of RRN are useful for regional lymphadenectomy as

well as tumor thrombectomy and subsequent vascular repairs. RRN also gives the surgeon a third operating arm which may provide some advantage in terms of retraction of the kidney and improved exposure compared to LRN (Fig. 5.3). However, for skilled laparoscopists, this potential advantage for the robotic approach does not result in any measurable difference in intraoperative outcomes or benefit to the

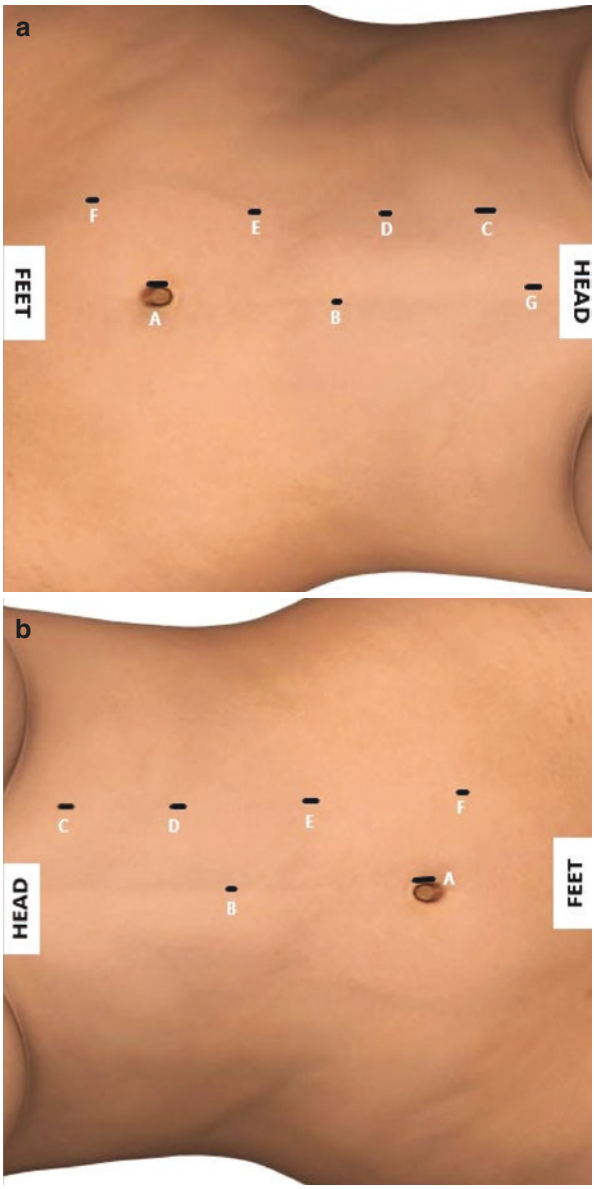

Fig. 5.3 Standard trocar placement for robotic renal surgery. Robotic trocars C-4 are placed along the lateral rectus line. Assistant trocars A and B are placed in the midline. Trocar A is typically a 12–15 mm size. Trocar B is usually a 5 mm trocar. Depending on the type of surgical robot, trocars C–F are 8 mm robotic ports. Some surgeons do not use the 4th arm and omit Trocar F for renal surgeries. (**a**) Trocar placement for right renal surgery. Note Trocar G which is usually a 5 mm trocar for a liver retractor. (**b**) Trocar placement for left renal surgery

patient. For both RRN and LRN, the tumor extraction incision can be made in the midline which avoids muscle-splitting which theoretically should expedite recovery.

Additional Procedures Associated with Radical Nephrectomy

Lymphadenectomy

Extensive lymph node dissection (LND) was historically considered a component of standard RN. The incidence of lymph node metastases in RCC ranges from approximately 13% to as large as 32%. It is well known that pathological lymph node involvement of RCC correlates with poor cancer-specific survival (CSS), and overall survival (OS) [25, 26]. The 5-year CSS and OS rates for lymph node involvement were found to be 26% and 21% while 10-year CSS and OS rates were found to be 25% and 15%, respectively [27]. However, despite the poor prognosis associated with lymph node involvement the therapeutic role of regional LND remains controversial. EORTC 30881 estimated that Lymph node dissection has resulted in the detection of metastases in up to 23% of patients in the absence of other evidence of metastatic disease. This same trial reported that in patients with T1 to T3 renal tumors who underwent RN with and without lymph node dissection there was no difference in overall survival, time to progression of the disease, or progression-free survival between the two groups [28]. It is worth noting that out of 346 patients in this study 332 patients were found to have no evidence of lymph node metastases. These findings were mirrored by the study by Radadia et al. which showed most patients undergoing LND will not have detectable metastases. This analysis also demonstrated that patients treated at academic centers were more likely to undergo LND [29]. Another study showed no survival benefit for patients undergoing LND irrespective of nodal involvement pathologically. The authors suggest that LND is overutilized in low clinical stage disease [30]. Thus, in light of this evidence, decisions on the necessity of lymph node dissection should be guided by preoperative risk stratification including imaging and biopsy, in addition to intraoperative pathologic rapid frozen sectioning [31].

Adrenalectomy

Adrenal involvement in RCC occurs in 1.9–7.5% of renal malignancies. Adrenal involvement can occur through hematogenous, lymphatic, or direct extension and is more likely when tumors are larger than 7 cm, pathologic stage T3 or T4, have an associated tumor thrombus, or are located in the upper pole of the kidney [32]. Historically, much like routine regional lymphadenectomy, ipsilateral adrenalectomy was once considered a required component of the traditional RN. Studies suggest that adrenal metastases from primary renal cell carcinoma were found significantly more often in patients with advanced tumor stages [33]. However, with the stage migration to lower stage disease with the increased use of cross-sectional

imaging, modern practice has moved away from the widespread adrenalectomy due to data demonstrating rare adrenal involvement with localized disease. Current recommendations now highlight that ipsilateral adrenalectomy should only be considered in patients who demonstrate adrenal involvement on preoperative imaging [34]. Furthermore, as the risk of developing contralateral adrenal metastasis is roughly 6% ipsilateral adrenalectomy would put patients at risk for adrenal insufficiency in the event of the need for contralateral metastatic adrenalectomy.

Tumor Thrombus

A unique feature in a small subset of patients with RCC is that the tumor may invade vasculature and form a tumor thrombus that propagate through the renal vein and extend into the IVC. Approximately 4–10% of RCC cases have a tumor thrombus involving the IVC, and in rare cases, the thrombus can extend as high as the right atrium [35, 36]. Patients with IVC tumor thrombus may present with edema of the lower body, varicocele, pulmonary edema, and in some cases a right atrial mass. While a caval thrombus below the main hepatic veins can be isolated and removed, a thrombus extending cephalad above the short hepatic veins will require full liver mobilization and occasionally extension of the incision into the thorax [37]. Venovenous bypass should be considered with supradiaphragmatic extension. A cardiopulmonary bypass procedure may be considered for a thrombus that reaches the right atrium. While open surgery has historically been the mainstay treatment for RCC with IVC involvement there has been a recent introduction of minimally invasive techniques for this clinical scenario.

There have been many classifications for tumor thrombus introduced since the first radical nephrectomy with IVC thrombectomy was described. Regardless of the classification used, determining the extent of the tumor thrombus' involvement is critical when planning a surgical approach. While there is no clear agreement on which classification best guides the surgical strategy for venous thrombus extension, the Mayo Clinic classification introduced by Neves and Zincke and later modified by Blute is the most common classification utilized [38] (Table 5.2).

Table 5.2 Mayo Clinic classification for tumor thrombus

Thrombus level	Description
0	Thrombus is limited to the renal vein
I	Tumor Thrombus extends into the IVC is working 2 cm from the confluence of the renal vein and IVC
II	Tumor Thrombus extends into the IVC and is greater than 2 cm from the confluence of the renal vein and IVC but remains infrahepatic
III	Tumor Thrombus involves the infrahepatic IVC but remains below the diaphragm
IV	Tumor thrombus involves the IVC above the diaphragm and may involve the right atrium

Prior to surgery, cross-sectional imaging is required to determine the cephalad most extent of the tumor thrombus. Computed tomography is adequate although gadolinium-enhanced MRI can provide high resolution imaging of thrombus propagation. During surgery, transesophageal echocardiography (TEE) may be a helpful tool to evaluate the extent of the thrombus. Additionally, a TEE will allow information on the patient's cardiac function to be obtained when the IVC is clamped. Depending on the extent of the caval thrombus, the procedure begins with mobilization of the kidney and ligation of the arterial blood supply and then is tailored depending on the anatomical extension of the thrombus.

Despite advances in imaging, surgical techniques and hemostatic agents, radical nephrectomy with IVC thrombectomy remains a difficult surgery that requires a specialized and well-trained surgical team. For level 0 thrombus in the renal vein, a radical nephrectomy with a laparoscopic approach can be considered as this does not represent a significantly greater challenge than a standard radical nephrectomy [39]. For a thrombus extension into the IVC but not extending into the intrahepatic portion (Level I and II) minimally invasive techniques can be considered based on the ability and preference of the surgeon [40]. For a thrombus greater than level III while minimally invasive techniques are generally not recommended and should only be considered appropriate for well-selected patients under the care of highly skilled surgeons operating at high-volume centers [41, 42].

For open radical nephrectomy with thrombectomy, 30-day mortality was 5% with 2-year overall survival and cancer-specific survival found to be 60% and 62%, respectively. Intraoperative complications were noted for 39% of patients and postoperative complications were observed in 58% of cases [40]. However, it must be noted that these findings were only observed in patients with level 1 and 2 tumor thrombus. In a Level III-IV study of robot-assisted inferior vena cava (IVC) thrombectomy the perioperative mortality rate was observed to be 7.7%, with one patient dying in the perioperative period. Intraoperative complications were noted on both laparoscopic and robotic series; they included spleen, liver, bowel, and IVC injury. Due to the relatively recent introduction of minimally invasive techniques in the management of tumor thrombus studies have not yet been able to prove any oncologic benefit compared to open approaches. It is unlikely that these techniques will demonstrate better oncologic control than open approaches but may eventually show some benefits in terms of blood loss or recovery. To this point, published studies have been unable to achieve meaningful conclusions on the oncologic benefits of minimally invasive IVC thrombectomy due to several limitations such as limited sample size, limited follow-up, and lack of detailed reporting of key outcomes such as cancer-specific and overall survival rates [40]. A recent meta-analysis of published series of RRN with caval thrombectomy demonstrated 18.4% transfusion rate and a 14.5% complication rate; both of which were lower in comparison to ORN with caval thrombectomy (p = 0.002) [36]. As was the case for radical and partial nephrectomy, it is likely that RRN with caval thrombectomy will become more common over time as providers comfort level and skill increase.

Outcomes

Oncologic Outcomes

The utilization of RN in the management of RCC has shown to produce outstanding oncologic outcomes. Multiple studies have shown that the use of both laparoscopic and open RN revealed no significant differences in 5-year recurrence-free, all-cause, and cancer-specific survival. Since it was first introduced LRN has shown outstanding oncologic outcomes for all stages of RCC with 5-year RFS, CSS and OS found to range between 92–95%, 97–98%, and 81–88%, respectively [19]. Oncologic outcomes are stage dependent, of course, with CSS rates much lower for more advanced disease stages for all approaches.

Operative Outcomes

The 30-day mortality rate for RN has been estimated to range from 0.5 to 0.9% [43, 44]. The 30-day mortality rate was found to increase with age, stage, estimated blood loss (EBL), operating time, and performance status. Laparoscopic RN is associated with favorable perioperative outcomes when compared to open RN [19]. These include significantly shorter length of hospital stay, reduced blood loss but no reduced transfusion requirement, reduced postoperative analgesic requirements, and earlier return to normal activity [21].

Considerations

Indications

Radical nephrectomy is indicated for cases that are too large to be completely excised with negative margins via partial nephrectomy and leave adequate functional renal parenchyma. Guidelines suggest that RN should be considered for patients with T2 or greater renal neoplasms as well as patients with localized renal tumors that cannot be resected with nephron-sparing surgery [3, 4]. Some of these cases include tumors associated with regional lymphadenopathy or venous thrombosis, tumors in nonfunctional kidneys, or substantial tumor masses that comprise a majority of the kidney. Occasionally, RN is preferred in chronically ill patients for whom the fastest operation with the least amount of blood loss is optimal.

Radical Nephrectomy Vs Partial Nephrectomy

Accurate preoperative assessment of tumor complexity through imaging is critical to preoperative decision-making in the treatment of RCC. This will include weighing the benefits and drawbacks of radical nephrectomy compared to partial

nephrectomy [45]. A decision must be made to balance oncological and perioperative outcomes with the risk of renal impairment. To date, EORTC 30904 remains the only prospective randomized trial comparing the Oncologic Outcome of partial nephrectomy (PN) vs. Radical nephrectomy (RN) [46]. The findings of this study have sparked significant discussions as they found that RN and PN have similar postoperative oncological outcomes and there was no difference in CSS with the PN group being observed to have a slightly lower OS. It is worth noting that this study was limited to renal masses <5 cm and limited by failure to fully accrue. The EORTC 30904 trial also demonstrated that PN does have a clear advantage over RN in terms of preservation of renal function. 86% of patients in the RN group were noted to have moderate renal impairment (eGFR <60 ml/min) compared to 65% of patients who underwent PN. However, the incidence of severe renal impairment (eGFR <30 ml/min) and renal failure (eGFR <15 ml/min) is nearly identical between PN and RN. These findings align with observation studies which showed that patients undergoing RN were two times more likely to have a >10% reduction in eGFR and were three times more likely to have eGFR fall below 45 ml/min. These findings are important and must be considered due to the well-known correlation between postoperative renal function and overall cardiovascular survival.

Preoperative Considerations and Contraindications

Prior to surgery, imaging should be obtained to aid in staging the tumor. A percutaneous renal biopsy may be performed in select cases to guide management and/or evaluate for metastases or lymphomas [47, 48]. Patients with sizable tumors with involved lymph nodes may undergo preoperative angioembolization to potentially reduce intraoperative blood loss. This is strictly based on surgeon preference and practice pattern as conflicting data exists to support this practice [49]. Potential risks of angioembolization include bleeding, severe pain and fevers, and embolization of tumor thrombi. Patients with locally advanced RCC should have a comprehensive preoperative consent that discusses increased risk of morbidity, bowel prep, vaccinations if a splenectomy is considered, and possible resection of adjacent organs.

Historically, larger tumor sizes were considered contraindications for laparoscopic surgery; but over time, this relative contraindication has lessened with increasing technical expertise and experience. Ongoing relative contraindications to laparoscopic surgery include hilum-limiting bulky disease, significant perirenal inflammation, associated adjacent organ invasion, and intra- and suprahepatic extent of venous thrombosis.

Complications

When consenting to undergo either an open or laparoscopic nephrectomy, the patient should understand all the benefits, risks, and potential complications that may arise. Complications will vary based on the technique employed (ORN vs.

LRN) as well as with which kidney is involved [22]. All complications must be thoroughly discussed with the patient before the procedure. Patients with prior abdominal procedures should also be aware of their higher risk for complications. In general complications of RN can be summarized into three categories: (1) bleeding, (2) infection, and (3) injury to surrounding structures. Blood loss estimates can range from 50 mL or less to >1000 mL depending on tumor stage, local invasion, collateralized vessels, and surgical approach (ORN vs. LRN). Infection risks are typically 4% or less and are predominantly incisional infections. However, it is important to note the unlikely risk of peritonitis associated with an occult bowel injury. Though the risk of this devastating complication is well below 1%, the morbidity and mortality associated with this complication are so significant that it may be worth including in preoperative consent. Intestinal complications such as celiac axis and superior mesenteric artery injuries are exceedingly rare but are potentially fatal complications of RN [50, 51]. Entry into the diaphragm is unusual except in cases of re-operation or extended flank approach; this can result in pneumothorax, hemothorax, or pleural effusion [52–54]. Additionally, as ORN involves the utilization of large incisions compared to minimally invasive procedures this may result in cosmetic complications such as flank bulges or incisional hernias [55]. Laparoscopic procedures may convert to open if complications emerge, therefore consent should be obtained for this possibility. When performing a left-sided nephrectomy, the structures at risk of injury include the spleen, pancreas, colon, aorta, SMA, and stomach. Splenic injury on the left side is among the most common of injuries found to occur in 0.8% of cases [22]. For right-sided nephrectomies, anatomic structures at risk include the gonadal vein, inferior vena cava, right adrenal vein, colon, liver, small bowel, and duodenum. Postoperatively, patients may experience neuropraxia due to poor positioning, deep vein thrombosis secondary to disease process or lack of prophylaxis, retained pneumoperitoneum or subcutaneous emphysema, or rarely rhabdomyolysis following very prolonged cases [56–58]. Finally, any major oncologic operation includes a non-trivial risk for venous thromboembolism (VTE) in the perioperative period [59]. This risk is low and perioperative anticoagulation helps mitigate this risk.

Postoperative Considerations

Postoperative management includes early ambulation, rapid advancement to regular diet, and early discharge within 36 h of surgery in most cases. Patients are instructed to avoid lifting more than 10 lbs or so for 4–6 weeks depending on surgical approach. Open approaches with longer incisions may have heavy lifting and exertional restrictions up to 8 weeks depending on patient factors (body habitus, nutrition, length of incision, and type of work). Post-surgical follow-up should be based on finals pathological tumor characteristics. Typically, patients with low-risk diseases should have imaging (CT, MRI, or US) done within a year of their surgery. Chest X-ray should be performed for the first 3–6 months post-surgery to evaluate for the presence of metastasis. Patients with moderate-to-high risk disease will require

MRI or CT scans every 6 months after surgery along with a yearly CXR or chest CT for up to 5 years to evaluate for metastasis [60].

Rarely, local recurrence after a radical nephrectomy can occur. Factors that increase this risk include high tumor grades, grossly positive surgical margins, and lymph node involvement. If a patient has a local recurrence, an intensive investigation for other sites of potential metastasis should occur. If metastatic evaluation reveals no other sites of recurrence, surgical resection may be considered for local recurrence after radical nephrectomy [61]. In some cases, complete resection of local recurrence is challenging due to post-surgical fibrosis resulting in the loss of tissue planes and dense adherence to surrounding critical anatomic structures. These factors may necessitate en bloc resection of adjacent organs.

Conclusion

Radical nephrectomy maintains a central role in the management of advanced stage RCC despite the technological advancements and increasing indications for and expertise with nephron-sparing surgical techniques. ORN and LRN have broad indications and selection is largely based on surgeon preference. Robotic approaches to RN should be reserved for technically challenging scenarios involving locoregional lymphadenectomy and/or vena cava tumor thrombectomy. RN by any approach is the oncologic gold standard for RCC although nephron-sparing techniques have demonstrated comparable oncologic control for lower stage disease. Mastery of a variety of incisions and approaches to accomplish RN are imperative for the practicing urologic surgeon.

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Surgical Management of Hereditary Kidney Cancer Syndromes

6

Nikhil Gopal, Bradley Webster, Maria Antony, and Mark W. Ball

Introduction

While hereditary kidney cancer only represents 5–8% of all kidney cancer diagnosed in the USA, it was through first studying these afflicted families that the central tenet of kidney cancer occurring through genetic mutations was established [1–3]. Indeed, kidney cancer is not a single entity, but rather a constellation of different tumors defined by unique genetic signatures. In the case of hereditary kidney cancer, there are over a dozen cancer predisposing genes that have been identified, each associated with a clinical syndrome that often additionally involves organs beyond the kidney [4, 5]. Just as with sporadic kidney cancer, patients with hereditary kidney cancer are often diagnosed at a localized stage. However, in contrast to their sporadic counterparts, hereditary tumors typically present earlier and at multiple times throughout a person's life, requiring a nuanced approach to management that, first and foremost, considers the expected tumor biology.

In the following, we review the most prevalent hereditary kidney cancers. For each entity, an overview of the genetic pathogenesis and clinical phenotype of the associated syndrome will be provided. Finally, we discuss management of each sydrome, focusing on the indications for surgery vs. active surveillance. Tumors in certain syndromes, due to their biological behavior, may warrant a specific approach to surgery, which is detailed in those cases. When relevant, other treatment modalities are discussed. Ultimately, we provide a "precision surgery" model to hereditary kidney cancer, with both indications for and type of surgery dependent on the specific germline alteration and associated tumor biology [6]. Table 6.1 summarizes the "take-home" points for each hereditary syndrome discussed.

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Table 6.1 Summary of genetics, clinical manifestation, and surgical management of hereditary kidney cancer syndromes

Hereditary kidney cancer syndrome	Altered gene	Renal tumor classification	Extrarenal manifestations	Screening recommendations	Active surveillance	Threshold for operation	Type of operation
VHL	VHL	Clear cell	CNS/retinal hemangioblastomas, pancreatic neuroendocrine tumors, pheochromocytomas, epididymal tumors, endolymphatic tumor of inner ear	Contrast-based MRI[a] every 2 years beginning at age 15 [7] or 16 [8]	Yes	3 cm	Tumor enucleation
HPRC	MET	Type I papillary	None	Contrast-based MRI[a] every 1–2 years beginning at age 30 [7]	Yes	3 cm	Tumor enucleation
BAP1	BAP1	Clear cell	Uveal/cutaneous melanoma, mesothelioma, hepatocellular carcinoma, cholangiocarcinoma, meningioma	Contrast-based MRI[a] every 1–2 years beginning at age 30 [7]	No	Radiologically visible	Partial nephrectomy with margin
BHD	FLCN	Most common: hybrid oncocytic and chromophobe Less common: clear cell, oncocytoma, papillary	Cutaneous manifestations (fibrofolliculomas most common), pulmonary cysts	Contrast-based MRI[a] every 3 years beginning at age 20 [7]	Yes	3 cm	Tumor enucleation
TSC	TSC1 or TSC2	Angiomyolipoma RCC: TSC associated RCC with fibromyomatosis stroma, TSC associated oncocytic tumor, eosinophilic solid and cystic tumor	Angiofibromas of skin, subependymal giant cell astrocytoma (SEGA), rhabdomyoma of heart, pulmonary lymphangioleiomyomatosis (LAM)	Contrast-based MRI[a] every 3–5 years beginning at age 12 [7]	Yes	3 cm (RCC), 4 cm (AML)	Tumor enucleation

HLRCC	FH	FH-deficient RCC (diverse histology pattern)	Uterine and cutaneous leiomyomas	Contrast-based MRI[a] annually beginning at 8–10 years [7]	No	Radiologically visible	Partial nephrectomy with wide margin, consider radical for large lesions, open surgery for cystic lesions, retroperitoneal lymph node dissection for large and/or complex lesions
SDH	SDHAF2, SDHA, SDHB (most common), SDHC, SDHD	SDH deficient RCC (diverse histology pattern)	Paragangliomas (head and neck), pheochromocytomas, and gastrointestinal stromal tumors (GISTs)	Contrast-based MRI[a] every 2–4 years beginning at age 12 [7, 9]	No	Radiologically visible	Partial nephrectomy with wide margin, consider radical for large lesions, open surgery for cystic lesions, retroperitoneal lymph node dissection for large and/or complex lesions
Cowden	PTEN	Papillary type I and II; clear cell; chromophobe	Mucocutaneous lesions (e.g., papilloma of lip), GI hamartomas, cancers of thyroid; breast; and uterus	No established recommendations: Can consider contrast-based MRI[a] every 1–2 years [9]	Unclear	Unclear	Unclear

(continued)

Table 6.1 (continued)

Hereditary kidney cancer syndrome	Altered gene	Renal tumor classification	Extrarenal manifestations	Screening recommendations	Active surveillance	Threshold for operation	Type of operation
HPT-JT	CDC-73	Wilm's tumor, MEST (mixed epithelial and stromal tumor), RCC	Parathyroid and uterine tumors, ossifying fibromas of mandible and/or maxilla	No established recommendations: can consider contrast-based MRI[a] every 5 years [9]	Unclear	Unclear	Unclear
MiTF	MiTF	MiTF associated RCC (can have clear cell or papillary features)	Cutaneous melanoma	No established recommendations: can consider contrast-based MRI[a] every 1–2 years [9]	Unclear	Unclear	Unclear
Chromosome 3 translocation	–	Clear cell	None	Can consider contrast-based MRI[a] every 2 years	Yes	3 cm	Tumor enucleation

VHL Von Hippel-Lindau Syndrome, *HPRC* hereditary papillary renal cancer, *BAP1* BRCA associated protein 1, *BHD* Birt-Hogg-Dubé, *TSC* tuberous sclerosis, HLRCC hereditary leiomyomatosis and renal cell cancer, *SDH* succinate dehydrogenase, HPT-JT hereditary hyperparathyroidism-jaw tumor, *MiTF* Microopthalamia transcription factor. References for screening recommendations provided by superscript. Unless otherwise indicated, either robotic or open nephrectomy can be performed based on surgeon's expertise

[a] CT can be substituted if MRI unavailable or impractical, given patient specific factors. Renal ultrasound is generally not recommended due to reduced sensitivity for detection of solid tumors, particularly for papillary RCC [10]

von Hippel-Lindau (VHL) Syndrome

Genetics, Pathogenesis, and Clinical Manifestations

von Hippel-Lindau (VHL) is the most common hereditary renal cell cancer syndrome with an incidence of 1/36,000 [11] and was the first to have its genetic underpinning solved. Nonetheless, nearly a century elapsed between the first clinical description of the characteristic central nervous system (CNS) and retinal angiomas of the syndrome [12, 13] and the localization of the *VHL* gene to the short arm of chromosome 3 (3p25-3p26) in the late 1980s/early 1990s [14]. Identification of a single gene responsible for the pathogenesis of a familial syndrome ushered in a revolution in the management of both hereditary and sporadic kidney cancer by outlining an approach for personalized medicine.

The *VHL* gene is a tumor suppressor gene inherited in an autosomal dominant fashion [14, 15]. Affected patients are born with one altered germline copy. Tumor formation begins in when the wild type allele is lost, typically by losing the entire short arm of chromosome 3. VHL is a multisystem disorder, in which affected individuals are at risk for developing clear cell renal tumors and cysts; pancreatic cysts and neuroendocrine tumors; adrenal tumors (pheochromocytoma); CNS/retinal hemangioblastomas; endolymphatic tumors of the inner ear; and epididymal cystadenomas [16, 17]. Because every cell in patients with VHL syndrome has one abnormal copy of the *VHL* gene from birth, only one additional hit to the remaining wild type copy is required in a given cell to induce neoplastic transformation, as opposed to two hits in the general population with initial inheritance of two wild type copies of the *VHL* gene [15]. As a result, VHL patients are more susceptible to forming tumors, such as in the kidney, than in the larger population. In particular, kidney cancer occurs in 25–45% of VHL patients and is nearly uniformly bilateral as well as multifocal. Additionally, patients develop renal malignancy at an early age (2nd to 4th decades of life) [3, 16]. The likelihood of manifestation of renal and extrarenal tumors has been linked to specific genotypes [18–20]. Namely, the more common VHL variant (type 1) is characterized by nonsense mutations or intragenic deletions resulting in CNS and renal tumors without pheochromocytomas. On the other hand, VHL type 2 has predominantly missense mutations and presents with pheochromocytomas [21, 22].

Understanding the biological basis of VHL disease has allowed for therapeutic advancements in both localized and advanced hereditary and sporadic kidney cancer, as loss of VHL is seen in over 90% of sporadic clear cell tumors [23]. The protein encoded by the *VHL* gene forms a complex with additional transcription factors (Elongins B and C [24, 25]; cullin-2 [26]; and Rbx1 [27]) that, under non-hypoxic conditions, bind to hypoxia inducible factor alpha (HIF-α) and target it for ubiquitin-mediated degradation [28–30]. If any components of the VHL protein complex are abnormal and/or missing, with a resultant inability to bind to HIF-α, HIF-α inappropriately persists in the cell. As HIF-α is a transcription factor that increases expression of proteins implicated in neo-angiogenesis (vascular endothelial growth factor (VEGF)); cell proliferation (platelet derived growth factor beta

(PDGFβ) and transforming growth factor alpha (TGF-α)); and glucose metabolism (glucose transporter 1 (GLUT1)) [31], it is easy to see that constitutive HIF-α can lead to unchecked cell growth and division, hall-markers of malignancy. Prior to the advent of immunotherapy, drugs targeting downstream HIF-α effectors (i.e., sunitinib inhibiting VEGF and PDGF receptors [32]) were first-line treatment for metastatic clear cell kidney cancer [33], and just recently, an agent specifically targeting HIF-2α has been approved by the FDA for treatment of localized renal tumors in VHL patients [34, 35].

Clinical and Surgical Management of VHL Renal Tumors

Given the high penetrance of kidney cancer in VHL patient, parenchymal sparing surgery is paramount to remove localized tumors with risk of metastasis, while preserving residual renal function. VHL tumors are generally surrounded by a fibrous pseudocapsule, beyond which minimal, if any, tumor is present [36]. By establishing a plane between the tumor pseudocapsule and the surrounding renal parenchyma, one is able to excise the tumor without a rim of renal parenchyma, a process referred to enucleation. As patients often have multiple tumors in a single kidney, minimization of renal ischemia induced hilar clamping is done by restricting clamping of the renal hilum only to tumors in close proximity to underlying renal vasculature as identified on preoperative imaging. In this manner, enucleation of multifocal renal masses has been demonstrated in multiple retrospective series to reduce risk of metastasis while maintaining baseline preoperative renal function in the long term, even in patients with chronic kidney disease [37–41]. Within the last decade, robotic multiplex (multifocal renal masses) partial nephrectomy has been shown to have similar oncologic and functional outcomes as open surgery, with more favorable perioperative outcomes such as total blood loss.

It is important to realize that, even after removal of renal mass(es), VHL patients remain at high risk for forming repeat renal tumors given their positive germline mutation. Microscopic examination has revealed an average of 1000 cysts with clear cell lining (pre-malignant) and 600 clear cell neoplasms in kidneys of VHL patients at a median age of 37 years [42]. With an early age of onset of renal cell cancer phenotype, it is inevitable that many patients will require several operations throughout their lifetime [43]. Surgery in VHL patients is thus not considered curative as in the sporadic population; rather, one is resetting the clock towards needing an operation [44]. Re-do partial nephrectomies, whether open or robotic, are associated with higher rate of complications, such as transfusion; hospital stay; and/or urine leak [38, 45], so another consideration in the management of VHL patients is minimization of the required number of renal surgeries.

Active surveillance, while only recently established as an acceptable option in sporadic RCC [8, 46, 47], has, by necessity, remained a tenet of hereditary kidney cancer management. The VHL Alliance recently published surveillance guidelines, with recommendation to initiate screening at 16 years, given that the youngest age at which a VHL renal tumor occurred was at 15 years [48]. In the absence of renal

insufficiency, contrast-based MRI is preferred over CT due to absence of radiation. Patients should have screening done every 2 years if no solid renal mass is present. If a solid and/or enhancing mass is present, the interval of imaging is dependent on the growth rate of the mass, with 5 mm/year viewed as the cut-off for fast vs. slow growth.

Initial observation of VHL patients with renal masses demonstrated a 0% rate of metastasis in patients with solid tumors under 3 cm, as compared to 22% rate of metastasis for solid tumors greater than 3 cm [49]. As such, the current practice of managing VHL patients involves serial imaging until a solid renal tumor reaches 3 cm, at which point surgical removal of that tumor along with any other identifiable solid lesions on the ipsilateral kidney is performed. Excising all visible solid and cystic lesions in a kidney, with the aid of an intraoperative ultrasound, is recommended, when feasible, to minimize need for re-operation on that kidney. While the size threshold for operation applies to solid tumors, due to the malignancy risk of VHL cysts (21%), they are also removed at the time of operation, if reasonably accessible [50].

Alternative Options for Localized VHL Renal Masses

An alternative, yet increasingly utilized, strategy to manage solid renal masses in VHL patients is image-guided ablation. This modality is particularly attractive for patients who are not medically fit for surgery. Other benefits over nephron-sparing surgery include greater likelihood of renal function preservation and less morbidity, particularly with re-do operations [51]. In centers of excellence, there is a 0–8% risk of major complications (e.g., large pneumothorax or bowel injury) [52–55]. Minor complications (e.g., small pneumothorax; hematuria; perinephric or subcapsular hematoma) occur 58–66% of the time, but generally resolve without intervention. The rate of residual disease or local recurrence is more common than partial nephrectomy; it was as high as 50% in initial series, although incidence has since decreased with experience, with one recent series having a rate of 5% [55, 56]. However, the vast majority of local disease persistence/recurrence can be successfully treated with another ablation session.

The most common types of ablation utilize either electric current (radiofrequency ablation) or freezing (cryoablation). Newer non-thermal based technology, such as irreversible electroporation, may be beneficial for masses in close proximity to structures such as the ureter or renal hilum [55]. These procedures can be done either percutaneously or laparoscopically, although the former is more prevalent due to being less invasive and not requiring general anesthesia. Ablation is restricted to renal masses less than 3 cm. Depending on the modality used, the ablation zone should be at least 5–10 mm beyond the tumor itself, so the ideal zone for larger tumors would risk either damaging normal parenchyma or adjacent structures such as bowel or renal pedicle. There are several reasons that, in our practice, ablation is not utilized in patients fit for surgery. First, not all lesions are amenable to ablation, depending on proximity to the vasculature. Partial

nephrectomy following ablation can be challenging as normal planes are obliterated [57, 58]. Secondly, in patients with many lesions, the additional ablation zones beyond the tumor margin are additive across many lesions and have an overall negative impact on renal function. Finally, surveillance after ablation can be challenging compared to surgery and require increased scrutiny to ensure lack of contrast enhancement [57]. In summary, image-guided ablation remains a consideration for older and/or highly co-morbid patients with fast-growing lesions (≥5 mm/year) between 1 and 3 cm.

The recent FDA approval of belzutifan, a HIF2-α inhibitor for VHL patients with localized renal tumors (also approved for pancreatic and CNS tumors), has brought yet another option for a disease entity once exclusively managed surgically [34]. The phase II trial of 61 patients resulted in an objective response rate of 49%, with an additional 49% of patients having stable disease [35]. Progression-free survival was 96% at 2 years, demonstrating a durable response. The side effect profile of this regimen is comparatively favorable to other systemic agents in kidney cancer. Given that HIF also serves as a transcription factor for erythropoietin (EPO), anemia was seen in all patients; however, only a minority (7%) required blood transfusion. Long-term data and additional clinical trials will no doubt better define the role that this drug will play in the management of VHL localized renal tumors. Currently, we are prioritizing drug administration to patients with tumors approaching but not yet 3 cm or fast-growing tumors that will reach 3 cm in 1–2 years in an effort to delay surgery.

Summary

VHL (Von Hippel-Lindau) is the most common type of hereditary kidney cancer syndrome, with patients having multifocal, bilateral clear cell renal cell carcinomas. Additional manifestations include CNS and retinal hemangioblastomas; pancreatic cysts and neuroendocrine tumors; and pheochromocytomas. Surgical management of localized VHL tumors requires a balance between preservation of renal function and oncologic control. Patients undergo lifelong surveillance imaging, with frequency dependent on presence and/or growth rate of renal tumors. Kidney surgery is performed only when a solid tumor in a kidney is at least 3 cm. Whenever possible, nephron-sparing surgery (i.e., partial nephrectomy) is conducted. To maximally preserve nephrons, the tumor is removed with minimal surrounding normal parenchyma through a process known as enucleation. All visible renal masses on a given kidney are removed in a single setting so as to minimize repeat operations. Surgery can be done either robotically or laparoscopically, although patient referral to centers of excellence should be considered, particularly for repeat partial nephrectomies due to increased morbidity. Image-guided ablation can be an option for peripherally growing renal masses between 1 and 3 cm, particularly in patients who are not surgical candidates. Finally, the oral agent belzutifan is the latest advancement in the treatment of localized VHL tumors, although specific indications and duration of use will depend on additional experience and clinical trials.

Hereditary Papillary Renal Cancer (HPRC)

Genetics, Pathogenesis, and Clinical Manifestations

In 1994, a three-generation family was identified with multiple papillary tumors of varying sizes and no loss of heterozygosity at chromosome 3p, suggesting an inherited kidney cancer with distinct pathogenesis from VHL [59]. Analysis of blood and tumor samples from these and other families with a similar predisposition for developing bilateral, multifocal papillary type I tumors led to the identification of germline alterations in the *MET* oncogene on chromosome 7p31 as the causative gene for this inherited syndrome, known as hereditary papillary renal cell cancer (HPRC) [60, 61]. The mutation is inherited in an autosomal dominant fashion.

MET is a receptor tyrosine kinase that binds hepatocyte growth factor (HGF). HPRC patients have mutations in the domain responsible for binding of MET to hepatocyte growth factor (HGF). MET is normally self-inhibited, with binding of HGF responsible for activation of the tyrosine kinase; the resultant MET/HGF signaling cascade is responsible for a number of biological processes, such as cell growth; differentiation; survival; motility; and angiogenesis. Alteration in the receptor binding domain results in constitutive MET activation, with resultant unregulated cell proliferation and tumorigenesis. As it is a gain of function mutation, only 1 abnormal gene is needed to express the phenotype, unlike the two hits required for tumor suppressor genes such as *VHL*.

While only a minority of sporadic type I papillary tumors (13–15%) have *MET* missense mutations [62], 81% have altered *MET* status defined as mutation, splice variant, gene fusion, or gain of chromosome 7 [63].

Unlike other hereditary kidney cancer syndromes, HPRC only has renal manifestations. Penetrance is over 90%, with median diagnosis of renal tumors at age 57, but tumors have been seen in families as early as the second decade of life [64]. Tumors tend to be slower growing than those in VHL (median growth rate of 0.15 cm/year vs. 0.37 cm/year) [65]. Nonetheless, patients with HPRC have died from untreated kidney cancer that metastasized [64].

Clinical and Surgical Management of Renal Tumors in HPRC

As with VHL, patients are at high risk for bilateral and multifocal tumor development throughout their lifetime, regardless of initial surgical excision. From extrapolation of microscopic examinations of grossly normal renal parenchyma in HPRC patients, as many as 1100 to 3400 distinct tumors can be predicted to be in a single kidney [7]. Thus, surgical management of HPRC involves balancing oncological control with preservation of renal function; as with most hereditary kidney cancer, it is an extension of the VHL experience, given the latter's greater prevalence. Namely, HPRC patients have routine lifelong cross-sectional imaging performed. MRI is preferred over CT due to the absence of radiation exposure and improved tumor characterization, as lesions have relative T1 hypoenhancement on MRI [66].

Given the median older age of onset of renal tumors as compared to VHL, guidelines suggest screening at age 30 every 1–2 years, with more frequent imaging dependent on presence and/or growth of a solid renal mass [67]. Parenchymal sparing surgery (enucleation) is offered when a lesion reaches 3 cm [37]. Image-guided ablation can be considered for lesions between 1 and 3 cm in appropriately selected patients. Currently, no drug is approved for localized HPRC lesions. However, understanding of the pathogenesis of this entity has led to the development of multiple MET inhibitors that have been studied in clinical trials, such as foretinib [68]. While initial results are promising, further studies are needed for these agents to be implemented in the clinical setting.

BRCA Associated Protein 1 (BAP1) Tumor Predisposition Syndrome

Genetics, Pathogenesis, and Clinical Manifestations

Germline *BAP1* mutations were first identified in 2011 in families with high incidence of mesothelioma and uveal melanoma, suggesting a common predisposing syndrome [69]. Exome sequencing of sporadic clear cell RCC led to the identification of *BAP1* mutations, which are found in about 15% of cases [70]. This finding prompted investigation into germline *BAP1* mutation occurrence in individuals with familial clear cell RCC, particularly those that had otherwise negative germline mutations (including *VHL*) [71]. Out of 83 such patients, only 1 had a pathogenic *BAP1* alteration. This individual was part of a three-generation family with five members affected by kidney cancer. The index patient had early onset, multifocal ccRCC associated with fast growth and high grade. While germline *BAP1* mutations are rare in families with predominantly RCC (1.2%) [71, 72], they are more common in families with other BAP1 predisposing cancers such as melanoma and mesothelioma (5.7–10%) [73, 74]. Given its recent discovery; rare incidence; and diversity of associated tumors, additional work is needed to fully characterize the clinical spectrum of this entity; other putatively associated tumors include breast; thyroid; neuroendocrine; non-small cell lung; and bladder [75].

BAP1 is a deubiquitinating enzyme on chromosome 3p (similar region as VHL) and is implicated in several cellular processes, such as DNA damage repair and cell cycle regulation [71, 74, 76, 77]. It is a tumor suppressor gene, with mutations in both alleles required to express a phenotype [74]. BAP1 was initially thought to be exclusively localized to the nucleus, mediating activity of proteins such as HCF-1 involved with transcription regulation and chromatin modification of genes responsible for cell growth and proliferation [70]. Recently, however, the role of BAP1 has been expanded to the cytoplasm, where it was found to mediate calcium (Ca^{2+}) efflux into the cytosol, promoting apoptosis. Loss of BAP1 would thus prevent Ca^{2+} release into the cytoplasm, allowing a cell to survive in spite of DNA damage, leading to unchecked growth/proliferation of mutated cells that is the hallmark of malignancy [78].

Clinical and Surgical Management of BAP1 Germline Renal Tumors

With less than 200 families worldwide identified with germline *BAP1* mutations at present and the low incidence of RCC in this syndrome [73, 74], there is a limited patient pool with which to draw experiences concerning management of localized BAP1 tumors. In this regard, we turn towards the experience with somatic BAP1 clear cell RCC tumors. Studies have demonstrated that BAP1 loss in tumors is associated with worse cancer-specific and overall survival compared to BAP1 wild type tumors [79–81]. BAP1-deficient tumors tend to have higher grade (i.e., ISUP Grade 3 or higher), be of larger size, and thus are more prone to metastatic disease. The mean growth rate for ccRCC in six tumors with BAP1 deficient tumor predisposition syndrome was 0.6 cm/year [65], which is above the 0.5 cm/year threshold commonly utilized for active surveillance [82]. Therefore, at present, while frequency of screening (preferably with MRI) for BAP1 patients is done similarly to other syndromes (i.e., every 1–2 years starting at age 30) [67, 83], if a solid renal tumor >1 cm is identified, it is our current practice to recommend nephron-sparing surgery upfront (either open or robotic, depending on the experience of the practitioner) as opposed to active surveillance due to the comparatively aggressive nature of these tumors. Additionally, rather than enucleation, tumors are excised with a grossly visible margin (i.e., 5 mm) of normal parenchyma [65].

Birt-Hogg-Dubé (BHD) Syndrome

Genetics, Pathogenesis, and Clinical Manifestations

Birt-Hogg-Dubé syndrome (BHD) was first described in 1977 by a group of Canadian dermatologists after observing a familial predisposition towards fibrofolliculomas, which are flesh colored papules emanating from hair follicles in the face; neck; chest; and upper back [84]. The trait appeared to be dominantly inherited, although the causative gene was unknown. Subsequently, pulmonary cysts, at times with spontaneous pneumothorax, was noted to occur frequently in BHD patients [85]. In 1993, an additional association of kidney tumors with BHD syndrome was posited after a patient with bilateral chromophobe renal cell carcinoma was noted to have trademark fibrofolliculomas [86]. This association became more robust after identification of three families with 13 individuals having renal malignancies and BHD cutaneous manifestations [87]. A decade later, scientists identified the *BHD* gene, known as folliculin (*FLCN)*, located on chromosome 17p11.2 that was responsible for the dermatologic, pulmonary, and renal manifestations of this syndrome [88, 89]. Currently, more than 200 families have been identified to have this germline mutation [90].

Despite the identification of *FLCN* as a tumor suppressor gene, its exact role in BHD pathogenesis is unknown, with *FLCN* mutations rarely seen in sporadic renal cancer [88, 91, 92]. One posited role is modulation of the mTOR1 pathway involved

in cell growth, with evidence coming from in vitro studies showing reduction in the size of FLCN-deficient renal lesions after treatment with mTOR inhibitors such as sirolimus [93]. Nevertheless, while there are some cases of successful response with mTOR inhibitors in BHD patients with metastatic tumors, these agents have not been successful in treating fibrofolliculomas [94–96].

Renal tumors occur in approximately 12–34% of BHD patients, with median age of onset at 50 years [97–99]. Though the penetrance of renal cancer in BHD syndrome is relatively low, patients still have a sevenfold increased risk of kidney tumors relative to the general population [90]. In contrast to VHL and HPRC, the bilateral and/or multifocal renal tumors in BHD can span a range of histologies. In an analysis of 130 renal tumors from 30 patients, hybrid oncocytic (combination of chromophobe and oncocytic features) was the most common tumor subtype (50%). Chromophobe renal cell tumors were also often seen (34%), with other subtypes being less common, albeit present: clear cell (9%), oncocytoma (5%), and papillary (2%) [100].

The most common BHD tumors, chromophobe and hybrid oncocytic chromophobe tumors (HOCT), are more indolent than other subtypes [101]. Nevertheless, in a series of 33 French BHD patients with renal tumors, 1 patient with HOCT and 2 patients with chromophobe RCC managed surgically did develop metastatic disease. However, all remained alive after 5 years with no disease progression, indicating that, in the rare case of metastatic development, these tumors still appear to have a more favorable course than clear cell [96].

Clinical and Surgical Management of Renal Tumors In BHD

Among carriers of the *FLCN* germline mutation, cross-sectional imaging surveillance for renal cancer (contrast MRI preferred) can be offered starting at age 20, to be performed every 3 years [102–106]. Once a solid renal tumor is identified, specific imaging interval is dependent on tumor size and/or growth rate. Given the diversity of histological subtypes in BHD patients, additional diagnostic imaging, such as technetium 99m sestamibii scan, to delineate whether a mass is clear cell vs. oncocytic in nature may be considered [107]. As most BHD tumors are indolent and slow growing (median growth rate of 0.1 cm/year) with low likelihood of metastasis, active surveillance is employed until the dominant lesion reaches 3 cm, at which time nephron-sparing surgery (NSS) via enucleation can be performed. No known metastasis has developed in BHD patients when following this surgical principle [65, 108].

Tuberous Sclerosis (TSC)

Genetics, Pathogenesis, and Clinical Manifestations

Tuberous sclerosis (TSC) is a clinical syndrome first described in the late nineteenth century, with an estimated incidence of 1/6000 to 1/10,000 persons worldwide [109, 110]. It was not until the 1990s that the genes responsible were identified. TSC

results from germline loss of function of either *TSC1* on chromosome 9 (hamartin) or *TSC2* on chromosome 16p13 (tuberin), both of which are tumor suppressors [111, 112]. Unlike other hereditary syndromes, 60% of germline *TSC* mutations occur as a de-novo phenomenon as opposed to an autosomal dominant inheritance [113]. TSC affects multiple organs, such as skin (angiofibromas); brain (subependymal giant cell astrocytoma and cerebral cortical tubers); heart (rhabdomyoma); kidney (angiomyolipoma, cysts, and renal cell carcinoma); and lung (lymphangioleiomyomatosis or LAM). Other clinical findings including epilepsy, behavioral disorder, and intellectual disabilities [114, 115].

There is high penetrance of renal manifestations in TSC, accounting for 80–85% of patients, with development beginning in childhood [116]. Angiomyolipomas (AML) are the most common renal lesion, occurring in 80% of TSC patients [117]. Macroscopic renal cysts are seen in 50% of individuals and increase in number throughout a person's lifetime [115]. A small subset of TSC patients have germline deletion of both *TSC2* and the adjacent *PKD1* on chromosome 16p13, resulting in early onset polycystic kidney disease and high risk of renal insufficiency [118]. About 2–4% of TSC patients develop renal cell carcinoma. Median age of onset is 30–40 years, although tumors have been seen in individuals as young as 7 years of age [119–121]. Additionally, there is a female predilection for tumorigenesis (70%). As with BHD, a variety of different tumor histologies are noted. Although the most common associated RCC in TSC was initially thought to be clear cell RCC, advancements in histological and immunochemical staining have led to the identification of three distinct RCC subtypes from traditional clear cell; papillary; or oncocytic tumors, listed in order of frequency: TSC associated RCC with fibromyomatous stroma (also known as TSC associated papillary RCC or RCC with leiomyomatous features); TSC associated oncocytic tumor (referred to as hybrid oncocytic/chromophobe tumors by some pathologists); and eosinophilic solid and cystic tumor.

The TSC complex regulates mammalian target of rapamycin complex 1 (mTORC1), which is responsible for protein and lipid synthesis; glycolysis and ATP production; lysosomal biogenesis; mitochondrial function and biogenesis; and autophagy. When this complex is non-functional, mTORC1 is hyperactive, leading to unchecked growth and tumorigenesis [122, 123]. As with VHL, understanding of the mTOR pathway in TSC pathogenesis has led to treatments for its common manifestations, such as AMLs or pulmonary LAM [124].

Renal disease is one of the leading causes of death in patients with TSC, mostly from renal insufficiency, either caused by or as a result of treatment of associated kidney lesions [125, 126]. The majority of patients develop bilateral and/or multifocal AMLs throughout their lifetime. While AMLs are generally a benign lesion, they are prone to spontaneous hemorrhage with increased size and/or hormonal changes (i.e., during pregnancy). The presence of fat on cross-sectional imaging is diagnostic for AML, although up to 1/3 of AMLs are fat-poor, which can be difficult to distinguish from malignancy [115, 127]. Fat can sometimes also be obscured due to hemorrhage. Provided that the lesion does not contain any co-existing calcifications (which would suggest malignancy), in-phase vs. opposed phase chemical shift MR imaging can be a useful test to characterize lipid-poor lesions. Alternatively, a renal

biopsy may be indicated to exclude malignancy. There is a class of AMLs that have metastatic potential, known as epithelioid AMLs (eAMLs) [128]. Immunohistochemical staining can readily distinguish between eAML and RCC (HMB45 is positive in the former).

42–50% of TSC patients with renal malignancies present with multifocal RCCs; 25% of them have bilateral involvement [119, 120]. Despite the heterogeneity of histology, the majority of tumors are indolent. Amalgamating recent surgical series of TSC patients with RCCs, 4% (2/49) of patients presented with concurrent lymph node positive disease [119–121]. None of these patients developed metastasis subsequent to surgery with a mean follow-up time of 4 years. Only 1 patient with localized RCC developed metastasis in 10 years.

Clinical and Surgical Management of Renal Tumors in TSC

Management of renal manifestations in TSC patients is, first and foremost, through regular cross-sectional imaging (contrast-based MRI preferred due to absence of radiation). National guidelines recommend screening interval every 3–5 years beginning at age 12 [67, 129]. Once a solid lesion is noted, modifications to screening frequency can occur, based on lesion size and/or growth rate. In regard to suspected RCCs, as with other hereditary cancer syndromes, active surveillance is employed until the tumor reaches 3 cm, at which time nephron-sparing enucleation of all solid masses on the ipsilateral kidney suspected to be malignant is performed.

AMLs in TSC have a faster growth rate than in the sporadic population (1.25 cm/year vs. 0.19 cm/year, respectively, with mean follow-up of more than 3 years) [130]. 4 cm has been traditionally accepted as the threshold for AML active surveillance, due to increased risk of interval growth; symptoms such as pain; spontaneous hemorrhage; and need for intervention of tumors beyond this size [131, 132]. A recent series, however, suggests that up to 2/3rd of patients with asymptomatic AMLs above 4 cm can be safely observed [133]. Intralesional aneurysm size >5 mm has also been associated with increased likelihood of rupture of AML, with this radiologic feature potentially being a stronger predictor of spontaneous hemorrhage than even tumor size [134]. As AML has hormonally mediated receptors, the pregnant state may predispose AML to increased growth and/or spontaneous hemorrhage, resulting in the recommendation for upfront treatment of AML in female patients of child-bearing age [135]. Treatment, when indicated, for AML consists of nephron-sparing surgery [136, 137] or selective angioembolization, the latter of which is increasingly utilized, particularly in cases of acute hemorrhage [127]. An alternative treatment for TSC patients with AMLs 3 cm or larger can be an mTOR inhibitor such as everolimus, which has been shown to generate a reduction in volume of AML by 50% in 42% of patients with 92% progression-free survival at 12 months. Additionally, the drug has an acceptable safety profile (most common reported side effect was stomatitis) [124]. This drug may be useful in a patient unfit for surgery. It appears to "reset the biological clock" with respect to AML progression, as lesion regrowth is noted after cessation of treatment [138]. Everolimus

demonstrated efficacy in the sporadic AML population, with a 55.6% response rate at 4 months (mean volume reduction of 58%); however, there was a high rate of treatment discontinuation (60%) [139].

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)

Genetics, Pathogenesis, and Clinical Manifestations

In 1973, Reed and others described two families with multiple members having cutaneous and uterine leiomyomas inherited in an autosomal dominant pattern; this familial disease entity was aptly named "Reed's syndrome" [140]. It was not until 2001 that renal tumors were also formally associated with this syndrome, that has since become known as hereditary leiomyomatosis and renal cell carcinoma (HLRCC) [141]. The underlying genetic link behind these clinical manifestations is a germline alteration in fumarate hydratase (*FH*), a tumor suppressor located on chromosome 1q42.3-q43 locus [142]. FH is a component of the Krebs /tricarboxylic acid (TCA) cycle catalyzing the conversion of fumarate to malate [143]. As with other tumor suppressor genes in hereditary renal cancers, HLRCC follows Knudson's "two-hit hypothesis" with the first hit being the initial germline mutation of one allele and the second being loss of heterozygosity later in life [144]. This process is distinct from the autosomal recessive condition known as fumarase deficiency where the patient is born with bi-allelic germline mutations of *FH* causing microencephaly and neurologic findings [145]. With the loss of FH in HLRCC, the oncometabolite fumarate builds up within the cell, effectively limiting oxidative phosphorylation and making the cell reliant on aerobic glycolysis, a condition known as the Warburg effect [146]. Fumarate buildup also promotes protein succination, which is a post-translational modification of cysteine residues. Succination of mitochondrial DNA polymerase results in attenuated mitochondrial DNA content, with resulting mitochondrial dysfunction and limitation of oxidative phosphorylation. Another target of succination by increased fumarate is KEAP1, a ubiquitin E3 ligase, resulting in activation of the NRF2 antioxidant system. Upregulation of this pathway is thought to allow survival of FH-deficient tumor cells despite the increased oxidative stress from impairment of mitochondrial function [147, 148].

Clinically, HLRCC is characterized by variable penetrance of renal cell carcinoma, uterine fibroids, and cutaneous leiomyoma. Skin manifestations are the most common findings in patients with known HLRCC, followed by uterine fibroids. Renal cell carcinoma has the lowest penetrance amongst the triad of findings in those with HLRCC, with incidence reported to be between 15 and 35% [143, 149–151]. As with most other hereditary renal cancers, RCC occurs at an earlier age in HLRCC as compared to the general population. One study showed that the average age of renal cancer presentation in HLRCC patients was 41, with up to 7% of cases presenting before the age of 20 [152, 153].

Pathologically, HLRCC related RCC was originally thought to resemble papillary type II RCC. However, the 2016 World Health Organization's classification of

RCC described HLRCC-associated RCC as its own unique RCC subtype [154]. Tumors are typically high grade with aggressive features, may present as small (<3 cm) to larger (>20 cm) masses, may present as unifocal or multifocal, and can be unilateral or bilateral with evidence of metastatic disease at the time of presentation. Architecturally, HLRCC can present with various forms with papillary being the most common, but tubular-papillary; tubular; and solid presentations have been described. In addition, HLRCC renal lesions can present as large cystic RCC (up to 50% of masses in one study), with the cells lining each cyst having malignant potential [155]. Given the heterogeneity of histological findings, loss of FH signal and/or the detection of elevated succination with S-(2-succinyl) cysteine immunohistochemistry can aid in the final diagnosis of HLRCC related RCC.

Clinical and Surgical Management of HLRCC

For those with confirmed *FH* germline mutations, RCC screening should consist of yearly abdominal imaging using 1–3 mm slices, starting at 8–10 years of age, given that renal cancer has occurred in an HLRCC patient at 10 years [152]. MRI is the preferred cross-sectional imaging modality, as it does not utilize ionizing radiation and has unique sequences, such as diffusion weighted imaging (DWI), that may improve our ability to detect small (i.e., ≤2 cm) lesions suspicious for malignancy [156, 157]. Once renal masses are identified, immediate surgery is warranted given the high rate of metastasis independent of tumor size. The use of active surveillance with the "3-cm rule" as utilized in conditions such as VHL does not apply [158]. The threshold for radical nephrectomy is lower than for other hereditary syndromes and becomes more likely with larger or deeper tumors. If partial nephrectomy is feasible, wide margins (i.e., 1 cm) should be taken with consideration of intraoperative frozen sections to ensure negative margins. In addition, cystic masses should be handled with care as cyst rupture can lead to tumor seeding within the abdomen; thus, an open approach is usually undertaken in these situations. Additionally, due to the increased propensity of these tumors for locoregional spread, retroperitoneal lymphadenectomy should be considered during partial or radical nephrectomy for large and/or complex lesions, even if lymphadenopathy is not appreciated on preoperative imaging. We generally perform a modified template node dissection on patients (i.e., paracaval/para-aortic depending on laterality from level of renal hilum to aortic bifurcation); any additional areas for node dissection are made based on intraoperative findings. For patients with clinical node positive disease, a full bilateral template resection is performed.

Treatment options for metastatic RCC in the setting of HLRCC are rapidly evolving. Given the high rate of glycolysis with *FH* mutation, FDG-PET has been shown to be effective in localizing metastatic lesions [155, 159]. National Comprehensive Cancer Network (NCCN) kidney cancer guidelines include the option of systemic treatment of metastatic HLRCC with the combination of the VEGF inhibitor bevacizumab and the EGFR inhibitor erlotinib [67]. This is based on the notion that, with decreased oxidative phosphorylation, there is increased

stabilization of HIF1α and HIF2α with the activation of their downstream targets [143]. The clinical efficacy of bevacizumab and erlotinib is based on a phase 2 trial (NCT01130519) at the National Cancer Institute that showed an overall response rate of ~72% for HLRCC patients with metastatic disease compared to only 35% for sporadic metastatic type 2 papillary RCC. The median PFS was 21.1 versus only 8.8 months for HLRCC and sporadic type 2 papillary RCC, respectively [160]. As with belzutifan in VHL, an effective treatment for HLRCC was thus developed through an understanding of the biological pathways affected by the specific genetic alteration.

Succinate Dehydrogenase Deficient Renal Cell Carcinoma (SDH-RCC)

Genetics, Pathogenesis, and Clinical Manifestations

SDH-RCC was first described by Vanharanta and others in 2004 with the description of families with germline mutations in *SDHB*, and SDH-RCC was added to the World Health Organization's RCC classification in 2016 [154, 161]. As with HLRCC, SDH tumor pathogenesis is linked to an abnormality within the Krebs/tricarboxylic acid (TCA) cycle, namely a loss of function of the SDH complex [162, 163]. The SDH complex functions in both the TCA cycle, converting succinate to fumarate, as well as in the electron transport chain (complex II), shuttling reducing equivalents/electrons from $FADH_2$ along the electron transport chain to generate adenosine triphosphate (ATP). SDH is composed of four subunits: SDHA, SDHB, SDHC, and SDHD; loss of any subunit via genetic alteration can lead to SDH-RCC, with SDHB loss being the most common. Additionally, SDHAF1 and SDHAF2 function to aid in the assembly of the protein complex and may play a role in tumorigenesis, as mutations in SDHAF2 have been described [163, 164]. The SDH complex is thought to be a tumor suppressor, with decreased sporadic expression being correlated to worse prognosis in VHL-deficient clear cell RCC tumors [165, 166].

Loss of SDH leads to the buildup of the oncometabolite succinate in the mitochondrial matrix, with resulting metabolic changes including reliance on aerobic glycolysis (Warburg effect), fatty acid synthesis, and augmented glucose uptake [167]. Additional work has shown that succinate accumulation results in the inhibition of prolyl-hydroxylase, preventing VHL-mediated degradation of HIF [168]. Augmented HIF stabilization then leads to increased GLUT1 and VEGF activity for glycolysis and angiogenesis, respectively. In addition, succinate accumulation can impair DNA repair mechanisms further promoting tumorigenesis in those with *SDH* mutations [164].

Clinically, the loss of SDH activity can lead to RCC; paragangliomas, most commonly in the head and neck; pheochromocytomas; and gastrointestinal stromal tumors (GIST) [169]. Some studies suggest that defects in SDH complex expression can also lead to pituitary adenomas, seminomas, renal adenomas, papillary thyroid carcinoma, and, like VHL, pancreatic neuroendocrine tumors [9]. The

incidence of each phenotypic finding has varying penetrance without a known clear linkage between clinical features and specific mutations of either *SHDA, SDHB, SDHC* or *SDHD*. SDH-RCC tends to be aggressive with high risk for metastasis even at small tumor sizes and presents at a younger age (as young as 15 years old in one series) with a median age of 30–35.5 years being reported [6, 163]. The incidence of SDH-RCC in those with germline *SDH* mutations has varying penetrance. The lifetime risk of RCC is not well characterized and is estimated to be ~14% for those with *SDHB* mutations [170]. Tumors are usually solitary but can be bilateral and/or multifocal in ~8–30% of patients [9, 164, 171]. Pathologically, SDH-RCC appears as tumors with eosinophilic cells, intracytoplasmic inclusion bodies, and with solid, nested, or tubular architecture [144]. Given the nonspecific histological patterns, loss of SDH seen on immunostaining is often needed for a definitive diagnosis [172].

Clinical and Surgical Management of SDH-RCC

No clear guidelines are available for the clinical management of those with *SDH* germline mutations. Patients with known germline *SDH* mutations should undergo surveillance for renal tumors every 2–4 years with dedicated abdominal imaging, ideally with MRI [6, 67, 144, 173]. Management for SDH deficient RCC is similar to that for HLRCC. Namely, given the aggressive nature of SDH-RCC, once a renal mass is identified, immediate resection is warranted as opposed to active surveillance. Partial or radical nephrectomy (for large masses) with wide surgical margins (i.e., 1 cm) is recommended. Additionally, for large and/or complex tumors, retroperitoneal lymph node dissection should be considered with similar modified template as for HLRCC tumors.

Other Hereditary Kidney Cancer Syndromes

Cowden Syndrome (CS), first described in a family in 1963 from whom the syndrome name is derived [10], has a large number of clinical manifestations, including but not limited to, mucocutaneous lesions (e.g., papilloma of the lip or oral pharynx); gastrointestinal hamartomas; and predisposition to cancers of the thyroid, breast, uterus, and kidney [174]. The gene responsible for this syndrome is *PTEN* (phosphatase and tensin homolog) on chromosome 10q23, a tumor suppressor, with germline alterations inherited in an autosomal dominant fashion [175]. However, as with tuberous sclerosis, there is a high rate of de-novo germline *PTEN* mutations (10.7–47.6%) [176]. 4–34% patients with CS develop renal cancer [177–179]. Similar to BHD and tuberous sclerosis, CS is associated with a heterogeneous pattern of tumor histology, such as papillary type I and II; clear cell; and chromophobe, the majority of which are bilateral and/or multifocal. Due to the limited penetrance of renal manifestations in this already rare syndrome (affecting 1/200,000 individuals) [180], there are no established guidelines concerning management of localized

renal tumors in patients with CS. Nevertheless, as with other hereditary kidney cancer syndromes, patients with CS should receive abdominal imaging every 1–2 years (contrast-based MRI preferred due to lack of ionizing radiation) [173, 177], with nephron-sparing surgery recommended when a solid renal mass is identified radiographically.

Hereditary hyperparathyroidism-jaw tumor (HPT-JT) syndrome was first described in 1990 and is characterized by parathyroid adenomas and/or carcinomas; ossifying fibromas of the mandible and/or maxilla; uterine tumors; and a variety of renal lesions [181, 182]. The implicated gene was identified in 2002 as *CDC-73*, a tumor suppressor with inheritance of the mutant allele occurring in autosomal dominant fashion [183]. Less than 300 cases of HPT-JT in 100 families are reported in the literature [184]; thus, our understanding of the disease phenotype is still incomplete. Renal involvement has been described in 13.3% of HPT-JT patients and consists of polycystic disease, Wilm's tumors, adenocarcinomas, and mixed epithelial and stromal tumors (MEST) [184, 185]. As even MEST has been associated with an invasive phenotype [186], currently, nephron-sparing surgery is recommended for all HPT-JT patients with a solid renal mass.

Translocation RCCs, characterized by abnormal gene fusion of the MiT class of transcription factors, were first described in 1996 [187]. While the more common *TFE3* and *TFEB* translocations are somatic alterations, a germline variant in *MiTF* (micro-opthalamia transcription factor) was identified in 2011, with increased predisposition to both renal cancer and cutaneous melanoma [188, 189]. The average age of onset of kidney cancer in patients with this p.E318K variant is 52.5 years (33–79 years) [190, 191]. Renal tumors can have either clear cell or papillary features, with definite diagnosis aided by karyotype to detect the specific translocation or immunostaining to note the MiTF amplification. Given the relatively recent description of this hereditary kidney cancer syndrome, there is no consensus as to the management of renal tumors. Sporadic translocation RCCs, particularly in adults, have been associated with a more aggressive infiltrative behavior compared to other types of sporadic RCC (i.e., higher grade and more prone to lymph node invasion) [192]. Thus, if active surveillance of a renal mass is chosen for patients with the germline *MiTF* variant, the tumors should be closely followed.

Although the MiT class of translocation RCCs has only been recently characterized, a balanced translocation involving chromosome 3 in a family with multiple members having RCC was first described in 1979 [193]. At least 6 other inherited chromosome 3 translocations have been described, with considerable variation in the location of breakpoints at chromosome 3. Patients that are germline carriers of chromosome 3 translocations have a similar phenotype to VHL, namely early onset and/or bilateral/multifocal clear cell kidney cancer [194]. Interestingly, patients with no family history of RCC whose renal tumors have a chromosome 3 translocation do not appear to have an increased predisposition to forming kidney cancer beyond the general population [195]. Management of patients with chromosome 3 translocation detected on karyotype analysis is similar to that of VHL.

Concluding Thoughts

Knowledge of the genetic basis of hereditary kidney cancer syndromes has been instrumental in both the diagnosis and management of these diverse group of renal tumors. Although personalized medicine for localized kidney cancer is still in its infancy, the so-called precision surgery has been practiced since the 1990s. Determining when and how to operate based on the underlying germline alteration allows for the optimal balance of oncologic control based on underlying tumor biology with nephron preservation, recognizing that these patients are at risk for multiple tumors throughout their lifetime. While the surgical management of syndromes such as VHL and HLRCC are well-defined, other more recently characterized entities such as BAP1 and MiTF have limited patients with which to develop surgical guidelines at present. It is hoped that, with increased clinician awareness and availability of genetic testing, patients and their families can be appropriately selected for screening in order to better determine the incidence and natural history of these less well-known hereditary syndromes.

As illustrated by the FDA approval of the HIF-2α inhibitor belzutifan for localized VHL tumors; bevacizumab/erlotinib for metastatic HLRCC; and everolimus for AMLs in TSC patients, understanding the genetic basis for kidney cancer has also been instrumental for drug design. As many of these disease pathways and genetic mutations are seen in sporadic renal tumors (particularly with VHL), it is hoped that we can both apply findings from the hereditary population to the sporadic population and continue to create clinical trials for targeted drugs for both localized and advanced hereditary and/or sporadic renal tumors in order to move towards fully realizing precision medicine for kidney cancer, as opposed to just precision surgery.

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Part II

Locally Advanced Disease

7 Management of Renal Cell Carcinoma with IVC Thrombus, Nodal Involvement, and T4 Disease

Laura Bukavina, Avery Braun, Michelle Higgens, Megan Prunty, and Sarah P. Psutka

Introduction

Background

Renal cell carcinoma (RCC) is one of the ten most common malignancies worldwide, with over 400,000 new global cases diagnosed annually and 74,000 new cases in the USA [1]. RCC comprises several different histologic subtypes, each varying in clinical presentation, features, and prognosis. The most common is clear cell type, comprising of 75% of new cases; the remaining dominant subtypes include papillary, chromophore, medullary, and collecting duct, comprising of 10%, 5%, 1%, and 1% of remaining cases, respectively [2].

The historic presentation of the "classic triad" of signs and symptoms—hematuria, flank pain, palpable masses—is identified in less than 10%, with most cases in

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the developed world found incidentally on magnetic resonance imaging (MRI), computed tomography (CT) scan, or ultrasound in asymptomatic patients [3]. As such, it is postulated that contemporary ubiquitous use of abdominal imaging contributes to recently observed increasing incidence rates of RCC worldwide with the highest rates in North America, Northern and Eastern Europe [3]. Other hypothesized explanations for the high incidence in developed nations include prevalence of modifiable risk factors for RCC such as smoking, obesity, physical inactivity, and hypertension [3].

RCC is twice as common among men as women. Additionally, female sex is associated with a higher likelihood of presenting with localized disease and improved cancer-specific survival [4]. By gender, RCC accounts for 5% in men and 3% women of all oncological diagnoses in the USA [1, 2]. RCC commonly presents in older individuals (median age at diagnosis: 64 years) with approximately 53% of patients diagnosed between the ages of 55 and 74, while less than 10% are diagnosed before the age of 45 years [4]. Patients with RCC commonly present with a high burden of comorbidities. On average, a newly diagnosed RCC patient has eight chronic comorbid conditions compared to only four in age-matched controls [5]. Within the United States, SEER data demonstrates a higher incidence rate of RCC amongst Black patients compared to other minority ethnicities [1, 4]. RCC tumor subtypes vary across racial groups with clear cell histology more commonly identified in Caucasians while medullary and papillary RCC are seen more often in Black patients [2, 3].

Incidence

With the increasing ubiquity of abdominal imaging, the incidence of incidental RCC detection in the USA has increased at 2.4%/year from 1992 to 2008 (incidence rate of 14.1/100,000) with a plateau from 2008 to present (incidence rate of 16.0/100,000) [6]. Clinically localized RCC accounts for 65% of cases, while 16% of patients present with regional spread and 16% have distant metastatic disease [6]. A large series of nearly 3000 patients found that 14% of patients undergoing cross-sectional imaging harbor an incidental renal mass larger than 1 cm in size while another review reported 15% of patients undergoing surgical management of renal masses were “incidentalomas” [3, 5].

Indeed, most renal masses are clinically localized, measuring less than 4 cm in size at time of diagnosis, accounting for 48–66% of new RCC cases [1]. Thompson et al. reported 25% increased odds of metastasis for every centimeter increase in tumor diameter [7]. Thus, in patients with tumor diameter <3 cm, the risk of metastasis is remote with several active surveillance cohorts reporting 0–1.1% metastatic events [7]. While we have noted an increased incidence of small renal masses, rates of locally advanced, node positive, and metastatic RCC at presentation have been stable with approximately 25% of contemporary patients present with nodal or distant metastasis (N1 or M1) while an additional 20–30% of patients presenting with organ-confined disease will ultimately develop systemic recurrence [5].

Mortality

Despite improvements in diagnosis and management over the last two decades, RCC remains one of the most lethal urological malignancies. The 5-year relative survival rates for patients with RCC in the USA improved from less than 50% in 1977 to over 75% (from 2009–2015) [8]. Similarly, incidence-based mortality rates peaked in the early 2000s and declined dramatically over the last decade with rates equilibrating around 30% [8]. It is estimated that 175,000 patients worldwide and 14,830 in the USA will die from RCC annually, accounting for 1.8% and 2.4% of all cancer deaths, respectively [4]. Increased access to care, lead-time bias from earlier diagnosis to treatment of small renal masses, and advancement in availability of local and systemic therapeutics may account for this decreased mortality-to-incidence ratio. However, survival rates vary and are contingent on cancer stage, with 5-year relative survival in patients with localized (cT1-2), regional (cN+), and distant (cM+) RCC being 93%, 70%, and 12%, respectively [8]. Beyond clinical stage, a patient's age, performance status (Karnofsky performance score <80), nodal involvement, fat invasion, tumor necrosis, and tumor size (>7 cm) have all been associated with increased risks of mortality [7].

Clinical Staging of Locally Advanced and Node Positive RCC

Accurate clinical staging of RCC is critical to selecting appropriate treatment approach and optimizing prognostication in a uniform and standardized manner. The tumor-node-metastasis (TNM) staging system developed by the American Joint Committee on Cancer (AJCC) remains the predominant means to risk-stratify RCC patients. Since inception in 1974, it has undergone major revisions with the primary goal to best approximate outcomes on a stage-for-stage basis [9, 10].

Based on the TNM system, locally advanced RCC (cT3-T4N0M0) is defined as having any of the following characteristics: extension into major veins, invasion the adrenal gland, extension into the peri-renal or peri-pelvic fat, or invasion beyond the Gerota's fascia. Updated TMN editions revised the definition of factors constituting locally advanced disease, specifically adjusting the definition of clinical stage 3 disease which is observed in 5–10% of patients [11]. One major change included reclassification of direct ipsilateral adrenal gland invasion to T4 from T3a to better reflect the worse prognosis associated with this pathologic feature. Direct adrenal gland invasion is rare, occurring in approximately 2.5% of cases and has been found to have worse cancer-specific survival than other high-risk features. Tumors involving the renal vein but without extension into the IVC were downgraded from stage T3b to T3a [10].

Table 7.1 describes the commonly utilized Mayo Clinic classification system for venous tumor thrombus according to the associated anatomic landmarks [12].

Table 7.1 Tumor thrombus level and definition

Level	Anatomic landmark
0	Thrombus limited to renal vein, detected clinically or during pathologic evaluation
I	Thrombus extending into IVC, <2 cm above renal vein
II	Thrombus extending into IVC, >2 cm above renal vein but below hepatic veins
III	Thrombus at/above the level of hepatic veins but below the diaphragm
IV	Thrombus extending above the diaphragm

Nodal Involvement

Clinically node positive disease in RCC is denoted cN1 vs. cN0, which represents a radiographic classification while pathologically node positive disease is denoted pN1 vs. pN0/pNx (a histologic classification). Of note, previously, in the 2002 TNM system stratified node positive disease by both the size and number of lymph nodes involved, but this was subsequently converted to a binary system as there is no historic consensus regarding oncologic outcome differences associated with involvement of one or more than one lymph node by RCC [11].

The most recent iteration of AJCC staging system for RCC patients published in 2018 categorizes node positive (cT1-3N1M0) malignancies as stage III. While the incidence of lymph node involvement has reportedly decreased overtime, historic series documented pN1 disease in 23–35% of surgical patients undergoing RN and LND [3]. Current pN1 rates in localized, low risk populations (cTxN0N0) range from 1 to 5% [4] and increase to 5.2–13.2% in pT1-2 disease and 23.4–36.1% in pT3-4 [1].

Determining candidacy for lymphadenectomy (LND) at the time of nephrectomy currently relies heavily on preoperative imaging; however, CT and MRI only have a 77% and 73% sensitivity for identifying nodal metastases with limited reliability in detecting nodal micrometastases [13]. For example, when LND is performed for lymphadenopathy over 1 cm in maximal diameter, final nodal pathology demonstrates benign or inflammatory changes in 58% of cases [13]. Radadia et al. similarly observed that the sensitivity of conventional imaging for detecting nodal metastases was only 67% while the NPV was 94% [14]. As a result, clinical nomograms and predictive tools have been proposed in the perioperative, intraoperative, and postoperative settings in an effort to identify lymph node involvement and those patients who would benefit most from LND at time of surgical intervention. Multiple variables have been proposed to be predictive of risk of nodal involvement including maximal LN diameter and presence of radiographic fat invasion, ECOG status, cN stage, LDH, and local symptoms and tumor grade, size, stage, necrosis, and sarcomatoid differentiation [15–17] with generally modest accuracy and generalizability of the published models. This will be further addressed in the section entitled "The Role of Lymphadenectomy in the Management of RCC".

Surgical Approach to Locally Advanced RCC

Preoperative Evaluation

For patients with large and locally advanced renal tumors, a focused history and physical exam is the first step in the evaluation. In addition, basic laboratory evaluation should include, at minimum, a complete blood count, serum electrolytes, coagulation profile, serum calcium, liver enzymes, and urinalysis [18]. Laboratory evaluation should furthermore be tailored to individual history and presenting symptoms, such as bilateral leg swelling, concern for paraneoplastic syndromes, weight loss, neurological deficits, bone pain or respiratory distress. Patients presenting with cachexia, weight loss, and anorexia warrant additional nutritional work up including liver function testing, albumin, prealbumin, BMI and nutritional assessment and rehabilitation. Furthermore, patients with neurologic symptoms (lethargy, neurologic deficits, mental status change, and new onset headaches) in setting of advanced renal tumors, warrant additional CT head imaging to rule out leptomeningeal carcinomatosis.

Cross-sectional imaging is a crucial next step in characterizing RCC with IVC tumor thrombus by evaluating (1) tumor thrombus presence and invasion into IVC wall, (2) volume of tumor and bland thrombus, and (3) surgical planning for resection, and reconstruction [19]. Historically, venography (venogram) was used for detection and evaluation of IVC tumor thrombus, however, this modality is limited by its invasive nature and moderate risk of complications. (Fig. 7.1) [20]. However, venography can be useful in establishing collateral blood supply if IVC resection is anticipated intraoperatively due to bulky venous tumor thrombus (VTT) with chronic IVC occlusion.

The portal venous phase of CT imaging is utilized to evaluate the endoluminal VTT level as well as to differentiate VTT from bland thrombus, and to detect VTT continuity with adjacent organs [20, 21]. While both CT and MRI are both considered high quality diagnostic imaging, MR is generally the preferred imaging modality for the detection of VTT, characterization of the extent of wall invasion, and evaluation of level of VTT extension [22]. For the detection of VTT, the sensitivity of MR approaches 100% while the diagnostic accuracy of conventional CT and multidetector CT lags behind (MDCT are 65% and 93%), respectively [22]. When comparing the two imaging modalities, timing of the imaging is considered more important than the imaging modality itself due to the potential for rapid VTT growth. Therefore, obtaining cross-sectional imaging to evaluate the VTT level within 14 days of surgery is generally recommended [23]. Images should be reviewed by the surgeon in conjunction with a radiologist to anticipate intraoperative challenges and facilitate operative planning. Aberrant anatomy, and relationship of the tumor to adjacent structures should be assessed. The contralateral kidney, adrenal gland, and regional lymph nodes should also be carefully evaluated to assess the risk of local invasion (Fig. 7.1).

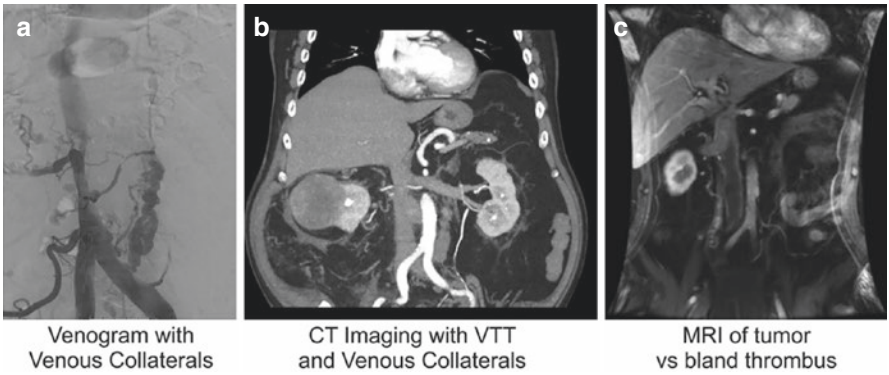

Fig. 7.1 (**a**) Venogram showing inferior vena cava filling defect with collaterals into the ascending lumbar vein and gonadal veins. (**b**) CT and (**c**) MRI imaging of the IVC thrombus. MRI imaging is used in conjunction to differentiate tumor from bland thrombus

Preoperative Management of Venous Thromboembolic Risk in Patients with RCC and Associated VTT

Patients with RCC and associated VTT represent a challenging group of patients, due to the nature of the disease and high risk for perioperative complications. Approximately 6% of patients with VTT are diagnosed with concurrent pulmonary embolism (PE), which carries a high mortality rate of up to 72% [21]. Furthermore, the presence of lower extremity thrombus alone increases risk of minor and major complications twofold [24].

Although there is no society-based consensus regarding anticoagulation, recent guidelines put forth by multidisciplinary group of experts recommended the use of anticoagulation (low molecular weight heparin) in all patients with VTT without contraindications such as active bleeding [21]. Similarly, others have proposed that symptomatic PE is an absolute indication for anticoagulation, while asymptomatic PE, bland IVC thrombus, complete or near complete IVC occlusion, and atrial tumor are considered relative indications [21]. Therapeutic anticoagulation is administered preoperatively, and is held 24 h prior to planned surgery. Placement of IVC filters is typically not recommended due to the risk of incorporation of tumor thrombus into the IVC filter (Fig. 7.2), which may complicate surgical thrombectomy and necessitate total IVC resection and reconstruction [25]. However, IVC filters may be placed at the discretion of the treating physician for continued PE despite anticoagulation or in patients with a contraindication to anticoagulation in setting of recurrent PE. If an IVC filter is required, it is recommended to place the filter <48 h before surgery to reduce the incidence of thrombus infiltration within the filter [21].

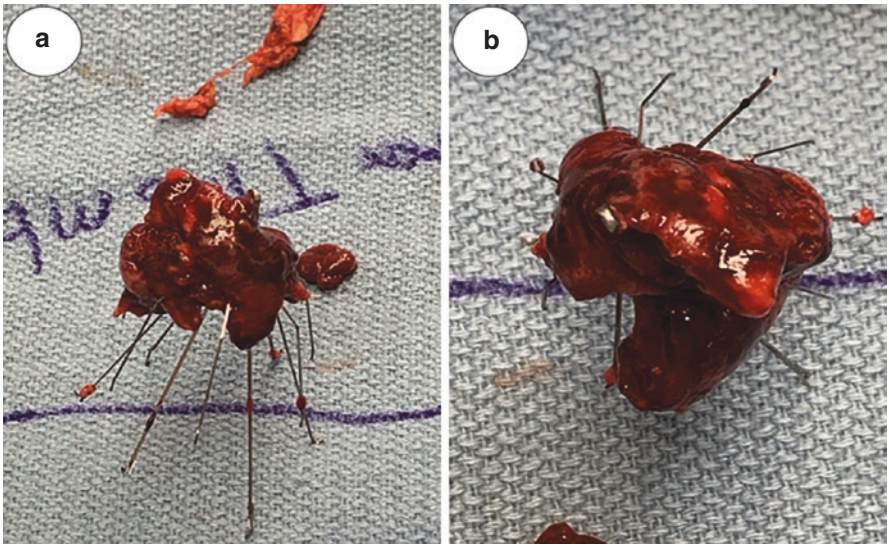

Fig. 7.2 Depiction of IVC filter placed preoperatively, with incorporation of tumor thrombus into the IVC filter (**a**, **b**) at the time of IVC thrombectomy, requiring IVC resection and reconstruction

Surgical Management of VTT

Surgical Preparation

For higher levels VTT (e.g., Level III, IV) cardiac anesthesia support is recommended, especially, for instances, with cardiopulmonary bypass or venovenous bypass is anticipated. Following induction of anesthesia and endotracheal intubation, adequate vascular access should be secured. Central access may be preferred in the setting of higher level VTT. Arterial lines are generally used for continuous blood pressure monitoring. Transesophageal echocardiography (TEE) is helpful to evaluate for involvement of the intra- and suprahepatic IVC, hepatic veins, and left atrium. It may also be utilized throughout the case to evaluate for embolization and cardiac function in real time [26]. After TEE is completed, orogastric tube or nasogastric tube placement may be considered and is especially helpful in the setting of a left-sided tumor. Given the high risk of intraoperative blood loss, the patient's blood type should be established and we recommend holding 2–4 units of packed red blood cells and fresh frozen plasma on standby.

Incisions

The surgical approach should be individualized according to the level of thrombus, surrounding organ involvement, regional lymphadenopathy, and variations in vascular anatomy. Regardless of the level of the VTT, surgical approach

requires excellent exposure and visualization of the IVC and retroperitoneum. While flank incisions are commonly utilized for open partial, simple, or radical nephrectomy, this incision is unlikely to provide adequate exposure of the IVC and therefore should be sparingly for patients with level 0 or 1 VTT where the thrombus is anticipated to be able to be easily milked back into the renal vein [18].

A midline incision provides excellent exposure to the entire abdomen including the lateral aspects of the tumor with adequate retraction. Similarly, a subcostal incision allows for versatility in exposure as well as the ability to extend the incision to the contralateral side or cephalad in setting of need for cardiopulmonary bypass (CPB) or liver mobilization. While there are no differences in postoperative pain, pulmonary complications, or incisional hernia risk at 1 year, chevron incisions have been found to be associated with an increased risk of rectus abdominus atrophy as compared to midline incisions [27, 28]. Large upper pole tumors can benefit from a thoracoabdominal incision, however, this approach is associated with a higher rate of complications including pneumothorax, phrenic nerve injury, increased postoperative pain, and need for chest tube placement [29] (Fig. 7.3). The Makuuchi incision is very helpful in large renal tumors with VTT, where IVC reconstruction and adjacent organ involvement in suspected. This incision is helpful for liver mobilization and IVC reconstruction, allowing for perfect surgical exposure while preserving the intercostal muscles, reducing muscle atrophy and postoperative pain [30]. The transverse portion of the incision can be extended to the contralateral side to improve visualization, analogous to a liver transplant incision. For patients with level 4 VTT necessitating sternotomy, the midline and Makuuchi incisions can be extended vertically to the sternal notch.

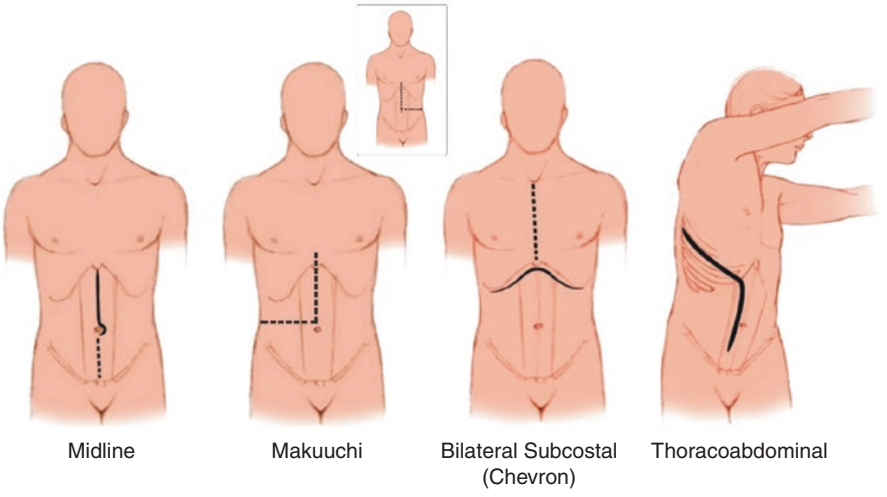

Fig. 7.3 Schematic representation of open surgical incisions utilized for radical nephrectomy with concomitant IVC thrombectomy. Source: Original

Approach to Level 0-I VTT

Following intraperitoneal access, the retroperitoneum is visualized via mobilization along the peritoneal reflection of the ascending/descending colon ipsilateral to the primary tumor. After mobilization of this avascular plane, the colon is reflected off of Gerota's fascia to expose the anterior surface of the kidney, the IVC, and the aorta. Any adhesions between the gall bladder and the omentum or visceral adhesions are lysed. Mesenteric lymphatics should be identified and ligated with either suture or surgical clips to reduce the risk of postoperative chyle leak.

For right-sided tumors, additional mobilization of duodenum medially (Kocher maneuver) is necessary to expose the IVC and right renal hilum. On the left, the splenorenal attachments are divided to expose the upper pole of the kidney and prevent a traction injury of splenic capsule during mobilization. Further mobilization of the tail of the pancreas along with splenic hilum off of Gerota's fascia is undertaken to expose the left renal vein. The mobilization of the spleen and the pancreas off Gerota's fascia is performed en bloc toward the midline, allowing for exposure of the entire upper retroperitoneal space from the diaphragm to the inferior border of the kidney. In certain circumstances, IVC exposure also can be obtained by mobilizing the root of the mesentery off the great vessels (Fig. 7.4) The bowel is

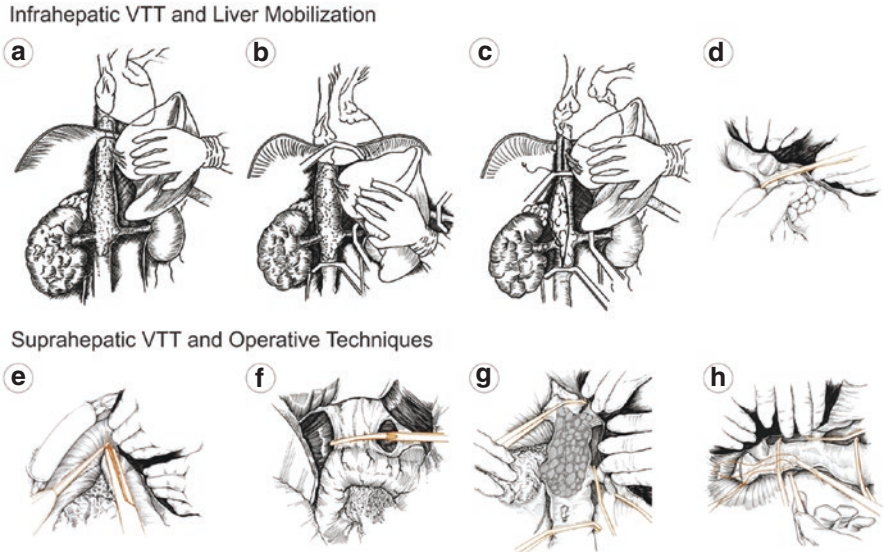

Fig. 7.4 (**a**–**c**) Depiction of liver mobilization with division of the ligamentum teres, the falciform ligament, then the right coronary ligament, and the left triangular ligament. (**d**) If the thrombus reaches a level above the major hepatic veins, surgeon can attempt to milk the thrombus downwards to the level below. (**e**) If control of suprahepatic portion of vena cava is necessary, the central tendon of the diaphragm can be opened to achieve proximal control. (**f**) The pringle maneuver allows of the vascular control of the liver, within the lesser omentum, to allow decompression of the liver in the setting of suprahepatic IVC clamping. (**g**) Once the hepatic hilum is secured, a new clamp above the hepatic veins is placed, and the inferior vena cava is incised to permit VTT extraction (**h**) Source: Reproduced with permission © Elsevier

then packed beneath a self-retaining (i.e., Thompson, Bookwalter, Omni) retractor. Early renal artery ligation should be performed next to reduce collateral circulation, decrease blood loss and potentially to facilitate VTT retraction. For large right-sided tumors, the renal artery may be more easily approached in the interaortocaval space. This minimizes kidney and IVC manipulation, theoretically reducing the risk of VTT embolization [16, 31]. For many of the level 0 VTT and some level I, "milking" of the thrombus gently into the renal vein can be attempted, with rein vein ligation or vascular clamp placement at the level of the renal vein ostium. The goal is removal of the VTT en bloc with the nephrectomy specimen without tumor spillage. If vascular clamps are used, venotomy is repaired with continuous 4-0 polypropylene suture in running fashion.

Approach to Level II–III VTT

Level II VTT necessitate control of the proximal and distal IVC control, as well as the contralateral renal vein exposure. Once the lumbar veins have been ligated and divided, the cranial extent of the VTT can be gently assessed either by manual palpation or intraoperative ultrasound. The short hepatic veins draining into the anterior surface of the IVC beneath the caudate lobe are ligated to permit exposure of the IVC superior to the thrombus. IVC control can be achieved either by Rummel tourniquets or vascular clamps. Rummel tourniquets are often favored due to the bulkiness of the vascular clamps in surgical field. In the absence of bland thrombus inferior to VTT, a trial of IVC clamping should be performed to confirm that the patient can tolerate a reduction in cardiac preload, thereby maintaining hemodynamically stability during the clamp maneuver. Following IVC clamp trial, venous flow is reestablished followed by sequential clamping of the infrarenal IVC, contralateral vein, then the suprarenal IVC.

In most cases of level II and III VTTs, where clamps are applied below the hepatic confluence and therefore, the Pringle maneuver (clamping of the portal venous triad/the hepatoduodenal ligament) is not required, bypass can be avoided due to the collateral venous return via the lumbar and portal system. For level III VTT, the thrombus may be able to be milked below the major hepatic veins [16], a technique that is facilitated by early renal arterial ligation. By retracting the VTT below the hepatic veins, hepatic drainage can be maintained, avoiding hypotension from decreased venous return, and minimizing liver congestion and postoperative hepatic dysfunction [32].

Depending on the cranial extent of the VTT, additional liver mobilization might be necessary. Liver mobilization begins with division of the ligamentum teres, the falciform ligament, then the right coronary ligament, and the left triangular ligament (Fig. 7.4a–c). The visceral peritoneum on the right of the hepatic hilum and the infrahepatic vena cava are incised in conjunction with right inferior coronary and hepato-renal ligaments, as the liver is rolled to the left [32]. We recommend involvement of a hepatobiliary or transplant surgeon to assist for this portion of the procedure, due to variety of additional liver transplant maneuvers which may be required to expose the retrohepatic IVC [33]. For a level III thrombus, vascular clamps are sequentially applied, starting with infrarenal IVC, the contralateral vein,

and hepatoduodenal ligament containing the portal vein and hepatic vein (Pringle Maneuver), and suprahepatic IVC. (Fig. 7.4d, e). It is important to clamp the hepatic hilum first when employing the Pringle maneuver, before applying the suprahepatic IVC clamp, as doing so allows the liver to decompress. It is often useful for some level III and level IV VTT to dissect the central tendon of the diaphragm until the supradiaphragmatic IVC is identified to assist with mobilization of suprahepatic IVC [32, 34, 35] (Fig. 7.4e).

Once vascular control is secured, an "L"-shaped cavotomy is performed longitudinally along the IVC starting along the anterior surface of the renal vein. The VTT and kidney are removed en bloc, and lumen of IVC is inspected for residual thrombus (bland or tumor), tumor invasion into the wall of the IVC, or small venule invasion. If vascular wall invasion is suspected or confirmed via frozen section, additional IVC resection might be necessary. As a general rule of thumb, narrowing of IVC lumen more than 30% necessitates reconstruction with biological, autologous, or synthetic graft [36]. Closure of the IVC is performed in similar fashion to level I after aspiration of air. This may be completed in Trendelenberg position, with the release of infrarenal clamp to allow for back bleeding prior to completion of cavorraphy [33]. A final renal vein margin can be excised prior to vascular repair to confirm negative vascular margins. In the event that vascular reconstruction with either patch graft or tube interposition graft is anticipated, preoperative collaboration with vascular surgery is recommended.

An additional maneuver that can be beneficial in the management of free-floating left-sided level II–III thrombi to limit hepatic ischemia and rapidly return venous drainage to the right kidney is to perform the cavotomy, reduce the thrombus into the cavotomy then replace a diagonal vascular clamp from beneath the right renal vein ostium to superior to the left renal vein ostium, then removing the suprahilar IVC clamp and Pringle's clamp. The cavotomy can then be repaired in a controlled fashion with limited blood loss while maintaining perfusion and drainage of both the right kidney and liver.

Approach to Level IV VTT

Level IV VTT resection may require sternotomy, cardiopulmonary bypass (CPB), and hypothermic circulatory arrest (HCA), which is performed in collaboration with experienced cardiothoracic surgical and cardiac anesthesia teams. As with level III VTT, some authors recommend dissection of central tendon of the diaphragm until the intrapericardial IVC is identified, where the IVC can be encircled at its confluence with the right atrium. The atrium at this point is gently pulled beneath the diaphragm, avoiding the need for sternotomy [35]. There is significant morbidity associated with higher level III and IV thrombi, including risk of myocardial infarction, brain ischemia, and shock liver, which can be minimized by circulatory bypass [19, 37]. Critics of CPB argue that it is associated with the release of inflammatory mediators, leading to coagulopathy, platelet dysfunction, and increased bleeding risk. As such, care must be taken to cauterize or ligate any bleeding vessels before CPB is initiated [38]. In addition, this maneuver is associated with risk of hepatic and renal dysfunction, with and increased risk of renal failure of

approximately 12%. Despite the associated risks of CPB and HCA, the operative mortality is significantly lower (8.3% vs. 37.5%, $p = 0.006$), than those resected using CPB alone [39].

Venovenous bypass (VVB) can be utilized for some level IV and most level III VTT, entailing the cannulation of the infrarenal IVC or femoral veins in addition to venous cannulation above the IVC (e.g., axillary, subclavian, superior vena cava, internal jugular veins) or the right atrium. VVB provides many of similar advantages of CPB in allowing for continuous venous return to the heart during clamping, without systemic heparinization [18].

Minimally Invasive Approaches in VTT Management

Advances in minimally invasive surgical (MIS) techniques have allowed surgeons to perform radical nephrectomy with venous tumor thrombectomy using laparoscopic and robotic-assisted laparoscopic techniques. Purported benefits of robotic-assisted MIS approaches include shorter postoperative stay, lower estimated blood loss, and lower transfusion rates. Single institution retrospective studies and case reports evaluating use of MIS in level I-III VTT, and hybrid approaches to the management of level IV VTT have been published, demonstrating the feasibility and safety of this approach when applied by an experienced robotic surgeon applying open surgical principles via robotic platform [40]. A recently published review of 24 robotic-assisted radical nephrectomies with venous tumor thrombectomy (92% Level I) reported non-transfusion-related complications in 26% of patients with a median LOS of 1 day [40]. Gill et al. reported their initial experience with level III venous tumor thrombectomy in 16 patients. Their study highlighted a total blood loss of 379 cc, median operative time of 4.9 h, and hospital stay of 4.5 days, and no conversions to an open approach [41]. Recent meta-analysis comparing robotic vs. open VTT perioperative outcomes reported a 39% reduction in blood transfusion rate and 22.2% reduction in complications [42]. The results, however, have to be interpreted with caution, as nearly 75% of the patients were level I and II VTT. Although these early results are encouraging, careful oncologic comparison with open surgical IVC thrombectomy is lacking and warranted to determine the proper place of robotic surgery in this arena. Additionally, the available series highlight the importance of a very experienced high volume robotic surgeon and surgical team, with the availability to rapidly convert to an open approach, if necessary, as well as prudent patient selection.

Surgical Team and Preoperative Management

Preoperative Care Coordination: (i.e., hepatobiliary, transplant, cardiothoracic, vascular surgical team and cardiac anesthesiology) consultations should be made, as appropriate for the anticipated VTT level. If the primary surgeon does not have expertise in IVC reconstruction, vascular surgery should be involved in planning and conduct of the operation in patients with higher level VTT [33]. Cardiac anesthesia should be consulted for the care of patients older than 50, as well as those with level III and IV VTT in anticipation of possible need for VVBP or CPB. Patients

with two or more risk factors for coronary artery disease as identified by American Heart Association, might require a cardiac catheterization in anticipation of CPB [43].

Hemodynamic Monitoring and Access: In all VTT patients, the anesthesiology team is of critical importance in the pre- and intraoperative planning. In addition to American Society of Anesthesiology (ASA) standard monitors, resection of tumors involving the IVC and right atrium mandates an arterial line at minimum. For intravenous access, large bore peripheral intravenous lines should be placed *above* the diaphragm due to potential IVC interruption during the case [44]. In the case of intrahepatic IVC VTT, invasive lines should mirror a liver transplantation set-up, generally including a pulmonary artery catheter, two large bore venous catheters, arterial line, and femoral line.

Massive Blood Transfusion and Coagulopathy: In conjunction with hemorrhage, acidosis, and dilution, CPB activates fibrinolysis and impairs platelet function further worsening intraoperative coagulopathy. As such, in addition to conventional coagulation assays such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen levels, it has been suggested that assays such as thromboelastographic (TEG) and rotational thromboeleastometry (ROTEM) might be considered, to inform blood component transfusion requirements [45]. Viscoelastic monitoring assays (VEM) are routinely used in cardiac surgery and liver transplantation with the benefits of rapid turnaround and providing a personalized hemostatic profile. The turnaround time for ROTEM and TEG have been shown to be significantly shorter, with a time saving of 30–60 min in detection coagulation abnormalities [46].

In cases with large volume blood loss (>5000 ml), a massive transfusion protocol (MTP) should be initiated intraoperatively. This requires clear and concise communication between the surgical and anesthesia teams and the blood bank to achieve appropriate resuscitation. Principles of MTP include speed of transfusion, which should occur at a rate greater than exsanguination, augmented by optimal vascular access and pressurized tubing. Blood and fluid warming is important as to not to exacerbate hypothermia (<35 °C), which is exceedingly dangerous in patients undergoing MTP [47]. Generally, MTPs entail a predefined ratio of RBCs, FFP/cryoprecipitate and platelets units (random donor platelets) in each pack (e.g., 1:1:1 or 2:1:1 ratio) for transfusion, with administration of 1 unit cryoprecipitate if level for fibrinogen <100 mg/dL [48].

As noted, transesophageal electrocardiography (TEE) can provide supplemental information during surgery, including defining the cranial extent of the VTT, as well as consistency, fragility, adherence, and mobility of the thrombus. Furthermore, should the need arise for CPB, TEE provides additional benefit in its ability to guide cannula placement, and assess systolic ventricular dysfunction. Furthermore, any invasive central line placement in patient with level IV thrombus, should be performed with TEE, due to the presence of VTT in atrium, and potential risk for inadvertent dislodgment with placement [49]. With its relative ease of use, TEE is a valuable adjunct in surgical management of VTT.

Surgical Management of Locally Advanced RCC

Metastatic or locally invasive RCC remains a significant surgical challenge. While resection of localized cancer can be curative for some solid tumors, the evidence for extensive consolidative surgery for renal cell carcinoma with local invasion or metastatic disease is conflicting [50, 51]. However, despite advances in the developments and approvals of newer targeted systemic agents, a body of observational evidence supports a survival benefit in patients with locally invasive RCC who undergo complete surgical resection of all visible disease [52]. As such, careful preoperative preparation is mandatory to determine the resectability of a tumor and to anticipate what additional adjunctive procedures may be necessary in the case of locally advanced RCC to render a patient without evidence of disease.

Management of RCC with Hepatic Involvement

In the contemporary care of patients with locally advanced RCC involving the liver, surgical resection of hepatic disease in the form of partial hepatectomy or wedge resection remains an underutilized therapeutic option [53]. Overall, across all locally advanced or metastatic RCC, liver involvement is estimated to occur in about 20% of cases. Although there is substantial technical difficulty and perioperative morbidity of surgical hepatectomy, improved survival has been observed following complete resection of hepatic lesions. In a multicenter study from the Netherlands, ablation or surgical resection of liver metastases was associated with overall survival at 1, 3, and 5 years of 79%, 47%, and 43%, respectively [54]. Similarly, Joyce et al. performed a matched cohort analysis comparing outcomes between patients undergoing nephrectomy with hepatic resection to those undergoing nonhepatic, adjacent locally advanced or metastatic disease, demonstrating no significant increase in the risk of cancer-specific mortality (HR 0.63, $p = 0.53$) or all-cause mortality (HR 0.67, $p = 0.13$) between the cohorts [53]. Although this difference did not reach statistical significance, the median survival was modestly longer at 1.5 years in patients who underwent hepatic resection compared to 0.9 years in those who did not [53]. Surgical hepatectomy confers an inherent high risk with in-hospital mortality of up to 5% and a prevalence of postoperative morbidity of up to 41% [55]. Therefore, careful patient selection is key and surgical expertise in the necessary maneuvers is critical. Optimal candidates for concurrent hepatic resection include those with low metastatic burden that is anticipated to be completely surgically resectable, excellent preoperative performance status, robust nutritional status, and limited burden of comorbidities.

Management of RCC with Adrenal Involvement

The ipsilateral adrenal need not to be removed with the kidney in the absence of gross tumor invasion/ipsilateral metastatic involvement. Contrary to previously accepted clinical dogma, Lane and colleagues presented evidence that there is no "penalty" for adrenal preservation, as patients in their series who underwent delayed adrenal metastases resection ($n = 11$) fared no worse than those who had the adrenal resected at the time of renal surgery [56, 57]. Routine resection of healthy adrenal

glands exposes the patient to generally minor but unnecessary intraoperative risks. Furthermore, adrenalectomy may give rise to challenging clinical circumstances where patients may be subject to life-long adrenal insufficiency—a condition that significantly impacts quality of life and possibly life-expectancy [58, 59].

However, certain tumor characteristics have traditionally been associated with an increased risk of adrenal involvement such as tumor size (>7 cm), tumor location (upper pole), venous thrombus status, and radiographic appearance [60]. In the presence of these risk factors, concurrent adrenalectomy at the time of nephrectomy should be considered to optimize the likelihood of an R0 resection, and adrenalectomy/partial adrenalectomy should be undertaken as necessary to excise all evidence of gross disease.

Preoperative cross-sectional imaging (e.g., CT and MRI) are highly accurate at detection of adrenal gland involvement, with sensitivity and negative predictive value approaching 100% [57, 60–63]. Of note, if the adrenal gland cannot be appropriately visualized on preoperative imaging, the gland should be presumed infiltrated by the renal mass and adrenalectomy should be undertaken at the time of surgery [63]. Lane et al. suggested that intraoperative assessment of adrenal adherence/invasion by the renal tumor is reliable and could be used to guide final decisions regarding adrenal resection in cases where preoperative imaging suspicious for adrenal involvement [56].

Overall, when assessing the risk of adrenal involvement at the time of nephrectomy, the estimated risk is around 2.2%, while the risk of subsequent adrenal metastasis is 3.7% [60]. In other words, the practice of routine adrenalectomy in the average patient today would necessitate removal of nearly 199 normal adrenal glands for one involved with the RCC [64].

Management of RCC with Bowel and Pancreas Involvement

Involvement of bowel, especially duodenum at the time of surgery is rare, while involvement of pancreas via direct extension is more commonly observed [65]. In fact, the involvement of isolated adjacent organs without clinically evident metastatic disease in RCC is exceeding uncommon, occurring in <1% of patients undergoing nephrectomy [66]. The kidney's retroperitoneal location coupled with the isolation offered by Gerota's fascia, provides theoretical protection against direct tumor invasion into surrounding organs. More commonly, renal masses are observed to "indent" or compress adjacent organs than to directly invade them [65]. With that said, direct pancreatic, duodenal, and colon involvement have been reported. Ciancio et al. evaluated 11 patients with pancreatico-duodenal involvement in their study, observing isolated duodenal involvement in two cases [67]. Similarly, Karellas et al. reported no isolated duodenal involvement, while 3/40 patients had pancreatic involvement. Isolated pancreatic-duodenal resection at the time of nephrectomy may be managed with a Whipple procedure if partial duodenal resection in conjunction with distal pancreatotomy and splenectomy is unable to be safely performed [51]. Median recurrence-free survival in the setting of pancreatic or duodenal invasion can be relatively short, at approximately 2.3 months [51]. However, other authors have reported an actuarial 15% improved 5-year OS with

combined pancreatic-duodenal resection group [67].The variation in survival is most pronounced in patients with exclusive pancreatico-duodenal involvement compared to resection of other adjacent organs, which may reflect the oncologic potential related to direct invasion (as more commonly occurs in the setting of pancreatico-duodenal involvement), while involvement of the liver and other sites may reflect coexisting direct invasion and hematogenous dissemination [65].

Despite the significant improvement in OS, pancreatectomy is associated with substantial postoperative morbidity (34.8%), with 21.7% developing fistulae and 7.2% developing delayed gastric emptying [66]. Again, while there are no concise guidelines regarding patient selection to determine who will most benefit from consolidative surgery and R0 resection, a careful risk–benefit calculus incorporating performance status and tumor biology should drive decision-making regarding the resection.

The Role of Lymphadenectomy in the Management of RCC

Patients with nodal disease have poor prognosis and N stage is independently associated with reduced CSS and DFS. Conversely, as reported by Srivastava et al., lymph node positive stage III disease patients experienced similar 5-year survival to stage IV RCC as compared to LN negative stage III disease (22.7% vs. 15.6% vs. 61.9%) [68]. Overall, CSS in patients with RCC with lymph node involvement (LNI) is limited, ranging from 22% to 39% at 5 years and 11–29% at 10 years (Table 7.2) [75, 76]. LNI has shown significantly worse 5-year CSS

Table 7.2 Survival outcomes in pN10M0 RCC stratified by LND

Study	Median follow-up (months)	MFS At median follow-up	CSS At median follow-up	OS At median follow-up
1° LND for pN1Mo				
Chen (2011) [69]	15.5	29%	38% 22% at 5 years	–
Delacroix (2011) [70]	43.5	22%	– 39% at 5 years	– 37% at 5 years
Gershman (2017) [71]	102	– 16% @ 5y 15%@ 10y	– 26% at 5 years 21% at 10 years	– 25% at 5 years 15% at 10 years
Sun (2013) [72]	NR	–	– 38% at 5 years	–
Terrone (2006) [11]	14	–	– 25% at 5 years	–
Trinh (2012) [73]	17	–	– 38% at 5 years 26% at 10 years	–
Zhang (2010) [74]	42	–	– 32% at 5 years	–

MFS metastasis-free survival, *CSS* cancer-specific survival, *OS* overall survival

for node positive patients compared to node-negative stage to stage and numerous series identified LNI as one of the most important prognostic factors for survival [77, 78]. Yu et al. examined oncologic outcomes of stage III RCC (pT3N0M0 and pT1-3N1M0) patients and noted survival patterns of node positive patients resemble that of stage IV patients [79]. Others have proposed reclassification of the TNM scale to better reflect the impact of nodal involvement on survival [11, 73].

A challenge in the management of high-risk RCC is the unpredictable anatomic localization of metastases due to the heterogeneous spread by both hematogenous and variable lymphatic routes [75]. The most common lymphatic loco-regional retroperitoneal landing sites for nodal disease include paracaval and retrocaval nodes (right kidney), paraaortic and preaortic nodes (left kidney), and interaortocaval nodes (both right and left kidneys). However, lymphatic drainage may extend beyond these predicted retroperitoneal landing sites in over a third of cases [76]. At the same time, a significant number of patients present with metastatic RCC due to early hematogenous dissemination without lymph node involvement [77]. For example, Nini et al. examined dissemination patterns for node positive RCC patients and observed positive LN in right-sided tumors in the paracaval (44%), interaortocaval (40%), and renal hilar regions (16%), compared to the pre/paraaortic (67%), renal hilar region (24%), and interaortocaval (9%) regions for left-sided tumors [80]. A meta-analysis of 25 studies reviewing the role of lymph node dissection (LND) in RCC highlights the heterogeneity in reporting LND extent and the ambiguity surrounding RCC drainage patterns and LND templates [75]. Due to this variability in lymph node involvement, the role of regional LND at the time of RCC extirpation remains controversial.

Surgical Technique: Retroperitonal Lymphadenectomy for Locally Advanced Renal Cell Carcinoma

A traditional template recommended for right-sided tumors, includes hilar, paracaval (lateral side of IVC), and precaval (anterior side of IVC) with the extended right-sided templating retrocaval, interaortocaval, common iliac with or without the pre/paraaortic nodes. The analogous templates for left-sided tumors include the hilar, para/preaortic (anterior and lateral side of aorta) lymph nodes with extended templates incorporating retroaortic, interaortocaval, common iliac, and paracaval lymph nodes. Lymphadenectomy is accomplished with a standard "split and roll" maneuver along the renal vessels, aorta, and IVC, and common iliac arteries, according to the laterality of the tumor. Meticulous placement of surgical clips or suture ligatures is employed to optimize lymphostasis. Care is taken to identify the cistern chyli anterior to the first and second lumbar vertebral bodies, medial to right diaphragmatic crus and appropriately ligate lymphatics in this area to prevent a high-volume chylous leak/chylous ascites. Following synchronous LND and RN, drainage of the retroperitoneum is variably performed [81].

The optimal lymph node yield has not been defined for LND in the setting of locally advanced or cN1 RCC. Joslyn et al. observed a positive correlation between the increasing number of nodes resected and number of positive LN identified, reporting when ≥13 lymph nodes were removed, the rate of pN+ increased from 10.2% to 20.8% ($P < 0.001$) [82]. Conversely, in subgroup analysis of patients with higher risk for LN involvement, Kokorovic et al. found no association between LND and improved outcomes with higher LN yield [83].

Overall, postoperative complications following retroperitoneal LND and RN for RCC are observed in 17–26% of patients [84, 85]. One perioperative complication that may occur after RPLND is persistent lymphatic drainage with development of chylous ascites, occurring in 0.6–5.9% of cases with an average time to presentation of 17 days after surgery [86]. Risk factors include preoperative protein deficiency and electrolyte imbalances [86]. This complication can be mitigated by meticulous lymphatic control with titanium clip placement and/or suture ligasure of the lymphatic channels that are disrupted by the dissection. If detected, first line treatment includes conservative management such as bed rest, salt restriction, and a medium chain triglyceride (MCT) diet with high protein (2 g/kg body weight/day) and low fat (<20–40 g/day). Persistently high output drainage, defined as more than 1000 mL per 24 h is unlikely to resolve to conservative therapy alone, and may require subcutaneous octreotide, avoidance of oral intake with total parenteral nutrition (TPN), lymphangiogram with embolization, or surgical reintervention with ligation of perihilar lymphatic tissue if resolution or improvement is not identified in the first 2–6 weeks following treatment initiation [87].

Oncologic Outcomes Following LND

Proponents of LND advocate for the practice citing both staging (diagnostic) and therapeutic benefits citing the potential to resect micrometastatic disease, in patients who otherwise appear to have clinically organ-confined tumors [88–91]. Canfield et al. argued that extended lymph node dissection (eLND) is a critical staging tool to avoid under-staging, reporting that 17.5% patients with clinically node-negative and localized RCC had pathological node positive disease on eLND [92]. In a contemporary series of high-risk patients with RCC and tumor thrombus (cT3b-cM0), nodal involvement in cN0 patients was observed in nearly 10% of patients [93].

Several historic studies argue for the therapeutic efficacy of systemic LND at time of RN. Early work suggested that LND at the time of RN for patients with cN1 disease was associated with improved 5-year survival of 43.5% vs. 25.8% [94]. Pantuck et al. compared 129 patients with node positive disease who underwent RN and concluded those who underwent LND had an approximately 5-month survival advantage over the patients who did not undergo LND ($p = 0.0002$). In patients with pT1-3N0-3, M0 disease with an associated increase in 5- and 10-year OS of 58% vs. 55% and 56% vs. 41%, respectively

[84]. Capitanio et al. reported a statistically significant decrease in CSM in pT4M0 RCC patients treated with eLND (CSM at 1, 2, and 3 years were 65.0, 36.1, and 90% vs. 13.3, 13.0, and 6.7%, for pN0 vs. pN+ cases, $p = 0.004$) [95], with similar findings echoed by others [96, 97]. Whitson et al. performed a population-based analysis in N+M0 RCC patients and showed an association between increased LN yield and improved disease-specific survival in individuals with pN+ disease (HR 0.8, 95% CL 0.7–1.0, $p = 0.04$); however, separate analysis by Sun et al. utilizing a similar cohort with different statistical techniques found no prevailing association [72, 98].

In recent years, however, the oncologic benefit associated with LND at the time of nephrectomy for RCC has been called into question [71, 99, 100]. Most notably, EORTC 30881 was a randomized controlled trial evaluating LND in patients with cN0M0 RCC with a primary endpoint of overall survival. This trial demonstrated a prevalence of nodal involvement of 4% with no significant difference in postoperative complication, time to progression, progression-free or overall survival between patients who did and did not undergo LND at the time of RN [85]. Criticisms of the study include the high proportion of low risk patients enrolled.

To account for concerns regarding unmeasured confounding and selection bias in the retrospective literature, recent retrospective studies have evaluated associations between LND and oncologic outcomes using propensity score modeling [71]. In a multi-institutional cohort of 2722 patients with M0 RCC treated between 1990 and 2010, 45% of patients underwent LND [71]. The rate of pN1 disease was 6.3%. LND was not significantly associated with a reduced risk of distant metastases, cancer-specific or overall survival overall or among patients with cN1 disease. Furthermore, the authors noted that neither extended LND nor the extent of LND was associated with an improvement in oncologic outcomes. Using similar methods, Kokorovic et al. performed a large, multi-institutional analysis of M0 RCC patients undergoing RN and demonstrated no association between LND and improved OS, CSS or RFS [83]. A systematic review on the topic including 51 studies similarly demonstrated that LND yields independent prognostic information, such that nodal involvement is independently associated with adverse prognosis in the M0 setting [pooled OS hazard ratio 1.02 (95% CI 0.92–1.12)] [101]. Among patients with high-risk M0 disease, the authors noted that a small proportion of patients with pN1 disease did demonstrate durable long-term oncologic control with 10-year cancer-specific survival of 21–31%, however, LND was not significantly associated with either cancer-specific or overall survival.

As such, the 2019 EUA guidelines have removed recommendation for the use of routine LND during surgery for RCC, while National Comprehensive Cancer Network (NCCN) and American Urological Association (AUA) Guidelines emphasized the use of LND to provide information primarily for staging and prognostic purposes but did not recommend routine LND in patients with clinically negative node [102–105].

Surgical Decision-Making in Locally Advanced RCC and Patient-Specific Risk Factors

Surgical intervention for advanced RCC is associated with substantial risk of morbidity and mortality. Therefore, careful patient selection weighing the risks and benefits of intervention is imperative. An in-depth evaluation of the patient-specific factors, such as comorbidities and performance status, and the tumor's oncologic potential, must be weighed carefully with patient preferences and priorities. What follows is a discussion of objective evaluations of patient and tumor-centric factors that can be employed to provide an evidence-based preoperative patient evaluation for prognostication and treatment election. This section will also discuss strategies for patient optimization related to preoperative evaluation findings ("prehabilitation" interventions), and will discuss indications for consideration of preoperative systemic therapy.

As previously discussed, the average age of diagnosis of RCC in the USA is 64 years old [106]. More importantly, patients with RCC have approximately twice the number of comorbid conditions as their age-matched peers [5]. Thus, assessment of perioperative and postoperative risk for morbidity is critical in RCC patients. Patient comorbidities are often quantified by the Charlson Comorbidity Index (CCI) or the ASA Physical Status Classification System (ASA) score. Both CCI and ASA have been correlated with higher complication rates in patients with advanced RCC [107].

Beyond comorbidities, specific and highly predictive patient-centric prognostic factors include functional status and frailty, which is defined as a state of increased vulnerability to developing complications or mortality after a stressor event [108]. The most widely utilized measure of patient performance status (PS) is the Eastern Cooperative Oncology Group (ECOG) criteria [109, 110] which evaluates a patient's physical abilities, ranging from with "fully active" (0) to "completely disabled" (4). ECOG PS, and the analogous scale of Karnofsky Performance Status (KPS) are strong predictors of OS and PFS in metastatic RCC [111]. However, it is important to remember this measure is an estimate made by physicians that is subject to bias and may not match the patient's assessment of their own functional status [112].

Similarly, frailty can be challenging to reproducibly quantify. A commonly employed assessment is the Fried Frailty criteria, which incorporates assessments of fatigue, weight loss, grip strength, walking speed, and low energy expenditure [113].The Fried criteria and other frailty metrics can aid in prediction of outcomes in cancer patients with advanced age. However, poor sensitivity and interobserver variability of many of these scales has been used to support the contention that all cancer patients of advanced age should undergo a complete geriatric assessments (CGA) [114].

A CGA is a multidimensional evaluation of a patient's health that may identify potentially modifiable risk factors to improve outcomes. The core domains assessed in a standard CGA include functional status, comorbidities, polypharmacy, cognition, psychological status/mental health, social support, and nutritional reserve, using validated assessments. GCAs are generally administered by trained medical professionals with expertise in geriatric medicine however recently validated

self-assessments have been developed and implemented successfully in patients with cancers such as the Cancer and Aging Resilience GA (CARE-GA) [115]. CGAs offer additive specificity over conventional assessments of performance status. For example, in patients with a normal ECOG PS or normal ASA score, actionable vulnerabilities will be detected in 61% and 65% of patients, respectively, if a CGA is utilized. As such, multiple current guideline bodies advocate for the use of a geriatric screening tool or CGA in older adults with cancer prior to treatment election [116–119].

Body composition, nutritional status, and the presence of systemic inflammation are important "host" factors that are associated with prognosis in RCC. Sarcopenia, a critical loss of muscle mass, is associated with increased risk of mortality and recurrence after nephrectomy in both localized and metastatic RCC [120, 121] and provides more nuanced measure of a person's body composition than the traditional body mass index (BMI) measurement. In addition, poor nutritional status, as measured by hypoalbuminemia, has been associated with a 10-fold increased risk of early mortality in advanced RCC with TT [122]. Pro-inflammatory states can also be assessed using accessible preoperative laboratory tests. Low albumin, elevated CRP and ESR, neutrophil-to-lymphocyte ratio (NLR) and IL-6 portend a worse prognosis in advanced RCC [123, 124]. A common prognostic model for metastatic RCC, the International Metastatic RCC Database Consortium (IMDC) score, relies on the combination of serum inflammation markers and patient performance status to predict oncologic outcomes [125].These patient-centric metrics are readily accessible to clinicians. Gathering these important data during the preoperative patient assessment can provide powerful insights into the patient's potential disease trajectory.

Surgical Management versus Neoadjuvant Systemic Therapy in Advanced RCC

Neoadjuvant therapy for RCC has been proposed with the goal of reducing metastatic burden prior to surgical resection. In the nonmetastatic setting, proposed benefits of neoadjuvant therapy include facilitating surgical resection with reductions in the morbidity and mortality associated with nephrectomy and resection of neighboring organs. With advent of novel targeted agents and immunotherapies, there is interest in the potential of presurgical therapy to shrink tumors, reducing the need for synchronous adjacent organ resection, facilitating partial nephrectomy when feasible, and downstaging of IVC thrombus [126]. Figure 7.5 depicts a representative patient's burden of disease following 3 months of neoadjuvant immunotherapy prior to surgical debulking in advanced non metastatic RCC.

Neoadjuvant therapy theoretically offers the advantage of potential tumor cytoreduction, improving prospects for subsequent surgical resection or feasibility of nephron-sparing surgery [127]. The utility of neoadjuvant tyrosine kinase inhibitors (sunitinib and sorafenib) has been investigated in advanced RCC patients with tumors deemed unsuitable for primary resection. One initial study demonstrated

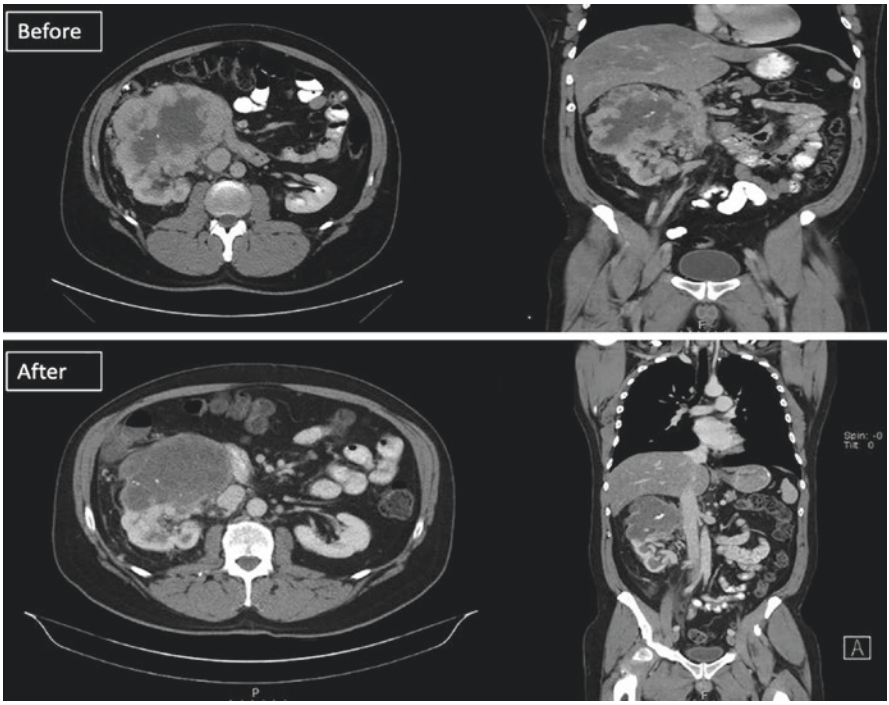

Fig. 7.5 Depiction of neoadjuvant immunotherapy (Axitinib 5 mg BID and Pembrolizumab 200 mg Q3weeks), with change in tumor volume and nearby organ infiltration over 3 months. Prior to neoadjuvant therapy, infiltration into the pancreas, duodenum and large bowel visualized on the scan. Post infusion reduction 22% in tumor volume with cystic degeneration as well as regression of disease from nearby organs, allowing for organ preservation during radical nephrectomy. Source: Original

tumor shrinkage in 42% of patients, with an average decrease in size of 24% and 21% of patients undergoing subsequent nephrectomy [128]. Additional small, early studies demonstrated reduction in tumor size in 77–85% of patients [129, 130]. Subsequently, a small prospective trial has demonstrated a reduction of tumor diameter of 28% with axitinib [131], while another retrospective study found a reduction of 32% with sunitinib with no additional morbidity after partial nephrectomy [132]. Overall, several smaller studies demonstrate modest reduction in tumor size with subsequent feasibility of surgical intervention. However, most studies are small retrospective or phase II prospective trials, thus are insufficient to inform broader guidelines. Larger prospective studies are lacking to further support the utility of TKIs in the neoadjuvant setting.

Recent approval of immune checkpoint inhibition therapy for first line advanced RCC treatment has propelled further investigation of these agents in the neoadjuvant setting. Specifically, using PD-L1 inhibitors, which block tumor expression of the programmed death ligand (PDL) and allow for T-cell recognition and attack of cancer cells, preventing the cancer cells from avoiding immune response [133]. In a

trial of immunotherapy in previously untreated patients with advanced RCC, the combination of avelumab (a PD-L1 inhibitor) and axitinib resulted in a progression-free survival of 13.8 months, versus 8.4 months with sunitinib [134]. Several ongoing studies are aimed at evaluating the potential of PD-L1 inhibitors and other immunotherapies for neoadjuvant therapy in advanced RCC using the response evaluation criteria in solid tumors (RECIST) criteria [133]. It remains to be determined the full impact of these immunotherapies on RCC treatment, but they have exciting potential to expand the arsenal of treatments available for patients with advanced RCC not amenable to up-front surgical resection.

At this time, selection for presurgical therapy in the absence of clinical metastatic disease is not considered standard of care and should be considered only within the context of a clinical trial. Integration of this approach into routine practice is predicated upon expected benefit with respect to clinically significant downstaging balanced with a patient's willingness and ability to tolerate the potential toxicity profile of systemic therapy without substantial decline in functional status, and carries the risk of progression that may preclude surgical excision [131].

Adjuvant Therapy for Locally Advanced RCC

High-risk RCC is associated with high rates of recurrence despite definitive surgical resection. Due to the presence of micrometastases, up to 40% of patients will experience local or distal recurrence after surgery; this number approaches 75% for patients with high-risk features (≥T3 or node positive disease) [135]. Surgery followed by surveillance is the mainstay of care for patients with advanced RCC. While more than 80% of patients with locally advanced disease are considered at high risk of recurrence, limited adjuvant treatment recommendations have been available for these patients, until recently.

Due to the success of VEGF therapy in metastatic RCC, there have been a plethora of adjuvant anti-angiogenic drug trials. To date, six large randomized controlled trials have evaluated the efficacy of such agents in the postoperative setting. Most of these trials use drugs approved for the treatment of metastatic RCC under the assumption that moving these agents to the adjuvant setting could eliminate micrometastatic disease or prolong progression to radiographically detectable recurrence [136]. With the exception of the disease-free survival (DFS) advantage observed in S-TRAC, these trials have had limited success [137].

Several critical trial design differences (patient selection, study design, and drug exposure) could partially explain the observed disparate results. The first discrepancy centers around trial endpoints and outcome measures. Overall survival (OS) is the most intuitive outcome and has historically been considered the primary outcome of interest. However, the dogma of OS as "gold standard" has recently come into question. As the number of therapeutic options increases rapidly, surrogate endpoints (such as DFS) have increasing relevance. When death occurs longer after randomization, OS becomes more susceptible to confounding factors that may not

influence DFS, making DFS an appealing primary outcome [138]. Most importantly, DFS and OS are equally valued by RCC survivors [139].

Clinical trial enrollment for adjuvant treatment of high-risk RCC requires thoughtful risk stratification to select patients that are at highest risk of subsequent metastasis, thus most likely to benefit from treatment. Given that the risk–benefit ratio does not favor adjuvant therapy for all people, appropriate risk stratification helps avoid harm/treatment toxicity in patients with low risk of recurrence/metastasis. There are two validated prognostic methods assess relapse risk for RCC, the University of California Los Angeles Integrated Staging System (UISS) and the stage, size, grade, and necrosis (SSIGN) score [140, 141]. Unfortunately, there is no consensus on which prognostic model to use in clinical trial design, which adds heterogeneity to trial comparison. By standardizing clinical trials to the use of one prognostic model, there is potential to streamline clinical trial inclusion and homogenize outcomes. Finally, differences in drug exposure, including the starting dose, de-escalation protocols, and dose maintenance, may also influence outcomes.

Historical Trials

Historically, many adjuvant therapies have been evaluated for patients with high-risk RCC, including radiotherapy, hormone-based therapy, cytokine therapies, vaccine therapy, and chimeric monoclonal antibody studies, though these studies were largely unsuccessful. A meta-analysis showed that radiation therapy after resection of RCC with a high risk of relapse decreased the risk of local recurrence (OR 0.46, 95% CI 0.29–0.71; $p < 0.001$) but not the risk of DFS (HR 0.73, 95% CI 0.30–1.79; $p = 0.49$) or 10-year OS OR 0.77, 95% CI 0.25–2.39; $p = 0.65$) [142]. Given RCC's potentially hormone-responsiveness (reported estrogen and androgen receptor expression), a prospective randomized trial compared medroxyprogesterone acetate to observation after radical nephrectomy and found no significant difference in relapse rate (32.7% vs. 33.9%) [143].

Cytokine therapies (interferon-alpha and Interleukin-2) in the adjuvant setting ultimately failed to improve DFS or OS, and were associated with high levels of treatment toxicity [143–148]. There have been five vaccine therapy trials using autologous irradiated tumor mixed with bacillus Calmette-Guérin, tumor-derived heat-shock protein-peptide complex, and autologous renal tumor cells [149–152]. The only study of the five to demonstrate improvement in DFS (the autologous renal tumor cell study) had significant flaws (study was unblinded and baseline characteristics were unbalanced) limiting its impact and resulting in concerns regarding its external validity. As such, adjuvant vaccine therapy has not been implemented clinically. Finally, the chimeric monoclonal antibody gerituximab, which targets carbonic anhydrase IX, was studied for high-risk RCC without improvement in DFS (HR 0.97, 95% CI 0.79–1.19, $p = 0.74$) or OS (HR 0.99, 95% CI 0.74–1.32, $p = 0.94$) (Table 7.3) [153].

Table 7.3 Historical adjuvant therapy trials in RCC

Category	Author	Year	Study type	Therapy details	DFS At median follow-up	OS At median follow-up
Radiotherapy	Rodriguez-Fernandez et al. [142]	2019	Meta-analysis	High-dose IL-2 bolused postoperatively	HR 0.73, 95% CI 0.30–1.79; $p = 0.49$	*3 years*: OR 0.58 (95% CI 0.30–1.10); $p = 0.09$ *5 years*: OR 0.71 (95% CI 0.46–1.11); $p = 0.14$ 10 years: OR 0.77, 95% CI 0.25–2.39; $p = 0.65$
Cytokine	Clark et al. [144]	2003	Clinical trial	Interferon alpha-NL for 12 cycles	IL-2 32% (95% CI 16–66%) vs. OBS 45% (29–69%), $p = 0.431$	
	Messing et al. [145]	2003	Clinical trial	Low dose IL-2 and IFNa for one 4-week cycle	41% vs. 37%, $p = 0.33$	62% vs. 51%, $p = 0.09$
	Passalacqua et al. [146]	2014	Clinical trial	IL-2, IFNalpha, 5-FU	HR 84% (95% CI, 0.54–1.31); $P = 0.44$	*5 years:* HR 1.07 (95% CI, 0.64–1.79); $p = 0.79$
	Aitchison et al. [148]	2014	Clinical trial	Autologous, tumor-derived heat-shock protein (glycoprotein 96)–peptide complex	HR = 0.84 (95% CI 0.63–1.12); $p = 0.233$	
Vaccine	Wood et al. [150]	2008	Clinical trial	Autologous renal tumor cell vaccine	HR 0.923 (95% CI 0.73–1.17); $p = 0.506$	–
	Jocham et al. [151]	2004	Clinical trial	Gerituximab (targets carbonic anhydrase IX)	HR 1.58 (95% CI 1.05–2.37)	–
Chimeric monoclonal antibody	Chamie et al. [153]	2017	Clinical trial	High-dose IL-2 bolused postoperatively	HR 0.97 (95% CI 0.79–1.19), $p = 0.74$	3 years: HR 0.99 (95% CI 0.74–1.32), $p = 0.94$

DFS disease-free survival, *OS* overall survival

Current Approaches to Adjuvant Therapy

Anti-angiogenic Therapies (Anti-VEGF, TKI and mTOR Inhibitors)

Angiogenesis plays a known role in the pathogenesis of RCC; however, anti-angiogenic therapies targeting the VEGF pathway through tyrosine kinase (TKI) and mammalian target of rapamycin (mTOR) inhibition have shown mixed results for survival and progression when used in the adjuvant setting.

S-TRAC was a prospective, randomized, double-blind, phase 3 trial that randomized patients with ccRCC, ECOG ≤2, stage III or higher and/or regional lymph node positive disease using the UISS criteria to adjuvant sunitinib vs. placebo [140]. Among patients treated with sunitinib, median DFS was 6.8 years (95% CI 5.8-NR) versus 5.6 years (95% CI 3.8–6.6) in the placebo arm (HR 0.76, 95% CI 0.59–0.98, $p = 0.03$). At 3 years, 64.9% of the sunitinib group and 59.5% of the placebo group were disease free [137]. Similarly, at 5-year timepoint, the sunitinib-treated patients had 8.0% higher disease-free rate than placebo, which the authors argued confirmed the durability of benefit associated with adjuvant sunitinib over time. Serious adverse events occurred in 21.9% of the sunitinib group vs. 17.1% of the placebo group. In comparing QLQ-C30 and ED-5D scores for QOL, clinically significant declines in QOL were seen with diarrhea (mean difference, 12.0 points; 95% CI, 9.6–14.4; $p < 0.001$) and loss of appetite (mean difference, 10.0 points; 95% CI, 7.9–12.2; $p < 0.001$); no clinically meaningful difference in EQ-5D or EQ-VAS occurred in either group [137]. This publication led to the approval of sunitinib for adjuvant treatment of patients at high-risk of recurrence of RCC following nephrectomy in the USA [154].

However, due to the adverse-event profile and conflicting conclusions of S-TRAC vs. other similar trials (e.g., the ASSURE trial, discussed below) regarding overall benefit, adjuvant therapy with sunitinib is not approved in other parts of the world [155]. Real-world data has shown that even among high-risk cM0 patients, only 2.6–3.5% receive adjuvant targeted therapy [156]. Secondary analysis with mature data from S-TRAC confirmed DFS improvement with adjuvant sunitinib for groups at higher risk of recurrence (T3, no or undetermined nodal involvement, Fuhrman grade ≥2, and ECOG PS ≥1; or T4 and/or nodal involvement) and those with Fuhrman grade 3/4. Unfortunately, neither the original nor updated analysis for S-TRAC had mature data with overall survival; however, these updates suggest that there was no detrimental effect on OS for sunitinib treatment [157].

Additional trials are noteworthy in the study of adjuvant therapy for RCC with high risk of relapse, despite failure to meet primary outcomes.

The predecessor to S-TRAC was the **ASSURE** trial, which was the first trial to investigate VEGF inhibitors as adjuvant therapy for locally advanced, high-risk RCC [158, 159]. This phase III study enrolled pT1b (grade 3–4), pT2-4 or Tany, N+ M0 disease to sunitinib, sorafenib or placebo. Unfortunately, this study showed no difference between treatment and control arms in terms of DFS and OS. Median DFS was 70 months (5.8 years, IQR 1.6–8.2) for sunitinib, 73.4 months (6.1 years, IQR 1.7–NE) for sorafenib, and 79.6 months (6.6 years, IQR 1.5–NE) for placebo,

which did not differ between groups. Because ASSURE allowed enrollment of any histologic subtype of RCC, subgroup analysis was performed for ccRCC and no benefit was seen with sunitinib or sorafenib when compared to placebo (sunitinib vs. placebo, HR 1.02, 97.5% CI 0.85–1.22, stratified log-rank p=0.89; sorafenib vs. placebo, HR 0.99, 97.5% CI 0.83–1.19, stratified log-rank $p = 0.8734$).

In comparing the results of the ASSURE and S-TRAC trials, noteworthy differences may have impacted the trial outcomes. The two trials had distinctly different inclusion criteria, which created dissimilar patient populations (e.g., ASSURE allowed enrollment of non-ccRCC and stage 1 tumors). Although both trials started with 50 mg/day dosing of sunitinib, ASSURE amended the study protocol to 37.5 mg/day and allowed dose reduction to 25 mg/day, whereas S-TRAC remained consistent with 50 mg/day but allowed dose reductions to 37.5 mg/day [157, 160].

The **PROTECT** trial (pazopanib, a tyrosine kinase inhibitor (TKI)), failed to show improvement in DFS over placebo (HR 0.86; 95% CI, 0.70–1.06; $P = 0.165$) with 600 mg dosing; however, secondary analysis of 800 mg dosing did show significant improvement in DFS (HR of 0.69 (95% CI, 0.51–0.94)) [161]. Subsequent studies have suggested that it is not the dose of pazopanib itself that is predictive of clinical response, but alternatively the serum trough concentration of pazopanib that derives clinical benefit; this knowledge may be of use in the design of future trials [162].

In the **ATLAS** trial, axitinib (a selective inhibitor of VEGFR 1, 2, and 3) was evaluated for DFS and OS. Ultimately, the trial was stopped after interim analysis due to futility. Of note, ATLAS was designed to include patients at lower risk of recurrence, and subgroup analysis of patients at high risk of recurrence demonstrated a significant improvement in DFS associated with axitinib receipt (HR 0.641, 95% CI = 0.468–0.879); $P = 0.0051$). This led investigators to conclude that adjuvant therapy may have the most potential for individuals at highest risk of recurrence [163]. As such, future trials may choose to homogenize inclusion criteria and focus only on high risk of recurrence in order to have the greatest chance of trial success.

In the 3-armed **SORCE** trial, adjuvant sorafenib administration for 1-year and 3-year durations were compared with placebo. Restricted mean survival time (RMST) was equivalent for 3 years of sorafenib vs. placebo (6.81 vs. 6.82 years, respectively; RMST difference, 0.01 year; 95% CI, −0.49 to 0.48 year; $P = 0.99$) [164]. Given these findings, sorafenib was not recommended as adjuvant therapy after nephrectomy for RCC.

In a meta-analysis of the five major TKI trials (S-TRAC, ASSURE, PROTECT, ATLAS, and SORCE), analysis suggested significantly longer DFS (pooled HR: 0.88, 95% CI: 0.81–0.96, $P = 0.004$), but not OS (pooled HR: 0.93, 95% CI: 0.83–1.04, $P = 0.23$) with adjuvant therapy compared with placebo. However, TKI therapy was associated with significantly higher rates of high-grade treatment-related adverse events (OR 5.20, 95% CI: 4.10–6.59, $p < 0.00001$). Based on this meta-analysis, authors conclude that the risk-to-benefit ratio of adjuvant TKI is insufficient, except for select patients with very poor prognosis [165].

Immune Checkpoint Inhibitors

The recent success of antibody-based immunotherapy and approval of both nivolumab monotherapy and combination of nivolumab with ipilimumab for mRCC have shifted adjuvant clinical trial evaluation to immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway.

Keynote-564 evaluated pembrolizumab monotherapy vs. placebo for patients with advanced clear cell RCC (ccRCC) (tumor stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumor stage 3 or higher, regional lymph node metastasis, or stage M1 with NED) in a phase III RCT [166]. At present, the first interim analysis has suggested that adjuvant pembrolizumab therapy improved its primary endpoint (DFS) when compared to placebo (HR 0.68 (0.53–0.87), $p = 0.002$), though the median DFS was not reached for either group. At 24 months, the estimated percentage of patients who were alive and recurrence-free was 9.2% higher for the adjuvant pembrolizumab group [77.3% (95% CI, 72.8–81.1) vs. 68.1% (95% CI, 63.5–72.2)]. Serious adverse events were observed in 20.5% of the pembrolizumab group vs. 11.3% of the placebo group; similarly, 34.6% of pembrolizumab and 5.8% of placebo group experienced immune-mediated adverse events. The difference in DFS was further analyzed in a subgroup analysis based on PD-L1 status, where having a PD-L1 combined score of ≥1 incurred a HR 0.67 (0.51–0.88). There was no clinically meaningful change in the pembrolizumab treated group in terms of symptoms or quality of life (as measured by FKSI-DRS and EORTC QLQ-C30 scores, respectively). The authors conclude that this trial supports the use of pembrolizumab as adjuvant immunotherapy in patients with renal cell carcinoma at intermediate- or high-risk of disease recurrence, and these results have led to recent FDA approval of pembrolizumab for this indication.

Ongoing Clinical Trials

Given the success of ICI in metastatic RCC and success of adjuvant pembrolizumab within Keynote-564, there is eager anticipation of the final results of several recently closed clinical trials, which unfortunately all demonstrated negative results. The **PROSPER RCC trial** (NCT03055013) was a phase III randomized trial evaluating perioperative (both neoadjuvant and adjuvant) nivolumab. In theory, the neoadjuvant treatment is designed to prime the immune system for enhanced efficacy of the subsequent adjuvant treatment; the neoadjuvant aspect of this study design distinguishes PROSPER from the other studies. **IMmotion010** (NCT03024996) was a phase III RCT of atezolizumab monotherapy versus placebo for patients with RCC at high risk of recurrence after nephrectomy. The **CheckMate-914** (NCT03138512) phase III RCT will evaluate nivolumab monotherapy, nivolumab combined with ipilimumab, and placebo for patients with localized RCC after radical or partial nephrectomy.

In addition to trials for ICIs, the EVEREST trial of mTOR inhibition using everolimus is being evaluated in patients with histologically confirmed RCC (all histologic subtypes) after surgical therapy [167].

Summary: Adjuvant Therapy for High Risk Localized RCC After Nephrectomy

After surgical intervention for high-risk RCC, many patients experience disease recurrence or metastasis, so advancements in adjuvant therapy are critically needed. Despite many clinical trials in this space, there has been a high rate of failed RCTs. Upon review, some clinical trial failures may be attributable to the heterogeneity of enrolled patients (although all were categorized as "high-risk" of recurrence, there is a stark contrast between not-so high risk and stage IV RCC). The major RCTs used different risk stratification methods (ATLAS and PROTECT use TNM and FG; ASSURE and S-TRACT used UISS). Similarly, histopathologic heterogeneity (ccRCC and non-ccRCC in the same study) may be responsible for differential outcomes and skewed results. As we move forward studying adjuvant therapy for RCC, standardizing inclusion criteria, risk stratification, and inclusion of molecular features has significant potential to help move these treatments into clinical practice. Urologic oncologists have a key role in this space and should consider referring patients with locally advanced, high-risk RCCs to medical oncology for a balanced discussion regarding the risks and benefits of adjuvant therapy.

Conclusions

In this chapter we reviewed the management of locally advanced, nonmetastatic renal cell carcinoma. While the prevalence of incidentally detected small renal masses increases, a considerable proportion of patients present with locally advanced disease. We highlighted the importance of careful diagnostic evaluation and risk stratification of patients, the critical need for meticulous preoperative preparation and the often-multidisciplinary care patients with these tumors to optimize patient outcomes. The field is moving forward as we further evaluate and define the role for perioperative systemic therapy in this space, with the goal of improving survival and reducing treatment-associated morbidity and mortality.

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Adjuvant Therapies in Renal Cell Carcinoma

8

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Introduction

Renal cell carcinoma (RCC) is a common malignancy in both men and women, and is estimated to account for 76,080 new cases of cancer diagnosis and 13,780 cancer deaths in the USA in 2021 [1]. The incidence of early stage RCC has increased over time due to improvements in early detection with computed tomography scans [2], and the proportion of stage I RCC diagnoses has risen while stage III and IV diagnoses have down trended [3]. Until recently, advances in detection strategies have not been met with improvements in treatment and survival for stage I–III RCC. For patients with locally advanced RCC, curative-intent nephrectomy is the standard of care, however, a subset of patients develop recurrent disease. The rate of local or distant recurrence for patients with initial stage II and III disease is heterogenous, however, some individuals can have a recurrence risk as high as 60–80% [4]. While overall survival for metastatic RCC has significantly improved over the last decade due to highly effective systemic therapy options such as targeted therapies with tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), the development of distant metastases is associated with lethal disease in the majority of patients.

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With successes in systemic therapy for advanced disease, a series of clinical trials in the adjuvant setting have tested agents which have demonstrated efficacy for patients with metastatic RCC. The goal of adjuvant therapy is to improve cure rates and overall survival after surgical resection. The first clinical trials for adjuvant therapy for RCC were done in the 1980s and evaluated the efficacy of interferon-alpha [5]. Over the subsequent decades, several noteworthy clinical trials of various systemic therapies including cytokines, chemotherapies, and TKIs have been conducted.

Initially, cytokines were studied in patients with locally advanced RCC at high risk for recurrence (≥pT3, node-positive disease) after resection. Adjuvant cytokine-based trials were largely negative and did not alter clinical management. Subsequently, a series of studies investigated the role of adjuvant TKIs following surgical resection. With the exception of the S-TRAC study of adjuvant sunitinib, these studies were largely negative [6–8]. We have now entered into a new era with the introduction of ICI in the adjuvant setting. KEYNOTE-564 is the first adjuvant ICI trial showing an improvement in disease-free survival (DFS).

In this chapter, we hope to review historic and current data on adjuvant cytokine, TKI, and ICI therapies for RCC. We provide a summary of data and application and integration into clinical practice.

Risk Stratification

After nephrectomy for localized RCC, while the risk of recurrence is heterogenous, over 20% of all patients diagnosed with RCC will develop distant metastases [9, 10]. Risk stratification of these patients has prognostic value and utility in determining who will derive benefit from adjuvant therapies. Currently a variety of clinical factors including tumor stage, positive surgical margins, sarcomatoid differentiation, high nuclear grade, and microvascular invasion have been associated with shorter DFS and OS after nephrectomy and are integrated in risk stratification methods [11, 12]. The tumor, nodes, and metastasis (TNM) staging system is the most broadly used method to determine prognosis following surgical resection for locally advanced RCC. The most recent TNM staging system from 2018 is based on physical tumor characteristics that guide surgical management as well as the extent of disease spread that is correlated with overall survival. The primary tumor size and disease extent, or T stage is one of the most important prognostic factors in RCC. When broken down by all-comer stage categories, the postoperative local and distant recurrence rates for T1, T2, T3a, and T3b tumors were 0 and 4.4%, 2.0 and 5.3%, 8.2 and 11.5%, and 10.6 and 14.9%, respectively, with a mean postoperative follow-up time of 55.6 months [13]. While T1a tumors (<4 cm) have the highest likelihood of cure, T3 tumors with invasion into the renal vein, perinephric tissues, or renal sinus have a significantly higher risk of recurrence [13, 14]. Nodal involvement has relatively low incidence in patients with localized disease (2–9%) [15], and when present, is associated with poor prognosis and increased risk of disease recurrence.

Table 8.1 Models for RCC prognostication in the setting of localized disease

Model	Parameters	Outcome	Type
UISS	TNM, grade, ECOG PS	OS	KM analysis
Leibovich	TNM, pN+, tumor size, grade, tumor necrosis	MFS	Algorithm
SSIGN	TNM, pN+, pM+, tumor size, grade, tumor necrosis	CSS	Algorithm
MSKCC	TNM, tumor size, grade, tumor necrosis, symptoms	RFS	Nomogram
Kattan	TNM, tumor size, histology, symptoms	RFS	Nomogram
Yaycioglu	Tumor size, symptoms	RFS	Formula
Karakiewicz	TNM, age, sex, + margin, tumor size, symptoms	CSS	Nomogram
Cindolo	Tumor size, symptoms	RFS	Formula

In addition to individual factors, multiple prognostic nomograms incorporating the American Joint Committee on Cancer (AJCC) TNM stage, ECOG performance status, and histologic features have been developed to identify patients at high risk of recurrence following resection (Table 8.1) [10, 12, 16–21]. One of the most frequently utilized nomograms is the UCLA Integrated Staging System (UISS). The UISS uses TNM stage, Fuhrman grade, and performance status to stratify patients into five risk categories. It has been validated for both clear cell and non-clear cell patients and is used to predict overall survival following nephrectomy [16]. Another notable risk stratification system is the Leibovich score, which incorporates histology, tumor stage, lymph node status, tumor size and grade, and tumor necrosis into the scoring algorithm designed to predict DFS after surgery for patients with localized clear cell RCC. The algorithm generates a score between 0 and 11, and patients are stratified into three risk groups: low (0–2 points), intermediate (3–5 points), or high (above 6 points). More recently, the Leibovich score has been validated in patients with non-clear cell, papillary, and chromophobe RCC [12]. These classification systems, along with several of the other available algorithms, have application in guiding clinical expectations following surgical resection and also are important in understanding recurrence risk in the context of adjuvant clinical trial design.

While most of the data to date used to help risk stratify patients following surgical resection has been limited to clinical, anatomic, and histologic characteristics, genomic biomarkers are being explored to better predict recurrence following nephrectomy. Molecular signatures have been investigated to predict recurrence after nephrectomy, and prognostic assays based on gene expression signatures have been explored in RCC [22–26]. One prognostic molecular signature that has been validated in the context of a large phase 3 study is a 16-gene assay comprised of genes associated with recurrence-free interval, from which a recurrence score algorithm is generated. The recurrence score has been validated as a predictor of tumor recurrence in patients with stage I–III clear cell RCC [22]. Its prognostic significance was later confirmed in the S-TRAC trial of adjuvant sunitinib as it may identify high-risk patients who may further benefit from adjuvant therapy [23]. Additionally, a 34-gene classifier (ClearCode34) was developed to assign clear cell RCC to subtypes associated with recurrence-free survival and overall survival, and provides additional prognostic stratification [24]. Lastly, the cell cycle proliferation

(CCP) score is based on an RNA expression assay that measures the activity of cellular proliferation genes. CCP is a significant predictor of recurrence and disease-specific mortality after radical nephrectomy in patients with localized clear cell, papillary, or chromophobe RCC [25]. Long non-coding RNA signatures may also have a role in prognostication. Qu et al. demonstrated that a four-long non-coding RNA classifier had higher accuracy in risk stratification compared to clinical staging systems based on clinical outcomes [26]. Though no molecular signatures at the present time have entered into clinical practice, their prognostic significance is promising and may be a valuable addition to clinical and pathologic methods for risk stratification.

Historic Data on Adjuvant Cytokine Therapy

In the late 1980s to early 2000s, a series of randomized trials were conducted to evaluate the role of adjuvant cytokine-based therapy for the treatment of high-risk RCC. The patient populations, treatment arms, and outcomes of these adjuvant cytokine therapy trials are summarized in Table 8.2. The earliest clinical trials were two large randomized studies that were conducted in the USA [28] and Germany [27], which were published in the 1990s. Both utilized adjuvant cytokine therapy with lymphoblastoid interferon (IFN) and recombinant IFNa2a, respectively, in radically resected Robson stage II (perinephric fat involvement) and III (tumor extension into renal vein or inferior vena cava) RCC. When compared to observation, these adjuvant treatments did not have a DFS benefit [27, 28].

The investigation into adjuvant cytokine therapy continued into the early to mid-2000s. Pizzocaro et al. [29] conducted a randomized, multicenter trial that compared the efficacy of IFN α2b (rIFNα2b) versus placebo post-nephrectomy in advanced RCC patients that had Robson stage II or III disease. The primary endpoints were 5-year DFS and OS, and the results showed that there was no significant

Table 8.2 Historic adjuvant cytokine therapy trials

Trials	Population	Arms	N	Primary	Outcomes
Porzsolt et al. [27]	pT3-4N0 or pTxN1-3	IFN-α vs. observation	270	TTF/ survival	No difference
Trump et al. [28]	pT3-4aN0 or pTxN1-3	L-IFN vs. observation	294	Recurrence	No difference
Pizzocaro et al. [29]	pT3-4aN0 or pTxN1-3	IFN-a vs. observation	247	5-year DFS	No difference
Messing et al. [30]	pT3-4aN0 or pTxN1-3	IFN-α vs. observation	283	5-year OS	No difference
Clark et al. [31]	pT3b-4Nx or pTxN1-3	IL-2 vs. observation	138	2-year DFS	No difference
Atzpodien et al. [32]	pT3b-4Nx or pTxN1-3	IL-2/IFN-a/5-FU vs. observation	203	2-year DFS	No difference
Aitchison et al. [33]	pT3b-4Nx or pTxNa-2 or +margins/vascular invasion	IL-2/IFN-a/5-FU vs. observation	309	3-year DFS	No difference

difference in DFS or OS between the treatment and placebo arms (event-free survival probabilities of 0.567 vs. 0.671, $p = 0.107$ for DFS and 0.660 vs. 0.665 for OS, $p = 0.861$, respectively) [29]. Messing et al. looked at 283 patients with resectable RCC having undergone radical nephrectomy and lymphadenectomy, who were randomized to adjuvant IFN alfa-NL versus observation. The primary endpoints were 5-year OS and relapse-free survival, and the results showed that adjuvant IFN treatment did not improve either compared to observation alone [30].

In addition to IFN-based treatment, IL2 has also been evaluated in the adjuvant setting. Clack et al. conducted a randomized phase III trial evaluating adjuvant high-dose bolus interleukin-2 (IL-2) in patients with resected high-risk RCC. The study did not meet its primary predicted endpoint of a 30% improvement in 2-year DFS in the treatment group, which resulted in early trial closure despite full accrual. Sixteen of 21 (76%) patients in the treatment arm relapsed compared to 15 of 23 (65%) patients in the observation arm ($p = 0.73$), [31].

A few trials evaluated combination cytokine and chemotherapy in patients with RCC at high recurrence risk after nephrectomy. Atzpodien et al. evaluated 203 patients with high-risk RCC stratified into three risk groups (patients with (1) tumor extending into renal vein/vena cava or beyond Gerota's fascia, (2) locoregional lymph node involvement, or (3) complete resection of tumor relapse or solitary metastasis), and randomized to receive either subcutaneous IL-2, subcutaneous IFN alpha2a, and intravenous 5-fluorouracil, or observation. There was no significant difference in the 2-, 5-, or 8-year DFS rates between the treatment and observation arms ($p = 0.24$), and 2-, 5-, or 8-year OS was actually inferior in the treatment arm ($p = 0.03$) [32]. Aitchison et al. performed a randomized trial to compare adjuvant 5-fluorouracil, alpha-interferon and interleukin-2 to observation, and endpoints were OS, DFS, and quality of life (QoL). Eligible patients included those with resected RCC who were 8 weeks post-nephrectomy and did not have macroscopic residual disease. As with the other cytokine studies, there was no significant difference in 5-year OS, which was 70% in the treatment group and 63% with the observation group ($p = 0.43$) [33]. In aggregate, these studies were negative and did not show a survival benefit with adjuvant cytokine-based treatment in patients with RCC at high risk of recurrence post resection.

Historic Data on Adjuvant Tyrosine Kinase Inhibitors

The utilization of targeted therapies for patients with metastatic disease has led to further investigation of vascular endothelial growth factor (VEGF) inhibitors in the adjuvant setting. A series of clinical trials were reported from 2017 to 2021 of adjuvant targeted therapy and are illustrated in Table 8.3. Although these trials had a mutual objective of studying adjuvant VEGF inhibitors post-nephrectomy, they varied in the duration of therapy administered, the agent under investigation, enrollment based on risk of recurrence criteria (some trials used stage while others incorporated Leibovich score), and the inclusion/exclusion of non-clear cell histology [7, 8, 34–36].

Table 8.3 Historic adjuvant tyrosine kinase inhibitor trials

Trial	Arms	Years	*N*	Primary endpoint	Clear cell only	Eligibility	Hazard ratio confidence interval
ASSURE	Sunitinib vs. sorafenib vs. placebo	1	1943	DFS	No	pT1bG3-4N0, pT2-4GxN0, TxGxN+	Sunitinib—1.02 (97.5% CI 0.85–1.23) Sorafenib—0.97 (97.5% CI 0.80–1.17)
S-TRAC	Sunitinib vs. placebo	1	615	DFS	Yes	pT3-4GxN0-x, TxGxN1-2	0.76 (95% CI 0.59–0.98)
PROTECT	Pazopanib vs. placebo	1	1538	DFS	Yes	pT2G3-4N0, pT3-4N0, pTxN1	0.86 (95% CI 0.70–1.06)
ATLAS	Axinitib vs. placebo	1–3	724	DFS	Yes	pT2-GxN0, pTxN1	0.870 (95% CI 0.66–1.147)
SORCE	Sorafenib vs. placebo	1–3	1711	DFS	No	Leibovich scores 3–11	1.01 (95% CI 0.83–1.23)
EVEREST	Everolimus vs. placebo	1	1545	RFS	No	pT1bG3-4N0, pT2-4N1	Pending

Two landmark trials of targeted therapies in the adjuvant setting were the ASSURE and S-TRAC trials. ASSURE was a phase III randomized, placebo-controlled, double-blind study that compared the efficacy of sunitinib, sorafenib, and placebo. Patients with at least stage T1b non-metastatic RCC who had undergone complete resection were enrolled from 226 sites from the USA and Canada; this was the largest adjuvant targeted therapy trial for RCC to date. Additionally, patients with non-clear histology were eligible. Patients were randomized in a 1:1:1 ratio into three treatment arms: 50 mg daily sunitinib for the first 4 of each 6-week cycle, 400 mg twice daily sorafenib throughout each cycle, or placebo. There was continued for a maximum of 54 weeks. The primary endpoint was DFS, and the trial demonstrated no significant difference in DFS among the treatment arms, with a median DFS of 5.8 years for sunitinib (HR 1.02 [97.5% CI 0.85–1.23, $p = 0.804$]), 6.1 years for sorafenib (HR 0.97 [97.5% CI 0.80–1.17, $p = 0.718$]), and 6.6 years for placebo (IQR 1.5-not estimable). A subgroup analysis was performed on patients with high-risk disease (clear cell histology, > or equal pT3, or node-positive disease) and did not demonstrate a significant difference in DFS or improvement in outcomes between sunitinib and placebo [6].

S-TRAC was a phase III randomized, placebo-controlled, double-blind study that compared the efficacy of sunitinib versus placebo in patients with locoregional high-risk clear cell RCC. The trial differed from ASSURE in that only patient with clear cell histology were eligible and patients were required to have at least stage pT3 disease. Patients were randomized to receive either 50 mg daily sunitinib 4-weeks on and 2-weeks off for up to 1 year or placebo. The primary endpoint was DFS, which was superior in the sunitinib group compared to placebo (median DFS 6.8 vs. 5.6 years, HR 0.76 [95% CI 0.59–0.98; $p = 0.03$]). Of all trials involving

targeted therapy in the adjuvant setting, S-TRAC was the only trial to successfully reach its primary endpoint of improved DFS. Despite this, S-TRAC did not demonstrate an OS benefit with sunitinib (HR for death 0.92 [95% CI, 0.66–1.28]), and sunitinib had increased incidence of grade 3 and 4 adverse events and lower quality of life scores. Grade 3 or higher toxicities were seen in 63.4% of sunitinib-treated patients compared to 21.7% in the placebo group, and dose interruptions were needed in 46.4% of patients in the sunitinib group versus 13.2% in the placebo group. Quality of life was impacted by adverse events related to sunitinib, with lower quality of life scores in the sunitinib group mostly due to diarrhea and appetite loss [37].

Current Data Regarding Checkpoint Inhibitors

ICIs for RCC were initially studied in the metastatic setting. Keynote 427 and CheckMate 025 were trials that evaluated the efficacy ICI monotherapy in patients with advanced RCC. CheckMate 025 demonstrated superior OS with nivolumab monotherapy compared to everolimus [38]. Additionally, Keynote 427 was a single arm phase 2 trial that invested the efficacy of pembrolizumab monotherapy in patients with clear cell and non-clear cell RCC. Pembrolizumab demonstrated encouraging response rates and tolerable safety profiles [39].

Recent trials have demonstrated superior efficacy of ICI combination therapies compared to standard of care in the front-line setting for advanced RCC, which include CheckMate 214 of nivolumab + ipilimumab, Keynote 426 of pembrolizumab + axitinib, Javelin Renal 101 of avelumab + axitinib, CheckMate 9ER of nivolumab + cabozantinib, and the CLEAR Trial of pembrolizumab + lenvatinib. While the features of these trials (agents utilized, primary endpoint) differed, in aggregate they have changed the front-line treatment paradigms for advanced RCC to include combination ICI therapy for the majority of patients.

Most recently, the first clinical trial evaluating immunotherapy in the adjuvant setting was published. Keynote 564 was an international phase III, double-blind trial that randomized patients with intermediate-high (pT2N0M0 or pT3N0M0) or high-risk (pT4N0M0 or pT any stage, N+ M0), fully resected RCC in a 1:1 ratio to either pembrolizumab 200 mg IV or IV placebo every 3 weeks for up to 1 year. The primary endpoint was DFS and a key secondary endpoint was overall survival. The trial demonstrated a statistically significant improved DFS for pembrolizumab compared to placebo (24-month DFS 77.3% vs. 68.1%, HR 0.68 [95% CI, 0.53-0.87; $p = 0.002$]). This was further supported by a superior DFS during interim analysis, with the treatment arm having 109 (22%) events compared to 151 (30%) events in the placebo arm (HR 0.68 [95% CI, 0.53–0.87; $p = 0.0010$]). The number of patients alive at 24 months were also reported (96.6% vs. 93.5%, HR 0.54 [95% CI, 0.30–0.96]). Currently, with only 26% of events needed for the final OS analysis, the preliminary OS results need to be interpreted with caution. There was no new safety signal that emerged with this therapy. The most commonly reported adverse events were musculoskeletal pain, fatigue, rash, diarrhea, puritis, and

hypothyroidism. There were more grade 3 or higher adverse events in the treatment group compared to placebo (32.4% vs. 17.7%, respectively). This is the first trial to demonstrate an improvement in DFS with adjuvant immune checkpoint inhibition in RCC [40]. The data derived from Keynote 564 are revolutionary, and ultimately led to the FDA approval of pembrolizumab usage in the adjuvant setting for intermediate-high and high-risk RCC patients after either nephrectomy or nephrectomy plus metastatectomy in November 2021.

Future Data Regarding Checkpoint Inhibitors

There are several ongoing clinical trials evaluating immune checkpoint inhibitors in the adjuvant setting for high risk, localized RCC that will likely further inform the field. These randomized phase III trials include IMmotion101, CheckMate 914, Prosper, and RAMPART (Fig. 8.1). The IMMotion101 (NCT 03024996) is a multicenter, placebo-controlled, double-blind study that will evaluate the safety and efficacy of atezolizumab versus placebo in high-risk RCC patients following nephrectomy. Similarly, CheckMate 914 (NCT03138512) is a double-blind study that will compare nivolumab monotherapy, nivolumab plus ipilimumab, and placebo. Prosper (NCT03055013) aims to compare nivolumab with placebo but is unique in that it include a neoadjuvant component to therapy, and RAMPART (NCT03288532) will compare durvalumab monotherapy, durvalumab/tremelimumab combination therapy, versus placebo. There is much heterogeneity in the study design features of these trials, with different immunotherapy drugs being tested, inconsistency with blinding, and variable therapy timelines. Even though these studies could illuminate the potential use of checkpoint inhibitors surrounding nephrectomy, it will be important to consider these differences in design when applying the study outcomes to clinical practice.

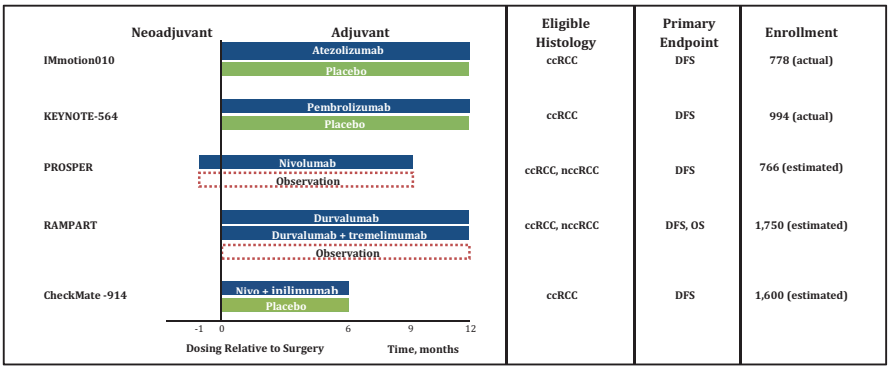

Fig. 8.1 Ongoing phase 3 adjuvant trials with immune checkpoint inhibitors

Keynote 564 is a landmark study that will influence the future of adjuvant therapy. It poses novel clinical questions surrounding the future of immunotherapy in the field, including which patients are more likely to derive benefit from therapy and who are those at the highest risk of recurrence. Future research is warranted to investigate potential tissue and blood biomarkers to characterize the risk factors of recurrence after patients receive a nephrectomy. Specifically, circulating tumor DNA or microRNA assays could help risk stratify patients who are at the highest risk of recurrence. Currently, predictive biomarkers are lacking, but could potentially be a crucial clinical tool in the adjuvant setting. It is also important to speculate further on future treatments following progression on post-nephrectomy adjuvant therapy, therapeutic use in non-clear cell RCC patients, and patient selection criteria that helps determine which patients derive most benefit from adjuvant therapy.

Conclusion

Recommendations for adjuvant treatment for RCC continue to evolve in the era of targeted therapy and immunotherapy. While data from adjuvant VEGFR TKI clinical trials have not provided robust support of their use in the clinic, there are promising results from prospective immunotherapy trials that are potentially practice-changing. Further investigation into how to optimally incorporate immune checkpoint inhibitors in the perioperative setting is ongoing and rapidly changing the management of locally advanced, resectable RCC. Whether ICIs are most efficacious in the form of adjuvant monotherapy, dual checkpoint inhibition, or combined neoadjuvant and adjuvant therapy remains to be discovered, and there are several ICI trials that aim to address these key questions. More importantly, targeting the ideal population for adjuvant therapy is an ongoing effort, and patient selection based on genomic biomarkers and various risk stratification algorithms will be crucial in determining candidacy for adjuvant therapy.

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Neoadjuvant Therapy in Locally Advanced Renal Cell Carcinoma

9

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Abbreviations

ccRCC	Clear cell renal cell carcinoma
CN	Cytoreductive nephrectomy
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DFS	Disease-free survival
HIF	Hypoxia inducible factor
HR	Hazard ratio
IFN-α	Interferon-alfa
irAE	Immune related adverse events
IVC	Inferior vena cava
M0	Non-metastatic disease
M1	Metastatic disease
mAb	Monoclonal antibody
mPFS	Median progression-free survival
mRCC	Metastatic renal cell carcinoma

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NCCN-FACT FKSI-19	National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index 19
NSS	Nephron-sparing surgery
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death receptor-1
PN	Partial nephrectomy
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RN	Radical nephrectomy
TKI	Tyrosine kinase inhibitor
VEGF	Vascular endothelial growth factor
VHL	von Hippel-Lindau

Introduction

In the USA in 2021, there are expected to be 76,080 new cases of kidney or renal pelvis cancer diagnosed with 13,780 deaths expected. Currently, the mainstay of management of early stage or locally advanced disease is surgery [1]. However, the advent of targeted therapeutics and immunotherapies for renal cell carcinoma has revolutionized the management of metastatic renal cell carcinoma (RCC) and led to long-term durable responses for some patients. As outcomes in the metastatic setting have improved with the introduction of these strategies, both as monotherapy and in combination, the concept of neoadjuvant therapy in the setting of locally advanced disease has gained traction as a potential path to allow for nephrectomy in those otherwise deemed unresectable, nephron-sparing surgery (NSS) in the form of partial nephrectomy (PN), and potentially long-term survival benefit. A common theme in this space is the repurposing of validated treatment options from metastatic disease as neoadjuvant therapy in locally advanced, non-metastatic disease. In this review, we summarize our current state of knowledge on neoadjuvant therapy in locally advanced RCC through the historical lens of the management of advanced disease.

The use of adjuvant therapy postnephrectomy for locally advanced tumors is also an area of active research; a complete characterization of this strategy for reducing the risk of disease recurrence is outside the scope of this review although we did incorporate studies that reported on adjuvant therapy *if* it was given in conjunction with a neoadjuvant component. While the goal of improving disease-free survival (DFS) and overall survival (OS) is shared between neoadjuvant and adjuvant approaches, treatment aims such as downsizing tumor thrombus, allowing for NSS, providing a direct, in vivo assessment of tumor response to systemic therapy, and improving surgical outcomes are unique to neoadjuvant therapy as are the safety

considerations for any therapy given in such close proximity to surgery. It is important to note that our knowledge on neoadjuvant therapies really stems from two populations of study including 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 therapy before a cytoreductive nephrectomy (CN) in the setting of distant metastases. To avoid confusion, it has been thoughtfully suggested that the term "neoadjuvant" refer only to those with M0 disease whereas therapy in those with M1 disease can more precisely be described as "pseudoneoadjuvant," all of which fall under the umbrella of presurgical therapy [2, 3]. While our focus is on neoadjuvant therapy in the curative-intent setting, we have also included relevant data on patients receiving pseudoneoadjuvant 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 [4, 5].

Targeted Therapy

Targeted Therapy in the Metastatic Setting

Tumor pathogenesis in clear cell RCC (ccRCC), which makes up as much as 85% of cases of RCC [6], is most often related to deletion, mutation or silencing of the von Hippel-Lindau (VHL) tumor suppressor gene, either through spontaneous deletion of chromosome 3p (on which VHL lies) or in autosomal dominant VHL disease [7]. When VHL is defective, this leads to the accumulation of hypoxia inducible factors (HIFs) which in turn induces the production of multiple factors implicated in RCC tumorigenesis including vascular endothelial growth factor (VEGF), a main driver of angiogenesis [8]. VEGF has been a major molecular target in the treatment of RCC in those with unresectable and metastatic disease.

The application of these agents in metastatic RCC (mRCC) began after the approval of the multi-tyrosine kinase inhibitor (TKI) sorafenib by the FDA in 2005 for this purpose [9]. Sunitinib, another multi-TKI active against VEGF, was approved by the FDA in January 2006 and became the mainstay of treatment of mRCC and comparison arm in trials of newer therapeutics for years to come [10]. This approval was based on the phase III trial of sunitinib compared to interferon-alfa (IFN-α) in 750 treatment-naïve patients which showed an objective response rate (ORR) of 31% vs. 6% ($P < 0.001$) and improvement in median progression-free survival (mPFS) of 11 vs. 5 months (hazard ratio [HR] 0.42, 95% confidence interval [CI] 0.32–0.54, $P < 0.001$). The multi-TKI pazopanib was initially approved in 2009 after it was shown to improve mPFS (9.2 vs. 4.2 months, HR 0.46, CI 0.34–0.62, $P < 0.0001$) compared to placebo in treatment naïve patients [11]. Motzer et al. (2013) later compared pazopanib to sunitinib in the phase III COMPARZ trial to determine the optimal first line agent and found pazopanib to be non-inferior to sunitinib with an improved side effect profile [12]. Also approved in 2009 was the combination of the antiangiogenic monoclonal antibody bevacizumab in

combination with IFN-a which showed an improved mPFS (8.5 vs. 5.2 months, CI 7.5–9.7, $P < 0.0001$) compared to IFN-a monotherapy [13]. Axitinib, another multi-TKI, was approved in early 2012 as a single agent in the second line setting based on the AXIS phase III trial that compared axitinib to sorafenib and showed improved mPFS (6.7 vs. 4.7 months, HR 0.665, CI 0.544–0.812, $P < 0.0001$) [14]. Lenvatinib was approved in combination with the mammalian target of rapamycin (mTOR) inhibitor everolimus in 2016 for patients having progressed on an anti-VEGF agent alone based on a phase II comparison of lenvatinib plus everolimus vs. lenvatinib vs. everolimus. This study showed improved mPFS of 14.6 months with the combination compared to 5.5 months with everolimus alone (HR 0.4, CI 0.24–0.68, $P = 0.0005$) and 7.4 months with lenvatinib alone, although the difference compared to the latter was not statistically significant (HR 0.66, CI 0.39–1.10, $P = 0.12$) [15]. Cabozantinib, an anti-VEGF2 agent with simultaneous activity against MET, AXL, and RET, is the only single-agent TKI currently recommended as a preferred regimen in the first line setting for poor/intermediate risk disease in the 2023 National Comprehensive Cancer Network guidelines [16, 17]. The second line approval came in 2016 after the METEOR trial but its first line approval stemmed from the CABOSUN trial which showed improved mPFS (8.2 vs. 5.6 months, HR 0.66, CI 0.46–0.95, $P = 0.012$) and ORR (33% vs. 12%) over sunitinib [18, 19]. Pazopanib, sunitinib, and sorafenib remain options in later lines of disease [17]. Most recently in March 2021, the anti-VEGF-1, -2, and -3 as well as c-kit and PDGFR inhibitor tivozanib was approved for the treatment of RCC progressive through at least 2 prior therapies based on the TIVO-3 trial in which tivozanib demonstrated a PFS of 5.6 months compared to 3.9 months with sorafenib (HR 0.73, CI 0.56–0.95, $p = 0.016$) [20].

Targeted Therapy as Monotherapy in the Neoadjuvant Setting

These advances in VEGF-directed therapy in the metastatic setting have predictably and somewhat sequentially led to the application of these agents in the neoadjuvant setting. The majority of published retrospective and prospective data available on neoadjuvant approaches involve the use of targeted therapy. The goals of preoperative therapy are several. These include conversion from unresectability to resectability, tumor downsizing to allow for NSS, and decreasing the level of inferior vena cava (IVC) tumor thrombi. Proponents of neoadjuvant therapy have argued that the above effects could lead to improved surgical outcomes due to less complex surgeries and potentially improved long-term survival due to the elimination of micrometastatic disease [2, 21]. The concerns about the use of neoadjuvant therapy have included a delay in definitive therapy that could potentially lead to local or systemic 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 [22]. The issue of highest concern is the potential for life-threatening adverse events from neoadjuvant therapies in

patients who may have been cured by surgery alone. We explore the safety profiles from data amassed to date below.

Tumor Downsizing to Allow for Nephrectomy on Bulky or Unresectable Primary Tumors

Outside of the minority of patients with metastatic disease treated with checkpoint inhibitor-based therapy that have a complete response to treatment, the ability to resect RCC provides the only opportunity for cure. Thus, there is great weight placed on the potential for converting a tumor from unresectable to resectable as deemed by an oncologic surgeon. Table 9.1 summarizes all prospective trials investigating neoadjuvant and pseudo-neoadjuvant therapy in patients with M0 or M1 disease, respectively. Although our focus is on the ability of neoadjuvant therapy to improve surgical outcomes in the curative intent setting, the effect of preoperative therapy on the in situ kidney in patients with metastatic disease still informs the feasibility of this approach; accordingly, responses according to Response Evaluation Criteria in Solid Tumors (RECIST) referenced here refer to the effect of therapy on the primary tumor rather than the sites of metastases in any studies involving patients with M1 disease.

As the first targeted agent available in the treatment of metastatic disease, sunitinib as a preoperative agent has been examined extensively [21, 22, 39–42]. Van der Veldt et al. (2008) published the first retrospective report of 17 patients with metastatic disease treated with sunitinib before nephrectomy with the focus on treatment effect on the primary tumor [39]. Three patients underwent CN who were initially felt to have an unresectable primary tumor due to liver invasion. Another retrospective investigation by Thomas et al. (2009) of neoadjuvant sunitinib in 19 patients with locally advanced or metastatic disease with primary tumor deemed unresectable showed that four patients were able to proceed to nephrectomy after median tumor size shrinkage of 24% [21]. A prospective trial by Rini et al. (2012) investigated the impact of 12 weeks of neoadjuvant sunitinib in patients with an unresectable primary tumor and found that 13 of the 28 evaluable patients (45%) met the primary endpoint of being able to undergo nephrectomy [27]. The median change in primary tumor diameter was −22% but this approach was much more successful in the patients with clear cell (−28%) vs. non-clear cell histology (+1.4%). Hellenthal et al. (2010) enrolled 20 patients into a single-arm trial of preoperative sunitinib in patients with cT1b-T3 disease regardless of nodal or metastatic status [23]. Seventeen of 20 patients (85%) had some tumor shrinkage after 2 months of therapy with a mean change in diameter of −11.8%. Bex et al. (2011) assessed the effect of preoperative sunitinib in patients with metastatic disease and noted a partial response (PR) in 1 of the 22 patients who were enrolled with an average change in primary tumor diameter of −9.6% (−40 to +16) [25]. The response in the primary tumor to preoperative therapy predicted long-term outcomes and the authors proposed this endpoint as a potential litmus test for determining the judicious use of cytoreductive nephrectomy in metastatic disease. Powles et al. (2011) conducted two separate

Table 9.1 Prospective studies of neoadjuvant/preoperative targeted therapy ± immunotherapy

Authors (year)	Drug	*N*	Dose	Duration (range)	Inclusion criteria	M1 (%)	Histology	Median tumor diameter change in cm (range)	Median percentage of tumor size change	RECIST response in primary tumor			RN	PN
										PR	SD	PD		
										n (%)	*n* (%)	*n* (%)		
Hellenthal et al. (2011) [23]	Sunitinib	20	37.5 mg	90 days	T1b-3, Nany, Many	20	Clear cell (cc)	N/A	−11.8 (−27 to +11)	1 (5)	19 (95)	0 (0)	12	8
Silberstein et al. (2011) [24]	Sunitnib	12[a]	50 mg[b]	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 (28.6)	10 (71.4)	0 (0)	0	14
Bex et al. (2011) [25]	Sunitinib	22	50 mg[b]	12 weeks	M1 with resectable, asymptomatic primary tumor	100	cc	N/A	−9.5% (−36 to +2.2)	1 (4.5)	21 (95.5)	0 (0)	18	0
Powles et al. (2011) [26]	Sunitinib	52	50 mg[b]	12–18 weeks[c]	M1	100	cc	N/A	−12% (−35 to +8)	3 (6.1)	46 (93.9)	0 (0)	37	0
Rini et al. (2012) [27]	Sunitinib	30	50 mg[d]	Median 18 weeks (6–120 weeks)	Unresectable primary (large tumor size, bulky LAD, venous thrombosis or proximity to vital structures)	63	All (76% cc)	−1.2	−22% (−100 to +13)	7 (25)	21 (75)	0 (0)	4	9

Cowey et al. (2010) [28]	Sorafenib	30	400 mg BID	33 days (8–59)	≥cT2, Nany, Many	43	All (70% cc)	−0.8 (−2.6 to +1.0)	−9.6 (−40 to +16)	2 (6.6)	28 (93.3)	0 (0)	30	0
Hatiboglu et al. (2017) [29]	Sorafenib	9[e]	400 mg BID[f]	4 weeks	cT1-3, N0, M0	0	All (83% cc)	−1.0	−29 (−61.1 to +4.9)	4 (44.4)	5 (55.5)	0 (0)	7	5
Karam et al. (2014) [30]	Axitinib	24	5 mg BID	12 weeks	cT2-3b, N0, M0	0	cc	−3.1	−28.3 (−5.3 to −42.9)	11 (47.8)	12 (52.2)	0 (0)	19	5
Lebacle et al. (2019) [31]	Axitinib	18	5 mg BID[g]	60 days (58–114)	cT2aN0M0	0	cc	−1.2 (−2.5 to −0.4)	−17.1 (−4.8 to −29.4)	4 (23.5)	13 (76.5)	0 (0)	1	16[h]
Hakimi et al. (2023) [32] PADRES	Axitinib	26	5 mg BID	8 weeks	RENAL nephrometry score 10–12 and cT1b-cT3M0	0	cc	−1.4	Unknown	9 (34.6)	17 (65.4)	0 (0)	7	19
Bex et al. (2022) [33]	Axitinib + avelumab	40	Axitinib: 5 mg BID Avelumab: 10 mg/kg q2w	12 weeks	cT1b-4cN0-1 M0, grades 3–4	0	cc	N/A	−20 (0 to −43.5)	12 (30)	N/A	N/A	40 (unknown RN vs. PN)	
Bilen et al. (2022) [34]	Cabozantinib	16	60 mg daily	12 weeks	≥cT3Nx or TanyN+[i]	0	cc	N/A	−24 (−6 to −45)	5 (31.2)	11 (68.8)	0 (0)	13	2

(continued)

Table 9.1 (continued)

Authors (year)	Drug	*N*	Dose	Duration (range)	Inclusion criteria	M1 (%)	Histology	Median tumor diameter change in cm (range)	Median percentage of tumor size change	RECIST response in primary tumor			RN	PN
										PR	SD	PD		
										n (%)	*n* (%)	*n* (%)		
Powles et al. (2016) [35]	Pazopanib	104	800 mg daily	13 weeks (11–14)	M1	100	cc	−1.7	−14.1 (−21.1 to −1.1)	8 (8.4)	86 (90.5)[j]	1 (1.1)	65	0
Rini et al. (2015) [36]	Pazopanib	25[k]	800 mg daily	8–16 weeks	≤cT3N0M0	0	cc	−1.8	−26 (−43% to +2)	10 (35.7)	18 (64.3)	0	8	20[l]
Bevcizumab ± erlotinib [37]	Bevacizumab ± erlotinib	50[m]	Bev: 10 mg/kg q14 days Erlotinib: 15 mg daily[n]	8 weeks	M1	100	cc	N/A	N/A	0 (0)	44 (97.8)	1 (2.2)	42	0
Karam et al. (2021) [38]	Sitravatinib + nivolumab	20	Sitravitinib: 120 or 80 mg oral capsule daily[o] Nivolumab: 24 mg IV q2w	Sitravatinib: 6–8 weeks[e] Nivolumab: 4–6 weeks	Locally advanced, candidate for curative intent nephrectomy	0	cc	N/A	N/A	2 (11.7)	N/A	N/A	20 (unknown RN vs. PN)	

[a] 12 patients, 14 kidneys (2 with bilateral tumors)
[b] 6-week cycle (4 weeks on, 2 weeks off)
[c] 19 patients received two cycles (12 weeks), 33 received 3 cycles (18 weeks)

[d] Continuous daily dosing
[e] 12 patients in the study, only 9 received sorafenib
[f] Versus placebo
[g] Allowed for uptitration to 7–10
[h] 1 patient did not undergo nephrectomy
[i] Or deemed unresectable by the surgeon
[j] Extrapolated from Figure 2
[k] 25 patients, 28 tumors (3 with bilateral tumors)
[l] 17 patients, 20 tumors (3 with bilateral tumors)
[m] 45 patients available for analysis via RECIST
[n] Only the first 23 patients received concurrent erlotinib until amendment removed it from the protocol
[o] Dose-limiting toxicities (DLTs) led to dose de-escalation, 7 pts received 120 mg daily sitra and 13 pts received 80 mg daily

studies of 2 or 3 cycles of preoperative sunitinib in 52 patients with mRCC and published the results as a composite [26]. All but three patients had stable disease (SD) at the end of therapy; the three achieved a PR prior to nephrectomy. The change in primary tumor diameter ranged from 35% shrinkage to 8% growth (median −12%). Notably none of the patients enrolled in these trials of sunitinib experienced PD during the treatment period.

Cowey et al. (2010) investigated sorafenib as a preoperative agent in their "window of opportunity" trial in which sorafenib was administered between 8 and 59 days prior to surgery (median 33 days) to 30 patients with cT2 or higher tumors with or without more distant disease [28]. Two patients achieved a PR although 23 (77%) had experienced some tumor size decrease. Amidst a sea of single-arm, phase II trials in the neoadjuvant space, Hatiboglu et al. (2017) conducted a small but randomized trial in which 12 patients with cT1-3N0M0 RCC received either 28 days of sorafenib or placebo prior to nephrectomy [29]. Patients who received sorafenib had a median 29% decrease in their tumor diameter; the three patients who received placebo had growth in their tumor of 0%, 1.9%, and 24.2% over the 4 weeks. The R.E.N.A.L. nephrometry score is a standardized, imaging-based classification system for the complexity of renal masses that incorporates the variables of radius, exophytic vs. endophytic quality, proximity to the collecting system, sinus or hilum, anterior or posterior location, and location relative to polar lines [43]. The authors scored the tumors of the subjects pre- and post-sorafenib, finding a reduction in complexity in 4 of the 9 patients in the sorafenib group and none who received placebo.

Axitinib, pazopanib, and bevacizumab have also been investigated in the neoadjuvant setting. Karam et al. (2014) prospectively assessed the objective response rate (ORR) of 12 weeks of axitinib in 24 patients with localized ccRCC without nodal metastases, noting an ORR of 45.8% and median tumor reduction of 28.3% compared to baseline with all patients experiencing some degree of tumor size decrease while on therapy [30]. Lebacle et al. (2019) in their prospective examination of axitinib reported a 17% decrease in median tumor diameter in the 18 patients treated and a median decrease in R.E.N.A.L. nephrometry score from 11 to 10 ($P = 0.03$) [31].

Powles et al. (2016) conducted a prospective study of preoperative pazopanib therapy in patients with clear cell RCC (ccRCC) with metastases; in terms of effect on the primary tumor, there was a median reduction in the size of the primary tumor by 14.4% (1.4–21.1) although one of 95 evaluable patients had PD per RECIST in the in situ kidney while receiving therapy [35]. This is one of the only trials accompanied by biomarker analysis. VEGFR2, c-MET, and VHL expression all decreased after pazopanib therapy while PD-L1 expression increased and CD8 expression decreased; none correlated with response or long-term survival. Jonasch et al. (2009) assessed the feasibility of preoperative bevacizumab with or without erlotinib in patients with advanced ccRCC who were felt to be candidates for cytoreductive nephrectomy [37]. Erlotinib, an EGFR inhibitor, was abandoned midway through the study in a protocol amendment due to contemporary data showing no benefit to the combination [44]. Of the 50 patients on study, 42 (84%) of them ultimately underwent CN; of those who did not, six experienced disease progression

and were unable to undergo CN while one came off study due to bevacizumab-induced hypertension and another died of causes other than RCC. Twenty-three of 45 evaluable patients (52%) had some degree of tumor shrinkage; 3 patients (7%) had between 20 and 30% tumor reduction and no patients achieved PR. One patient (2%) experienced progressive disease (PD) between baseline and first imaging.

Cabozantinib is the only antiangiogenic TKI recommended for single agent first-line use in patients with intermediate and poor risk metastatic disease, having outperformed sunitinib in the CABOSUN trial, [19, 45] but we have only fledgling data on its use in the neoadjuvant setting [46–48]. Roy et al. (2020) treated 2 patients deemed initially unresectable with neoadjuvant cabozantinib: one with a 10 cm renal tumor and adjacent retroperitoneal lymphadenopathy and another with remote history of resected RCC with new oligometastastic disease in the head of the pancreas adjacent to the superior mesenteric vessels [46]. The tumors decreased in size by 3.6 cm and 4.9 cm, respectively, and both patients were able to undergo resection with no evidence of disease at the time of analysis. Bilen et al. (2021) reported on a patient with locally advanced and unresectable RCC who was initiated on cabozantinib and after 11 months of therapy experienced a 44.2% reduction in primary tumor from 21.7 to 12.1 cm. More importantly, the tumor regressed from vital anatomic structures, making a complete resection achievable and allowing for a R0 resection and long-term survival [47]. Initial results from CABOPRE, a phase II trial of cabozantinib preoperatively in patients with mRCC slated to undergo CN, were presented at the European Society of Medical Oncology (ESMO) Congress 2021 [49]. Cabozantinib induced an overall (total body) PR in 26.7%, SD in 66.7% and demonstrated PD in 6.7% of patients; we are lacking reported data on the RECIST response in the primary tumor. Eleven of the 18 patients proceeded to CN. A phase II trial of neoadjuvant cabozantinib in high-risk localized RCC (≥T3Nx or TanyN+) (NCT04022343) enrolled 16 patients, all of whom received 12 weeks of intended therapy before surgery. A total of five patients (31.2%) experienced PR while 11 (68.7%) had SD; median reduction in size of the primary tumor was 24% (6–45%). Fifteen patients (93.8%) proceeded to surgery without delay after a 4-week drug wash-out; one declined surgery due to personal reasons and continued with systemic therapy. No postoperative complications related to drug were noted. One patient felt to be unresectable at the time of study entry was made resectable and 2 were converted from planned radical to partial nephrectomy (Tables 9.1 and 9.2) [34].

Taken together, the composite analysis of these prospective trials yields a median tumor diameter decrease of 9.5–29% depending on the trial and agent. Although modest, this decrease did allow for nephrectomy in some patients that were previously deemed unresectable. It is worth noting that the bounds of surgical resectability varies depending on the experience of the surgeon, tumor complexity encapsuled by the R.E.N.A.L. score better than absolute tumor diameter, and the volume of the treating center, all of which are difficult to standardize even in prospective trials. It is also critical to note that while the majority of our trials report the rate of partial response or the median tumor size decrease within each trial, the most important goal of neoadjuvant surgery is tumor regression away from vital structures such as

Table 9.2 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*	Inclusion criteria		Primary endpoint	Status
							Stage	Histology		
TKI monotherapy										
NCT01263769	II	Single	Axitinib	5 mg BID	12 weeks	40	cT2-T3b, N0,[a] M0	Clear cell (cc)[b]	ORR[c]	Active, not recruiting
NCT03438708	II	Single	Axitinib	5 mg BID	8–10 weeks	50	TanyNanyM0 with strong indication for PN	cc	% reduction of longest diameter of tumor in mm	Unknown (preliminary data presented 2022) [32]
PADRES									ORR; effect on tumor morphometry R.E.N.A.L score; feasibility of partial nephrectomy	
NCT04022343	II	Single	Cabozantinib	60 mg daily	12 weeks	17	≥cT3Nx or TanyN+[d]	cc[e]	ORR	Active, not recruiting [34]
Immunotherapy or immunotherapy combinations										
NCT04393350	II	Single	Lenvatinib and pembrolizumab	Len:18 mg daily Pembro: 200 mg q3w	12 weeks	17	≥cT3Nx or TanyN+[d]	cc[e]	ORR	Recruiting
NCT03680521	II	Single	Sitravatinib and nivolumab	Sitravitinib: Oral capsule daily	Sitravatinib: 6–8 weeks[f]	25	Locally advanced RCC	cc	ORR and point in treatment course of ORR	Unknown (preliminary data presented 2021) [38]
				Nivolumab: 24 mg IV q2w	Nivolumab: 4–6 weeks					

NCT04385654	II	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)	Unknown
NCT04118855	II	Single	Toripalimab and axitinib	Toripalimab: 240 mg IV q3w Axitinib: 5 mg PO BID	Up to 12 weeks	30	T2-3, N0, M0	cc	ORR	Completed
NCT04995016 PANDORA	II	Single	Pembrolizumab and axitinib	Pembrolizumab: 200 mg q3w Axitinib: 5 mg PO BID	12 weeks	18	≥T3Nx or TanyN+[d]	cc[e]	MPR	Not yet recruiting
NCT05024318 NAPSTER	II	Randomized	Stereotactic ablative radiotherapy (SABR) (arm 1) vs. pembrolizumab and SABR (arm 2)	Arm 1: SABR: 42 Gy in three fractions Arm 2: Pembrolizumab 200 mg q3w × 3 cycles with SABR administered after cycle 1	9 weeks	26	T1b-3, N0-1, M0 or low volume M1 planned for nephrectomy	cc[g]	MPR	Recruiting

(continued)

Table 9.2 (continued)

NCT trial #	Phase	Arm	Drug	Dose	Duration	Goal *N*	Inclusion criteria		Primary endpoint	Status
							Stage	Histology		
NCT03341845 NeoAvAx	II	Single	Axitinib and avelumab	Axitinib: 5 mg BID Avelumab: 10 mg/kg q2w	12 weeks	40	cT1b-4cN0-1 M0, grades 3–4	cc	Rate of PR	Recruiting (preliminary data presented 2022) [33]
NCT04028245 SPARC-1	II	Single	Spartalizumab and canakinumab	Spartalizumab: 400 mg q4w Canakinumab: 300 mg q4w	8 weeks	14	≥ cT2Nx or cTanyN1	cc[b]	% of patients who proceed to radical nephrectomy[h]	Recruiting
NCT03055013 PROSPER RCC	III	Randomized	Perioperative nivolumab vs. observation	Nivolumab: 480 mg every 14 days × 1 neoadjuvant cycle and up to 9 cycles adjuvantly	7–28 days preoperatively, up to 9 months postoperatively	766	≥ cT2Nx or cTanyN1	Any	EFS	Active, not recruiting
NCT04322955 Cyto-KIK	II	Single arm	Preoperative nivolumab and cabozantinib	Nivolumab: 480 mg every 4 weeks Cabozantinib: 40 mg daily	Up to 12 weeks[i]	45	Metastatic	cc[e]	CR rate	Recruiting

[a] RP LNs ≤ 2cm considered N0
[b] Clear cell must be predominant histology (>50%)
[c] ORR: objective response rate
[d] Or deemed unresectable by surgeon
[e] Clear cell component
[f] Begins 2 weeks prior to nivolumab
[g] Including rhabdoid and sarcomatoid differentiation
[h] Feasibility if >85% proceed
[i] First 3–6 subjects will hold cabo for 3 weeks prior to surgery; if safe, all other will hold for only 2 weeks prior

the superior mesenteric artery or proximal pancreas to then allow for successful and safe resection. Unfortunately, this is a difficult endpoint to quantify in clinical trial and may be best represented by the rate of radical nephrectomy or partial nephrectomy in those initially deemed unresectable or requiring radical nephrectomy, respectively.

Tumor Downsizing to Allow for Nephron Sparing Surgery

Another potential application of neoadjuvant therapy is to facilitate nephron-sparing surgery (partial nephrectomy). In current surgical guidelines, PN is the treatment of choice for any tumors less than 4 cm (T1a) and preferred over radical nephrectomy (RN) in any tumor <7 cm (T1b). Tumors larger than 7 cm are typically managed with RN [50]. The opportunity to downsize a tumor to allow for PN is a particularly attractive option in patients at risk for requiring dialysis after a RN due to preexisting renal dysfunction, bilateral renal tumors, or a solitary kidney at baseline. Of note, synchronous or metachronous bilateral renal tumors occurs in roughly up to 6% of patients diagnosed with RCC so it is an uncommon but not insignificant event requiring effective and safe clinical management [51, 52]. Lane et al. (2015) conducted a retrospective investigation of the effect of presurgical sunitinib on a highly selected population of 72 patients (with 78 affected kidneys) who had tumors potentially amenable to partial nephrectomy pending modest shrinkage and increased distance from hilar structures [41]. Tumor downsizing occurred in 65 tumors (83%) with RECIST partial response achieved in 15 tumors (19%). Partial nephrectomy was made possible in 49 kidneys (63%); when broken down by stage at diagnosis, that equated to 100%, 86%, 65%, and 60% of cT1a, cT1b, cT2, and cT3 tumors, respectively. Those with lymph node involvement, non-clear cell histology and high nuclear grade were less likely to be made eligible for PN with neoadjuvant therapy. McDonald et al. (2018) retrospectively assessed 125 consecutive patients who underwent partial nephrectomy for RCC and divided the cohort into two groups: those who had received neoadjuvant sunitinib at the discretion of the treating physician or in clinical trial for bulky tumors or tumor location that precluded PN compared to those who did not receive neoadjuvant therapy. After a median of two cycles of sunitinib, there was a decrease in median tumor size from 7.2 to 5.8 cm, a median reduction of 19.5% (P = 0.012) and a decrease in R.E.N.A.L nephrometry score from 11 to 9 (P = 0.001) [53]. The authors noted no differences in surgical outcomes between the two groups including median ischemia time, transfusion rate, or high-grade 30-day complication rate. Notably, both approaches resulted in similar renal function preservation including median 12-month postoperative GFR (60.9 vs. 59.6 ml/min/1.73 m^2, P = 0.639) and median change in GFR (6.4 vs. 6.1 ml/min/1.73m^2, P = 0.534). Taken together, these retrospective studies suggested a potential role for preoperative targeted therapy in facilitating PN.

In terms of prospective evaluation of neoadjuvant therapy in facilitating PN, Silberstein et al. (2010) assessed the impact of sunitinib on 14 affected kidneys in 12 patients with an indication for an attempt at this approach such as bilateral tumors

or a unilateral tumor in the setting of renal insufficiency [24]. Prior to surgery, all tumors displaced the collecting system and 71% abutted or invaded the hilar vasculature. After 12 weeks of sunitinib, 28.6% met RECIST criteria for PR in the primary tumor and all decreased in size with, most importantly, shrinkage away from the central kidney structures. PN was achievable in all cases with the pre- and postoperative glomerular filtration rate 57.7 vs. 53.4 mL/min/1.73 m^2, respectively; zero patients required dialysis after 2 years of follow-up. In the previously mentioned prospective trial of neoadjuvant axitinib by Lebacle et al. (2019), the primary endpoint in the 18 patients enrolled with cT2aN0M0 tumors was decreased tumor size to less than 7 cm (the equivalent of ≤cT1b) to allow for PN [31]. All tumors decreased in size, 12 of which downsized to ≤7 cm, and 16 patients were ultimately able to undergo PN (including the 12 with successful downstaging of their tumors). We discussed the anti-tumor activity of neoadjuvant axitinib as described by Karam et al. (2014) but the authors also conducted an interesting substudy in which pre- and post-axitinib CT scans from 22 patients were reviewed by five blinded urologic oncologists [30, 54]. All 5 of these investigators agreed that of the 8 patients who were felt to require RN pretreatment, only 5 required this approach posttreatment. Similarly, only PN was felt to be appropriate for just 3 patients before treatment and all 5 reviewed felt 10 patients now had PN as a surgical option [54]. The odds of PN feasibility were 22.8 times higher after axitinib compared to prior but there were lower rates of intra-observer agreement in cases of higher complexity compared to moderate complexity tumors. This was an unprecedented finding. In a trial of neoadjuvant pazopanib, Rini et al. (2015) enrolled 25 patients with localized ccRCC who met any of the following criteria: expected GFR < 30 ml/min/1.73 m^2 after nephrectomy (due to baseline CKD, solitary kidney or bilateral tumors) or complex expected PN due to tumor complexity (R.E.N.A.L. score 10–12) or proximity to hilar vasculature [36]. Thirteen of these 25 patients (52%) were felt to be unsuitable for PN at the time of enrollment and after a median of 8 weeks of pazopanib therapy, 6 of these 13 patients (46%) were downsized appropriately to be treated with PN. These data suggest that neoadjuvant targeted therapy may facilitate PN by decreasing tumor complexity, reducing tumor volume, and increasing distance from hilar and vascular structures without significantly affecting surgical outcomes. Due to subjectivity in decision making regarding the feasibility of partial nephrectomy, prospective, randomized data is sorely needed to determine whether neoadjuvant therapy should have a definite role in facilitating NSS in those with contraindications to radical nephrectomy. Interim data from the single-arm, phase II PADRES trial (NCT03438708) of axitinib in patients with complex localized RCC (RENAL nephrometry score 10–12 and cT1b-cT3M0) with an indication for NSS was recently presented. Of the 26 patients that enrolled, 19 (73.1%) had ≥ clinical T3a tumors and this number decreased to 17 (65.4%) posttreatment; PR rate was 34.6%. Ultimately, 73.1% pursued successful NSS with a 23.1% postsurgical complication rate (Clavien-Dindo III–IV) and a median decrease in GFR by 14.7% (Tables 9.1 and 9.2) [32].

Downstaging Inferior Vena Cava Thrombus

Extension of the tumor into the adjacent venous system is present in up to 5–10% of all RCC cases [55, 56]. Tumor 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% [57]. The current standard of care for this patient population is aggressive surgery including radical nephrectomy and tumor thrombectomy which is a more complex surgery. There are various staging systems used to classify IVC thrombi, one of which is the Mayo staging system: level 0, I, II, III, and IV correspond to extension into the renal vein, the IVC no more than 2 cm above the renal vein, the IVC more than 2 cm above the renal vein but not to the hepatic vein, above the hepatic vein but not to the diaphragm and into the supradiaphragmatic IVC or right atrium, respectively [55]. It is controversial whether the degree of tumor thrombus extension affects long-term prognosis but there is consensus on the correlation between increasing level of tumor thrombus and rates of perioperative and postoperative complications [58–60]. This is in part due to higher level thrombi requiring mobilization of the IVC, the liver, and for level IV thrombi, median sternotomy, cardiopulmonary bypass, and potential hypothermic circulatory arrest intraoperatively [61]. Understandably, there is interest in the effect of neoadjuvant therapy on reducing the degree of tumor thrombus extension and treating associated micrometastatic disease, thus improving both surgical outcomes and potentially long-term survival for these patients.

A series of case reports documenting the downsizing effects of targeted therapy on tumor thrombi preoperatively first demonstrated proof-of-concept and paved the way for larger, retrospective analyses [22, 62–71]. Cost et al. (2011) explored the use of neoadjuvant targeted therapy on IVC tumor thrombi in a retrospective study of 25 patients with IVC thrombi to above the level of the renal vein [72]. Patients were treated with sunitinib [12], bevacizumab [9], temsirolimus [3] and sorafenib [1]. Following treatment, 21 (84%) patients had stable IVC tumor thrombus level, while three (12%) patients experienced a decrease in thrombus level (one level IV to level III, one level III to level II, and one level II to 0). All three of these patients received sunitinib, of note, although the magnitude of tumor level thrombus did not differ significantly between the cohorts of patients who received sunitinib vs. other agents. In addition, the median decrease in thrombus cephalad height was less than 1 cm. Only one (4%) patient had a change in surgical plan because of thrombus level reduction. Bigot et al. (2014) retrospectively reviewed 14 patients with IVC thrombi who received neoadjuvant targeted therapy (sunitinib or sorafenib) before nephrectomy [73]. Thrombus reduction was noted in six cases (43%), stability in six cases (43%) and increase in two cases (14%). One patient (7%) had a downstage of thrombus level, but surgical approach was not impacted. The median thrombus height change was 0 cm (range −6 to +5 cm). The authors of both analyses concluded that there was minimal impact of neoadjuvant targeted therapy on IVC thrombi in a clinically meaningful way.

In contrast, Field et al. (2019) conducted a retrospective comparative analysis of 53 patients with RCC and associated IVC thrombi who received preoperative

sunitinib [19] and those who did not [34, 74]. There was no significant difference in thrombus level between the two groups at baseline. Of the 19 patients that received sunitinib, IVC tumor level was downstaged in 8 patients (42.1%) and stable in 10 (52.6%). The median thrombus size decreased by 1.3 cm. Surgical approach and outcomes were similar between the two groups although there was a significance decrease in perioperative blood loss in those who received neoadjuvant therapy. The authors noted a statistically significant improvement in cancer-specific survival (OR 3.25, $P = 0.021$) in multivariate analysis and longer median cancer-specific survival in Kaplan-Meier analysis (72 vs. 38 months, $P = 0.023$) in those who received neoadjuvant sunitinib. However, the authors included M0 and M1 patients in their analysis and these survival differences were in part due to the M1 patients and their poorer outcomes overall. Horn et al. (2012) assessed the impact of preoperative sunitinib on five patients with RCC associated with a level III or IV thrombus [75]. In 4 of the 5 patients there was tumor shrinkage in the craniocaudal direction (−10%, −20%, −18%, and −26%, respectively) and one of these patients was then able to undergo an abdominal approach for surgery and avoid median sternotomy with cardiopulmonary bypass. All surgeries were performed without major peri- and postsurgical complications including issues with wound healing. In a review of 18 patients receiving neoadjuvant sorafenib, Zhang et al. (2014) found that among the 5 patients who had IVC thrombus, 2 patients with grade II thrombi were converted to grade I and 0, respectively, 2 patients with grade III thrombi were converted to grade II and the fifth patient with grade IV tumor thrombus did not change grades but had improvement from right atrial to diaphragmatic level [76].

These studies on the impact of targeted therapy on tumor thrombi incorporate retrospective data, typically in the form of case series or small comparative cohorts, which is informative but of limited utility in actually informing clinical decision making and knowledge regarding long-term outcomes. Data from NAXIVA, the only prospective trial to date specifically investigating the impact of neoadjuvant therapy on the extent of tumor thrombus in patients with metastatic and non-metastatic RCC, were recently presented [77]. In this single-arm, phase II, multicenter trial, 20 patients with ccRCC, either M1 or M0, complicated by tumor thrombi received 8 weeks of axitinib prior to radical nephrectomy and thrombectomy. Venous thrombus length was reduced in 75% of patients; this included a reduction in Mayo level in 37.5% of patients with IVC thrombus and 25% of those with thrombus to the right ventricle. A less invasive surgery was possible in 41.2% of evaluable patients. Notably, non-responders to therapy had a lower baseline microvessel density, higher Ki67, and immunosuppressed T cell phenotype in common. Prospective, randomized data on the impact of tumor thrombus regression on surgical approach and most importantly long-term survival outcomes are needed.

Safety of Anti-VEGF Agents Preoperatively

A major concern about the use of targeted, antiangiogenic agents in the preoperative setting is the potential for delay of surgery or surgical complications due to side effects. As a class of therapeutics, agents such as sunitinib, sorafenib, axitinib, pazopanib, and cabozantinib can be difficult to tolerate and commonly reported adverse events including anorexia, fatigue, stomatitis, nausea, diarrhea, rash, and hand-foot syndrome [78]. Because of their antiangiogenic properties, these drugs as well as bevacizumab may cause hypertension, proteinuria, and extremely relevant when administered in the presurgical setting, impaired wound healing [78].

Harshman et al. (2013) conducted a retrospective review of 14 patients who underwent nephrectomy or metastasectomy after presurgical sunitinib or sorafenib and compared them to a reference cohort of 73 patients who underwent the same without any preoperative systemic therapy [79]. Patients received a median of 17 weeks (range 3–48) of therapy and median time between discontinuation and surgery was 2 weeks (range 1–9). In the neoadjuvant therapy group, the rate of perioperative bleeding was 36% and 7% of patients experienced wound healing issues. However, when compared to the case control cohort, the use of preoperative therapy did not significantly increase the rate of operative complications in univariate (UVA) and multivariate analyses (MVA) and in MVA, it was the size of the tumor and open surgical approach that predicted that associated with increased perioperative bleeding. Notably, there were more (86% vs. 58%, $P = 0.01$) and more severe (median grade 3 vs. grade 1, $P = 0.0001$) intraoperative adhesions of the primary tumor to surrounding structures in patients who received preoperative therapy, highlighting a potential worrisome surgical issue after neoadjuvant targeted therapy.

Margulis et al. (2008) conducted a case control study assessing surgical and perioperative complications in 44 patients treated with neoadjuvant sunitinib, sorafenib, or bevacizumab compared to 58 patients who underwent up-front surgery [80]. Subjects in the preoperative therapy cohort received a median of 6.0 (3.2–15.2), 7.7 (2.4–14.3), and 6.6 (3.0–15.4) months of therapy with a median presurgical hold of therapy of 20 [1–119], 11 [6–97], and 40 [28–75] days for sunitinib, sorafenib, and bevacizumab, respectively. A total of 39 complications occurred within 30 days of surgery and were split evenly between the two cohorts: 17 in the targeted therapy group and 16 in the control group ($P = 0.287$). When complications were broken down into categories of re-exploration, readmission, thromboembolic, cardiovascular, pulmonary, gastrointestinal, infectious or incision related, the non-significance persisted. In addition, the occurrence of complications was also not associated with the type of therapy or time between therapy discontinuation and surgery.

Chapin et al. (2015) evaluated postoperative complications after the use of preoperative targeted therapies in 70 patients with mRCC prior to cytoreductive nephrectomy compared to 103 who underwent immediate surgery [81]. The patients receiving presurgical systemic therapy did not have a higher rate of overall (65.7% vs. 51.4%; $P = 0.085$) or severe complications (≥ grade 3 per the Clavien-Dindo classification system). However, preoperative therapy was significantly associated with late postoperative complications (≥90 days after surgery) and with having a

wound complication (odds ratio 4.14, 95% CI 1.6–10.6, $P = 0.003$), even when controlling for other potential culprits such as body mass index (BMI), diabetes, tobacco abuse, and baseline nodal status in MVA. The authors postulated that their study may have detected impacts of preoperative targeted therapy not noted previously because of their use of a standardized system of classifying postoperative complications (Clavien-Dindo) and their extended, 12-month duration of surveillance for complications [81–83]. It is worth noting that the authors included a composite of multiple targeted therapies including tyrosine kinase inhibitors like sunitinib and sorafenib as well as bevacizumab, the latter of which has an extended half-life related to the two former (20 days vs. 40–60 h for sunitinib and 24–48 h with sorafenib). However, bevacizumab was not an independent predictor of overall surgical complications in this cohort. This contrasts with Jonasch et al. (2009) who found a 20.9% incidence of wound dehiscence or delayed wound healing in their prospective trial of preoperative bevacizumab with or without erlotinib in patients with clear cell mRCC compared to a rate of 2% in historical controls ($P < 0.001$) [37].

Prospective trials like that led by Jonasch et al. (2009) lend perspective on the impact of preoperative therapy on safety and surgical outcomes in a more controlled setting than retrospective analyses. The measures of efficacy in all reported prospective clinical trials of preoperative therapy is reported in Table 9.1 but reporting on safety endpoints within each trial was variable. In their study of preoperative sunitinib, Powles et al. (2011) noted CTCAE grade 3 toxicity in 30% of patients while receiving systemic therapy and 21% of patients required a dose reduction; no patients experienced a delay of surgery due to their toxicities [26]. Delayed wound healing (Clavien grade I) occurred in 16% of patients and bleeding requiring urgent reintervention was noted in one patient (Clavien grade IIIb). In another study of preoperative sunitinib, Hellenthal et al. (2010) noted that although only 60% of patients were able to complete the full 3 months of planned therapy at full dose due to toxicity, surgery was not delayed by these adverse events and there were no wound healing complications noted in the cohort [23]. Rini et al. (2012) investigated presurgical sunitinib as well and after a median time off sunitinib before surgery of 14 days (range 7–66), there were no thromboembolic or wound healing complications of nephrectomy [27]. Cowey et al. (2010) noted that a collection of fairly characteristic adverse events caused by preoperative sorafenib in a mixed cohort of patients with M0 and M1 RCC which led to dose reduction in 33% of patients but no delays of surgery [28]. Although one patient had superficial wound breakdown postoperatively on day 8 that was managed conservatively, there were no instances of delayed wound healing, wound dehiscence or excessive bleeding noted and this was despite a relatively short median 3 days between end of therapy and surgical intervention. Hatiboglu et al. (2017) found that in their study of neoadjuvant sorafenib, only 25% of patients completed the intended 28 days of therapy at the initial 800 mg dose [29]. Six patients (50%) experienced grade 3 toxicities requiring dose reduction but surgery proceeded without delay and there were no wound healing complications incurred. Karam et al. (2014) found that 22 of 24 patients were able to complete the planned 12 weeks of neoadjuvant axitinib; of the two patients who did not, one stopped at 11 weeks due to grade 3 transaminitis and

thrombocytopenia while the other experienced acute kidney injury at 7 weeks requiring discontinuation of therapy and subsequent early surgery [30]. One patient (4.2%) experienced superficial wound dehiscence after surgery which healed in short order with conservative measures alone. The two grade 3 postsurgical complications were chylous ascites requiring percutaneous drainage (grade IIIa) and concern for postoperative bleeding requiring same-day re-exploration during which no active bleeding was noted. These authors are in the minority in their inclusion of patient-reported assessment of quality of life while on therapy and found that the Functional Assessment of Cancer Therapy—Kidney Cancer Symptom Index Version 15 (FKSI-15) indeed showed worse quality of life by week 7 of preoperative therapy compared to baseline ($P < 0.0001$) but that these changes normalized by week 19 ($P = 0.3344$) at which time they were finished with neoadjuvant therapy and status postsurgery. In their study of preoperative pazopanib in patients with mRCC, Powles et al. (2016) noted that 25% of patients required a dose reduction prior to surgery and 3.8% of the 104 patients studied discontinued therapy due to toxicity [35]. Only 63% of the participants ended up proceeding to their planned cytoreductive nephrectomy. In some cases, this was due to progression of disease but in others it was related to patient preference or being found unfit for surgery; the authors concede that there is potential that pazopanib therapy and incurred adverse events may have contributed to this decision making. Among those who proceeded to nephrectomy, there was a 22% incidence of surgical complications including bleeding in 8% and delayed wound healing in 6%.

Another concern about the use of neoadjuvant therapy in the curative setting is the potential for progressive disease despite therapy that leads to worse surgical outcomes or long-term survival. In the prospective trials which incorporated M0 patients (Table 9.1), there were no cases of progressive disease. There were two patients with metastatic disease at baseline who experienced progressive disease in their primary tumor while receiving bevacizumab and pazopanib, respectively [35, 37]. In preclinical modeling, rebound angiogenesis after withdrawal of VEGF receptor blockade can lead to rapid tumor revascularization [84]. In an examination of 62 patients with mRCC who achieved clinical benefit with antiangiogenic agents in clinical trial prior to planned therapy interruption, 23 patients (37%) experienced disease progression on their first scan and this clinical outcome was associated with an increased risk of death in MVA (HR 5.56, 95% CI 2.29–13.5, $P < 0.01$) [85]. While these findings are concerning, they are specific to treatment with TKI therapy and not immunotherapy and it is difficult to extrapolate these outcomes to the non-metastatic setting given inherent differences in tumor biology in metastatic vs. non-metastatic disease.

In summary, the concern about the delay of surgery and risk of 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 typically resolve with dose interruption and/or reduction and there are no reports of surgical delay as a result of these adverse events [3]. While there are reports of delayed wound healing, these were noted in small, single-arm, phase II 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

Immunotherapy With and Without Targeted Therapy in the Metastatic Setting

Other than molecularly targeted agents such as anti-VEGF and anti-mTOR agents as discussed in detail above, the other primary therapeutic approach to RCC lies in immunotherapy with checkpoint inhibitors. Such an approach evolved after observation that the removal of the primary kidney lesion could result in spontaneous regression of metastatic lesions and demonstration that immunologic agents such as interferon gamma-1b and interleukin-2 (IL-2) had the capacity to induce relatively rare but durable complete responses in RCC [86–88]. The goal of checkpoint inhibition is to counteract the T cell exhaustion that happens at the tumor bed by disrupting the immunosuppressive interactions between programmed cell death receptor-1 (PD-1), a coinhibitory molecule expressed on activated B and T cells, and its ligand (PD-L1) on the tumor cell surface [89]. RCC also relatively highly expresses PD-L1 at tumor bed, also making it an attractive target for checkpoint inhibition [90]. Nivolumab, an anti-PD-1 agent, was initially approved as monotherapy based on the CHECKMATE025 phase III trial in which patients with advanced ccRCC were randomized to receive either nivolumab or everolimus. The mOS was 25.0 vs. 19.6 months, respectively (HR 0.73, 95% CI 0.57–0.93, $P = 0.002$) [91]. The combination of nivolumab with ipilimumab, a humanized monoclonal antibody (mAb) against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), was initially investigated in the phase III CHECKMATE214 trial and in the recently updated data from 5-years follow-up, the combination was found to have a median OS of 55.7 months compared to 38.4 months (HR 0.72, 95% CI 0.62–0.85, $p < 0.0001$) in those who received sunitinib [92, 93]. This combination remains the sole immunotherapy-only based approach used in the first line management of mRCC [17].

There is well-accepted that the combination of immunotherapy with targeted therapy has the potential to create synergy in its anti-tumor effect. Angiogenesis as a mechanism for tumor development requires immune tolerance and the antiangiogenic effects of targeted therapy in RCC may also be immunomodulatory; pazopanib, axitinib, and sunitinib have all been shown to reduce the in vitro expression of myeloid-derived suppressive macrophages and pazopanib was shown to increase the expression of PD-1 and PD-L1, potentially increasing concurrent or future responsiveness to checkpoint inhibition [94, 95]. Lenvatinib combined with an anti-PD-1 antibody in a preclinical mouse model showed an increased response rate compared to either single treatment. In addition, lenvatinib led to decreased monocyte/macrophage populations and increased CD8+ T cells at the tumor in a

hepatocellular carcinoma model regardless of the presence of the anti-PD-1 agent [96]. With these preclinical mechanisms in mind, the phase III KEYNOTE426 trial investigated pembrolizumab plus axitinib compared to sunitinib in metastatic ccRCC. Updated results after a minimum of 23 months of follow up were presented in 2020 and showed that the mOS was not reached in the pembrolizumab and axitinib cohort vs. 35.7 months in the sunitinib group (HR 0.68, 95% CI 0.55–0.85, $P < 0.001$); this appears to be driven by the survival benefit seen in those with IMDC intermediate and poor risk disease (HR 0.63, 95% CI 0.50–0.81) rather than those with favorable risk disease (HR 1.06, 95% CI 0.60–1.86) [97, 98]. It was approved by the Food and Drug Administration (FDA) for all risk categories in April 2019. Since that time, several other TKI/immunotherapy combinations have been approved in the metastatic space. Axitinib plus the anti PD-L1 agent avelumab was approved in May 2019 based on the phase III JAVELIN Renal 101 trial showing improved the median PFS in all patients regardless of PD-L1 expression compared to sunitinib (13.8 vs. 8.4 months, HR 0.69, 95% CI 0.56–0.84, $P < 0.001$) [99]. This combination does not have a category 1 recommendation as first or later line therapy in the NCCN guidelines as there was no significant difference in OS between the two regimens. Cabozantinib and nivolumab together were approved in January 2021 based on the CHECKMATE-9ER phase III trial which randomized treatment-naïve patients to this regimen compared to sunitinib and boasted an improved PFS, OS, and ORR with the combination therapy. The mOS was not reached in either arm but the HR was 0.60 (95% CI 0.40–0.89) with an ORR of 55.7% with the combination vs. 27.1% with sunitinib alone [100]. Most recently, the combination of lenvatinib and pembrolizumab were approved based on the phase III CLEAR trial in which patients received either lenvatinib with pembrolizumab, lenvatinib with everolimus, or sunitinib. Unsurprisingly, the combination therapy led to improved median overall survival compared to sunitinib although the mOS was not reached in either group (HR 0.66, 95% CI 0.49–0.88, $P = 0.005$) [101]. The ORR with lenvatinib and pembrolizumab in combination was 71% vs. 31% in the sunitinib arm with a corresponding complete response rate of 16% and 4%, respectively. While there was a PFS benefit noted for lenvatinib plus everolimus over sunitinib, there was no significant increase in OS with this combination. Based on these data, the combination of lenvatinib and pembrolizumab was approved in August 2021 for use across risk groups in the first line setting for mRCC. This approach utilizing a combination of immunotherapy and antiangiogenic mechanisms has come to dominant the metastatic space and given the potential for both rapid tumor response with the TKI and long-term durability with the immunotherapy component, it is no surprise that we now see these strategies being applied in the neoadjuvant setting.

Immunotherapy and Immunotherapy/TKI Combinations as Neoadjuvant Therapy

Just as the advent of checkpoint inhibitors changed the landscape of the management of metastatic disease in the last half decade, 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. The mechanism of action of neoadjuvant immunotherapy is the same as in metastatic disease, that is, via enhancement of anti-tumor immunity by allowing for the reactivation of exhausted and quiescent cytotoxic T cells. However, by administering the therapy before the primary tumor has been removed, the dominant source of tumor neoantigens capable of stimulating the expansion of T cell clones is present compared to a scenario when immunotherapy is administered in an adjuvant fashion [102, 103]. Based on the data in melanoma patients treated with checkpoint inhibitors, it is known that more diverse T cell clonality in the tumor microenvironment equates to improved responses to anti-PD-1 and anti-CTLA4 agents [104]. As a result of this extrapolation from melanoma, the goal of neoadjuvant immunotherapy is to harness this quality to induce a more robust immune response against micrometastatic disease and increase the likelihood of a curative surgery. To this end, preclinical data in a mouse breast cancer model showed improved CD8+ T cell anti-tumor responses when immunotherapy was administered in the neoadjuvant compared to the adjuvant setting [105]. We have ample data illustrating that the durability of responses to immunotherapy outflank those induced by chemotherapy and targeted therapy, a facet of these agents that makes their neoadjuvant application attractive [106]. Lastly, another potential benefit of preoperative immunotherapy lies in overcoming the immunosuppressive tumor microenvironment cultivated by surgery which may be conducive to the growth of micrometatases postoperatively [107, 108].

The application of immunotherapy in the neoadjuvant setting has lagged antiangiogenic agents, mirroring the history of therapy approvals in metastatic disease. Thus, only a handful of prospective studies have results available. Gorin et al. (2021) treated 15 patients with high-risk, non-metastatic, clear cell RCC (cT2-4, N0) with three doses of neoadjuvant nivolumab 3 mg/kg given every 2 weeks [109]. All patients completed the three doses and proceed to surgery within the prespecified 7-day window; the single intraoperative complication encountered was not felt to be related to nivolumab. Per RECIST version 1.1, all patients had stable disease at the time of surgery although one had a 15.7% reduction in their tumor diameter and evidence of an immune related pathologic response on the nephrectomy specimen characterized by tumor regression and immune cell infiltration. At median follow-up of 24.7 months, two patients had developed metastatic disease (one at 13 months and the other at 20 months postoperatively). Importantly, the quality of life was maintained during neoadjuvant therapy as measured by the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Kidney Symptom Index 19 (NCCN-FACT FKSI-19). Another pilot study by Carlo et al. (2021) of nivolumab was undertaken in 18 patients, this time given every 2 weeks for 4 doses [110]. 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 four doses due to grade 3 transaminitis and grade 2 arthralgias, respectively; another patient suffered grade 4 colitis 4 months after completion of therapy. A total of 819 patients with at least T2 or N+ disease were randomized to receive

perioperative nivolumab or placebo in the only phase III trial investigating perioperative immunotherapy, EA8143/PROSPER RCC. The study failed to reach its primary endpoint of recurrence-free survival, but of note only included 1 neoadjuvant dose (and nine adjuvant doses) [111]. Perioperative durvalumab (anti-PD-L1) with or without tremelimumab (anti-CTLA-4) was investigated in a multicohort phase Ib trial by Ornstein et al. (2020). 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 [112]. 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 are informative but given their relative novelty compared to the application of targeted therapy in this space, we 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 unable to be accommodated in the neoadjuvant setting; notably there was no signal regarding surgical complications across the studies.

We have limited data from prospective trials at this point as most studies are currently enrolling or active but not recruiting. A summary of ongoing trials investigating immunotherapy in the preoperative setting is found in Table 9.2. Just as combination 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. A trial borrowing from the CLEAR trial is currently enrolling patients with high-risk localized RCC (≥cT3Nx or TanyN+) in a trial of 12 weeks of neoadjuvant pembrolizumab plus lenvatinib prior to planned nephrectomy (NCT04393350) [101]. History repeats itself in the PANDORA trial of neoadjuvant pembrolizumab and axitinib in locally advanced RCC (NCT04995016), borrowing from KEYNOTE-426 in the metastatic setting [113, 114]. A post hoc analysis of patients enrolled in JAVELIN Renal 101 who had not undergone upfront CN showed that 34.5% of the 55 patients with renal target lesions who received avelumab and axitinib achieved a PR per RECIST in the primary tumor compared to only 9.7% of the 62 patients who received sunitinib and had their renal primary tumor in place [115]. The median time to PR was 4.4 months with avelumab and axitinib vs. 7.1 months with sunitinib. These data justified the NeoAvAx trial of avelumab and axitinib in the neoadjuvant setting. After 40 patients received 12 weeks of combination therapy, there was a PR rate of 30% with a median primary tumor decrease by 20% (0–43.5%). In those who experienced PR, 92% were disease-free after 23.5 months of follow-up; this number was only 68% in the entire cohort [33]. CHECKMATE-9ER spurned the currently enrolling CytoKIK trial of neoadjuvant cabozantinib and nivolumab (NCT04322955) [99,

100]. The combination of neoadjuvant sitravatinib, a multi-kinase targeting TAM receptors (TYRO3, AXL, MERTK), VEGFR2, c-Kit, and MET, and nivolumab in 20 patients with locally advanced disease induced only two PRs (11.7%); dose-limiting toxicities included 6 patients with grade 3 hypertension and 1 patient with grade 3 pulmonary embolism; surgery was delayed for one patient with immunotherapy-induced thyroiditis [38]. There has been a report of combined immunotherapy leading to complete regression of a level IV IVC tumor thrombus in a patient previously deemed unresectable such that she was able to undergo curative intent surgery [116]. Although we discussed the excessive immune-related events associated with neoadjuvant durvalumab and tremelimumab in combination, the hope for a tolerable and efficacy dual immunotherapy approach continues in the ongoing SPARC-1 trial of neoadjuvant IL-1β antagonist canakinumab combined with spartalizumab, a novel anti-PD-1 agent (NCT04028245) [117].

The combination of neoadjuvant immunotherapy with radiation therapy has been investigated in non-small cell lung cancer and melanoma and found to produce an improved anti-tumor response compared to either modality alone, potentially due to an amplified T cell response to tumor neoantigens unearthed after cell death from radiation therapy in the presence of checkpoint inhibition [118, 119]. We have very recent data in mRCC from Margulis et al. (2021) that neoadjuvant stereotactic radiation therapy is safe with early signs of efficacy and even the potential to induce an abscopal effect on metastatic sites of disease [120]. 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 tumor infiltrating lymphocytes and other immune cells.

Concerns have been raised regarding immunotherapy in the neoadjuvant setting. Although the potential for improved curative potential in localized disease looms large, our relative neophyte interest in neoadjuvant immunotherapy has not yet had the opportunity to provide data supporting this hypothesis. Next, although as clinicians we often describe immunotherapy as being more tolerable to the patient than targeted therapy or chemotherapy, the risk of irAEs is real; the most frequently reported irAEs are gastrointestinal, endocrine, and dermatologic while the most deadly include hepatotoxicity, neurotoxicity, cardiotoxicity, and pulmonary toxicity [121]. Although our intel to date in RCC as well as other curable malignancies suggests that it is very rare, the potential for irAEs to delay surgery remains [109, 110, 112, 122, 123]. As cited above, nivolumab-induced thyroiditis led to a surgical delay in 1 of 20 patients treated with neoadjuvant sitravatinib and nivolumab [38]. Despite this instance, there is data to suggest that checkpoint inhibitors may be safe to continue through surgery without interruption although this is debated in clinical practice [124]. Of course, the risk of irAEs and surgical complications including wound healing issues increases when checkpoint inhibitors are combined with other immunotherapies or with targeted therapies, respectively. Another consideration regarding trial design going forward is the recent approval by the FDA of 1 year of adjuvant pembrolizumab in high risk, clear cell RCC after nephrectomy based on an improvement in 3-year DFS vs. placebo (77.3% vs. 68.1%, HR 0.68, 95% CI 0.53–0.87,

$P = 0.002$) in the KEYNOTE-564 trial [125]. While we have the data from S-TRAC previously showing an improvement in DFS with sunitinib over placebo, the lack of OS improvement and the expected but difficult-to-tolerate side effect profile have limited its implementation into routine clinical practice [126]. Pending data on the impact of pembrolizumab on OS from KEYNOTE-564 will determine whether DFS is a meaningful proxy clinical endpoint in this situation but its improved tolerability over sunitinib makes it a more attractive adjuvant option and trials investigating neoadjuvant therapy may have to consider either incorporating an adjuvant component or allowing for standard of care therapy with pembrolizumab.

Predicting Response to Neoadjuvant Therapy

One of the holy grails in the management of metastatic disease lies in finding an all-encompassing predictive biomarker of immunotherapy efficacy and such a tool capable of predicting response in the neoadjuvant setting would be extraordinarily helpful in shepherding patients with advanced localized disease toward neoadjuvant therapy or upfront surgery. The expression of PD-L1 on tumor and/or immune cells has been imperfect at best in metastatic disease. In the KEYNOTE-426 trial of upfront pembrolizumab and axitinib, the combination was superior to sunitinib in both response rate and long-term survival outcomes regardless of PD-L1 expression although when examining subgroups with PD-L1 ≥ 1 and <1, the hazard ratios for PFS (HR 0.62 [95% CI 0.47–0.80] vs. 0.87 [95% CI 0.62–1.23]) and OS (0.54 [95% CI 0.35–0.84] vs. 0.59 [95% CI 0.34–1.03]), respectively, suggest at least some benefit to high PD-L1 expression in this population [113]. In CHECKMATE-214, improved OS and ORR across PD-L1 expression levels was seen in patients with intermediate/poor risk disease in response to ipilimumab and nivolumab over sunitinib although the differences were more pronounced in the higher PD-L1 subgroups [92]. One of the drawbacks of the use of PD-L1 as a predictive biomarker in any malignancy is the heterogeneity in expression within a single tumor and multiple assays available with variable definitions of positivity [127]. Tumor mutational burden (TMB) has been investigated as a predictive biomarker but despite the widespread efficacy and use of immunotherapy in the management of RCC, it has a relatively low TMB at 1.1 mutations/Mb compared to other diseases like melanoma and lung cancer which having TMB consistently higher than 10 mutations/Mb [128]. The investigation of CD8+ tumor infiltrating lymphocytes (TIL) and T cell inflamed gene expression profiles as biomarkers of immunotherapy response in the metastatic setting is ongoing but not ready for clinical practice [129]. This complexity only increases when we add the variable of targeted therapy into combination regimens. Voss et al. (2018) found that in patients with mRCC receiving first-line targeted therapy, mutational status of BAP1, PBRM1 and TP53 was prognostic [130]. Building on this work, Hakimi et al. (2020) found that angiogenesis gene expression signature correlates with response to sunitinib and pazopanib [131]. Bex et al. (2022) noted on serial biopsies in patients who received neoadjuvant axitinib and avelumab that those who had

disease progression had a significantly lower CD8+ T cell density within their tumor at the end of treatment compared to those who did not progress [33]. The *predictive* capabilities of these biomarkers remains to be seen and their application to the neoadjuvant setting requires inference at present time. In addition, just as is the case in metastatic disease, the majority of completed and ongoing trials of neoadjuvant therapy exclude patients with non-clear cell RCC. These patients often have a more aggressive disease course and are exactly the type of patients for whom novel approaches to disease management such as neoadjuvant therapy should be considered. Taken together, we need thoughtful correlative studies embedded within these ongoing neoadjuvant trials to aid in our understanding of both immunotherapy and targeted therapy in the presurgical setting and to allow us to better refine our patient selection for neoadjuvant therapy.

Summary and Future Directions

Neoadjuvant therapy, either targeted or immunotherapy-based, is not currently standard-of-care in the management of locally advanced RCC. However, a neoadjuvant approach to large tumors or node-positive disease may have benefits over upfront surgery. While the absolute tumor diameter reduction seen across neoadjuvant trials is modest and will be unlikely to consistently convert unresectable to resectable disease, there may be a role for neoadjuvant therapy in facilitating nephron-sparing surgery and potentially reducing tumor thrombus level in patients. Although concerns about the safety of targeted therapy in the preoperative setting exist due to angiogenesis being a necessary component of wound healing, this complication has materialized infrequently to date and resolved with conservative management in all reported cases. Application of novel therapeutics in the neoadjuvant setting reflects but lags behind the establishment of new treatment paradigms in the metastatic space. The bulk of the published data on neoadjuvant therapy involves targeted therapy alone but immunotherapy combination approaches dominate the current clinical trial landscape. Early readouts from just a handful of neoadjuvant immunotherapy trials suggest relative safety of this approach but we lack long-term survival data. We await more data to further define the role of immunotherapy in the neoadjuvant management of localized disease with special attention on the safety and synergy of combination approaches. The field of perioperative therapy in RCC is rapidly changing and we look forward not only the efficacy data from these ongoing clinical trials of neoadjuvant treatment but also insight into predictive biomarkers, surgical safety and patient-centered outcomes such as tolerability and long-term survival.

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Part III

Advanced Disease

Prognostic Factors in Advanced Renal Cell Carcinoma

10

Kosuke Takemura, Vishal Navani, Daniel Y. C. Heng, and Matthew S. Ernst

History of Prognostic Approaches

Metastatic Renal Cell Carcinoma (mRCC) exhibits a wide spectrum of clinical presentations and the disease course for an individual patient can vary considerably. While some patients experience rapidly progressive disease, others follow a more indolent course during which watchful waiting over years may be warranted before intervention with systemic therapy. The breadth of mRCC clinical behavior reflects the underlying heterogeneity of disease biology. Clinical factors and biomarkers associated with overall survival (OS) have been examined extensively for prognostic value in the stratification of patients.

Over the last decade, efficacious systemic therapy options for mRCC have multiplied. The continued expansion of treatment options is accompanied by an increasing necessity for reliable risk stratification strategies to facilitate a risk-directed approach to therapy, patient counseling, and clinical trial design. Multivariable clinical risk models have been developed to meet this need (Table 10.1). As systemic therapy has evolved through cytokine, vascular endothelial growth factor (VEGF) targeted therapy (VEGF-TT), and combination Immuno-oncology (IO)-IO or IO-VEGF based regimens, it is important to consider the eras in which prognostic models were derived and validated (Table 10.2).

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Table 10.1 Components of validated prognostic models for metastatic renal cell carcinoma

Prognostic factor	MSKCC	CCF	French	IKCWG	IMDC
KPS or ECOG PS	×	×	×	×	×
LDH	×			×	
Hemoglobin	×		×		×
White blood cell count				×	
Neutrophil count		×	×		×
Platelet count		×			×
Serum calcium	×	×		×	×
Time from diagnosis to treatment	×	×		×	×
Previous radiation treatment				×	
Number of metastatic sites			×	×	
Liver metastasis			×		
Bone metastasis			×		
ALP			×	×	
Prior treatment				×	
ESR ≥ 100 or CRP ≥ 50			×		
Time from renal tumor to metastasis			×		

MSKCC Memorial Sloan Kettering Cancer Center, *CCF* Cleveland Clinic Foundation, *IKCWG* International Kidney Cancer Work Group, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium, *KPS* Karnofsky performance status, *ECOG PS* Eastern Cooperative Oncology Group performance status, *LDH* serum lactate dehydrogenase, *ALP* serum alkaline phosphatase, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

Cytokine Era

The Memorial Sloan-Kettering Cancer Center (MSKCC) risk model was developed in the era of cytokine-based therapy and is used in many clinical trials. The MSKCC model incorporates five clinical and laboratory variables independently predictive of poor OS: Karnofsky performance status (KPS) <80%, lactate dehydrogenase (LDH) >1.5× upper limit of normal (ULN), serum hemoglobin <lower limit of normal (LLN), corrected serum calcium >10 mg/dL, and time from initial diagnosis to systemic therapy initiation less than 1 year. The MSKCC model was validated in 463 previously untreated patients with advanced RCC who were treated with interferon-α [1]. Favorable, intermediate, and poor risk groups are defined by the presence of zero, one to two, or three or more risk factors, and corresponding to a median survival of 30, 14, and 5 months, respectively. External validation of the MSKCC model was carried out by Mekhail et al. with 353 patients receiving cytokine-based therapy between 1987 and 2002 [2]. Mekhail et al. corroborated the prognostic value of the five factors considered by the MSKCC model and proposed an extension of this model to include two additional independent predictors of reduced OS—prior treatment with radiotherapy and more than one metastatic site. Median survival for favorable, intermediate, and poor risk groups designated by the extended MSKCC model were 26, 14.4, and 7.3 months, respectively; however, the extended model was never widely adopted for clinical use.

The Groupe Français d'Immunothérapie developed a prognostic model (the French model) using a dataset of 782 patients treated with cytokine regimens. Independent predictors of shorter survival validated in the French model were: the

Table 10.2 Summary of median overall survival (in months) by validated prognostic models for metastatic renal cell carcinoma

Line	Therapy	Risk	MSKCC	IKCWG	IMDC
First	IPI NIVO	Favorable			NR
		Intermediate/ poor			48.1
	PEMBRO AXI	Favorable			72.3% (42-month survival)
		Intermediate/ poor			50.6% (42-month survival)
	NIVO CABO	Favorable			88.6% (15-month survival)
		Intermediate			80.6% (15-month survival)
		poor			76.6% (15-month survival)
	AVEL AXI	Favorable			NR
		Intermediate			30.0
		Poor			21.2
	PEMBRO LEN	All	NR		
	VEGF-TT	Favorable		26.9	43.2
		Intermediate		11.5	22.5
		Poor		4.2	7.8
	VEGFT-TT in Papillary RCC	Favorable			31.4
		Intermediate			16.1
		Poor			5.1
	Cytokine-therapy	Favorable	30		
		Intermediate	14		
		Poor	5		
Second	Nivolumab	Favorable			32.8
		Intermediate			25.0
		Poor			10.4
	VEGF-TT post-VEGF-TT	Favorable			35.8
		Intermediate			16.6
		Poor			5.4
	VEGF-TT post-cytokine therapy	Favorable	22[a]		
		Intermediate	11.9[a]		
		Poor	5.4[a]		
Third	VEGF-TT	Favorable			29.9
		Intermediate			15.5
		Poor			5.5

MSKCC Memorial Sloan Kettering Cancer Center, *IKCWG* International Kidney Cancer Working Group, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium, *IPI NIVO* ipilimumab plus nivolumab, *PEMBRO AXI* pembrolizumab plus axitinib, *NIVO CABO* nivolumab plus cabozantinib, *AVEL AXI* avelumab plus axitinib, *PEMBRO LEN* pembrolizumab plus Lenvatinib, *VEGF-TT* vascular endothelial growth factor targeted therapy, *NR* not yet reached, *White* based on phase III randomized controlled clinical trial; *light gray* based on prospective single arm study, *dark gray* based on retrospective real-world study

[a]Based on modified MSKCC criteria (KPS, Serum calcium, and hemoglobin only)

presence of biological signs of inflammation (erythrocyte sedimentation rate [ESR] ≥100 or C-reactive protein [CRP] ≥50), interval from the diagnosis of the initial renal tumor to the diagnosis of metastases <1 year, neutrophilia (neutrophil count >ULN), liver metastasis, bone metastasis, Eastern Cooperative Oncology Group (ECOG) performance status (PS) >0, more than one metastatic site, elevated alkaline phosphatase, and anemia (serum hemoglobin <LLN) [3]. In addition, The Groupe Français d'Immunothérapie identified four independent predictors of early treatment failure with cytokine therapy: presence of liver metastasis, interval from renal tumor diagnosis to metastases <1 year, more than one metastatic site, and neutrophilia. Early treatment failure was defined as disease progression within 3 months despite treatment with cytokine therapy. Patients with 3 or 4 of these predictors had greater than 80% risk of early treatment failure with cytokine therapy and are a subgroup associated with poor survival.

VEGF-TT Era

The changing era from cytokine-based therapy to targeted therapy with the advent of VEGF inhibitors spurred the development of novel prognostic risk models reflective of contemporary standards of care. The Cleveland Clinic Foundation (CCF) developed a prognostic risk model for progression free survival (PFS). A retrospective cohort of 120 patients at the Cleveland Clinic was identified and time from diagnosis to current treatment (<2 years), baseline platelet >300 K/μL, neutrophil count >4.5 K/μL, serum calcium <8.5 mg/dL or >10 mg/dL, and initial ECOG PS >0 were independent adverse predictors of PFS [4]. The presence of zero to one, two, or greater than two risk factors defined favorable, intermediate, and poor risk groups and corresponded with PFS of 20.1, 13.0, and 3.9 months, respectively.

The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk score was informed by the CCF model and stratifies patients based on six adverse predictors of OS. The IMDC is comprised of pooled data from multiple, international institutions. The IMDC model was established using 645 patients with mRCC who were treated with first-line VEGF targeted therapy or VEGF targeted therapy following first-line interferon [5]. External validation was accomplished with a separate cohort of 1028 patients with mRCC who had been treated with VEGF targeted therapy (sunitinib, sorafenib, bevacizumab, axitinib, or pazopanib) [6]. The IMDC model retains four of the five MSKCC criteria (KPS <80%, serum hemoglobin <LLN, corrected serum calcium >ULN, and time from initial diagnosis to systemic therapy of less than 1 year) and incorporates two additional independent predictors of poor OS: neutrophilia and thrombocytosis. Prognostic risk groups are defined in a similar fashion as the MSKCC model where favorable, intermediate, and poor risk are defined by the presence of zero, one to two, or three or more risk factors and corresponded with median survival of 43.2, 22.5, and 7.8 months [6]. The IMDC model has also been found to be prognostic in non-clear cell carcinoma. In 252 patients with papillary RCC (type I and II included) identified retrospectively, median OS was 31.4, 16.1, and 5.1 months for favorable,

intermediate, and poor risk patients, respectively [6]. The *C*-indices for OS with the three IMDC risk groups compared favorably (0.66 [95% CI, 0.60–0.68]) with the MSKCC model (0.64 [95% CI, 0.60–0.68]) in this cohort of patients with papillary RCC.

The International Kidney Cancer Working Group (IKCWG) developed a prognostic model with a database of pooled data from 3748 patients treated with cytokine-based therapy between 1975 and 2002 [7]. External validation was conducted using data from an IMDC cohort of 645 patients who had received VEGF targeted therapy. The nine prognostic factors identified were: prior cytokine therapy, performance status, number of metastatic sites, time from diagnosis to treatment, hemoglobin, white blood count, lactate dehydrogenase, alkaline phosphatase, and serum calcium. Favorable, intermediate, and poor risk groups were assigned according to the 25th and 75th percentiles of the distribution scores in the validation cohort and corresponded with median survivals of 26.9, 11.5, and 4.2 months, respectively.

The IMDC conducted a comparison of established prognostic models using the 1028 patient cohort in whom the IMDC prognostic model was externally validated [6]. The *C*-indices of the models compared were 0.664 (0.639–0.689) for IMDC, 0.657 (0.632–0.682) for MSKCC, 0.662 [0.636–0.687 for CCF, 0.668 (0.645–0.692) for IKCWG and 0.640 (0.614–0.665) for the French model in this population. This comparison illustrates similar concordance between models with the exception of the French model. Furthermore, the more complex IKCWG model, which requires mathematical transformation and more clinical factors did not appear to significantly enhance discriminatory power when dividing patients into three risk groups.

Prior to the era of VEGF targeted therapy, a paucity of effective second-line strategies meant there was little need for prognostic stratification of patients beyond first-line therapy because survival outcomes were universally poor. As more effective first- and second-line therapeutic options have been implemented, prognostication beyond the first-line has become increasingly relevant. Motzer and colleagues identified that three of the five MSKCC criteria were independent predictors of poor OS (KPS <80%, hemoglobin <LLN, and corrected serum calcium>ULN) in a cohort of 251 patients were eligible for second-line therapy after progression on cytokine therapy between 1975 and 2002 [8]. Risk groups were defined as favorable, intermediate, and poor based on the presence of zero, one to two, or three risk factors and corresponded with median OS of 22.0, 11.9, and 5.4 months, respectively.

The IMDC prognostic model has been validated in patients previously treated with first-line targeted therapy embarking on second-line therapy (with either VEGF targeted therapy or mammalian target of rapamycin (mTOR). In an IMDC cohort of 1218 patients receiving second-line therapy, OS for favorable, intermediate, and poor risk groups was 35.8, 16.6, and 5.4 months, respectively [9].

The IMDC model has also been validated in the third-line setting in a retrospective cohort of 4824 mRCC [10]. The third-line therapies received were a heterogeneous collection of VEGF and mTOR targeted therapy and median OS for favorable, intermediate, and poor risk groups was 29.9, 15.5, and 5.5 months, respectively.

Contemporary IO Era

The treatment of RCC has evolved rapidly in recent years and as new treatment paradigms are introduced, the impact on survival outcomes must be taken into consideration. Although no prognostic criteria have been derived and prospectively externally validated, data with updated survival has been published with existing models. There is continued utility of the IMDC model in risk stratification among patients treated with first-line combination therapies (IO-IO or IO-VEGF). In a retrospective, real-world study, 18-month OS for IO-IO, IO-VEGF, and VEGF targeted therapies were 90%, 77%, and 49% respectively [11].

Prognostic stratification is an important consideration for the development of clinical trials and, therefore, the study and regulatory approval of contemporary IO combination therapies have relied upon established prognostic models. The CHECKMATE-214 phase III clinical trial examining the immune checkpoint inhibitor combination ipilimumab and nivolumab (IPI NIVO) compared to sunitinib in the first-line setting stratified patients based on IMDC risk group prior to randomization [12]. IPI NIVO is indicated only in patients with intermediate or poor risk disease, but use in patients with favorable risk disease is questionable due to a lack of OS benefit demonstrated in this exploratory subgroup analysis. The median OS demonstrated in an update of the CHECKMATE 214 study was 48.1 months in a pooled analysis of intermediate and poor risk patients and not yet reached in the favorable risk group receiving IPI NIVO with a median follow-up for 55 months [13]. Similarly, the phase III clinical trial KEYNOTE-426 stratified patients according to IMDC criteria and this has led to regulatory approval of first-line pembrolizumab plus axitinib combination therapy in all risk groups [14]. In a recent update from KEYNOTE-426 with a median follow-up of 42.8 months, median OS had not been reached, but 42-month survival was 72.3% in favorable risk patients and 50.6% in a pooled analysis of intermediate and poor risk patients treated with pembrolizumab plus axitinib [15]. The CHECKMATE 9ER phase III clinical trial examined first-line nivolumab plus cabozantinib combination therapy compared to sunitinib and stratified patients according to IMDC risk group [16]. The clinical benefit of nivolumab plus cabozantinib was demonstrated in all risk groups. Median OS was not yet reached in a recent CHECKMATE 9ER update; however, 15-month OS was 88.6%, 80.8%, and 76.6% for favorable, intermediate, and poor risk patients, respectively, in the nivolumab plus cabozantinib arm with a median follow-up of 23.5 months [17]. The JAVELIN Renal 101 phase III clinical trial examined avelumab plus axitinib versus sunitinib and stratified patients according to the IMDC model [18]. Median OS was 30.0 and 21.2 months for intermediate and poor risk patients who received avelumab plus axitinib, respectively, and not yet reach for favorable risk patients [19]. The MSKCC model was utilized for prognostic stratification in the phase III CLEAR trial, which examined lenvatinib plus pembrolizumab or everolimus versus sunitinib [20]. Subgroup analyses of OS by risk group from the CLEAR trial has not yet been published.

In second-line and subsequent lines of therapy, nivolumab has been studied in the prospective multicenter NIVOREN GETUG AFU 26 trial, which examined

the safety and efficacy of nivolumab in patients who had failed one or two previous tyrosine kinase inhibitors [21]. For IMDC favorable, intermediate, and poor risk groups, median OS was 32.8, 25, and 10.4 months, respectively. The phase III clinical trial CHECKMATE 025 also examined nivolumab in the second- and third-line setting compared to everolimus. The median OS for the nivolumab arm was 25 months [22]. Currently, no prognostic models that have been validated in the mRCC second-line therapy setting following contemporary first-line IO-IO or IO-VEGF combination therapies. This is an unmet need which may be satisfied as real-world clinical and institutional experience grows with contemporary therapies.

While clinical trial designs of novel combination therapies have incorporated previously identified prognostic factors, there is a need for validation of current and updated prognostic indexes to reflect clinical practice and outcomes in the changing landscape. Current prognostic models have utilized clinical and laboratory factors; however, molecular, and genomic testing may provide further insights. Future initiatives will need to balance harnessing burgeoning technologic capabilities and prognostic accuracy with ease of use and accessibility.

Additional Prognostic Factors

In this section, we will discuss proposed clinical biomarkers, to complement the established clinical prognostic models described in the previous section. We will also briefly discuss some predictive markers, though this will be covered in a separate chapter of this book. There are a growing number of studies conducted to develop tools for more accurate prognostication of patients with mRCC, as summarized in Fig. 10.1. However, it is difficult to determine the most reliable biomarker applicable in every setting given that there are more than a dozen of Food and Drug Administration-approved therapeutic regimens for mRCC, and that each study generally includes patients receiving a variety of sequential therapies [23]. Nonetheless, there is a need to identify prognostic and predictive factors in the contemporary era of IO therapy.

We should note that new prognostic factors need to be incorporated into existing models to see how much discriminatory ability they can add since a substantial increase is required to justify complicating existing models and the increased cost of obtaining them. Hence, comparison of *C*-indices is required to assess the added value for improvement of model accuracy in validation studies.

Histologic Subtypes

While the majority of RCC is of the clear cell subtype (ccRCC), characterized by the *von Hippel-Lindau* (VHL) genetic alteration and subsequent hypoxia-induced factor pathway upregulation, up to a quarter of RCC does not have clear cell features and is classified as non-clear cell (nccRCC). These variant histology subtypes

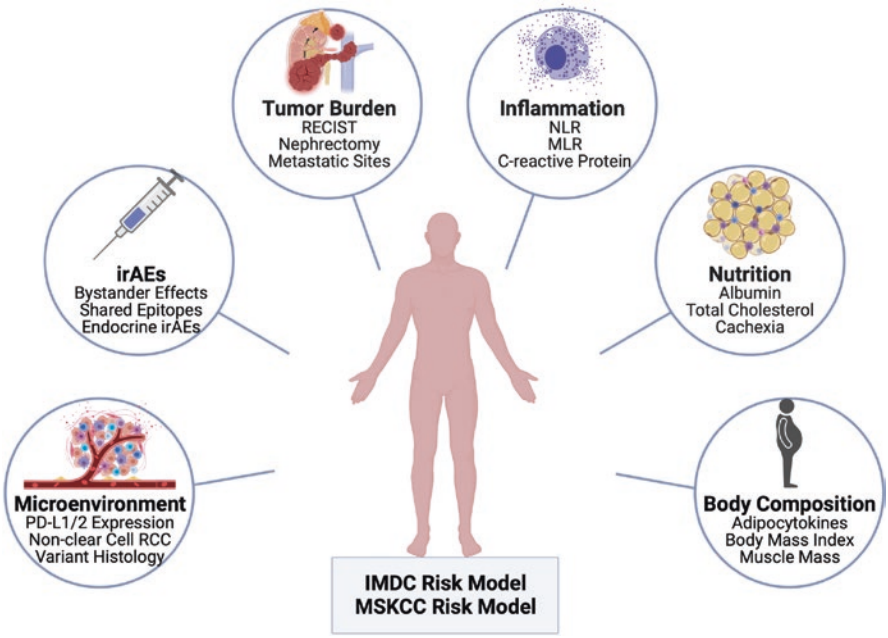

Fig. 10.1 Summary of Candidate Prognostic Factors Proposed to Date. (Created by Dr. K. Takemura with BioRender). *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium, *irAEs* immune-related adverse events, *MLR* monocyte-to-lymphocyte ratio, *MSKCC* Memorial Sloan Kettering Cancer Center, *NLR* neutrophil-to-lymphocyte ratio, *PD-L1/2* programmed death ligands 1/2, *RCC* renal cell carcinoma, *RECIST* response evaluation criteria in solid tumors

include papillary, chromophobe, collecting duct, renal medullary carcinomas, Xp11 translocation carcinomas, succinate dehydrogenase deficient renal carcinomas and a growing list of other rare subtypes [24]. These variants are generally associated with an aggressive phenotype, and decreased survival due to poor response to systemic therapy compared with the clear cell subtype [25]. Nonetheless, the treatment efficacy of immune checkpoint inhibitors (ICIs) in patients with nccRCC and/or rare histologic subtypes is still unclear since those patients are frequently excluded from randomized clinical trials.

According to results from the IMDC cohort by Yip et al., nccRCC was strongly associated with poor OS with a hazard ratio of 7.64 (95% CI 3.15–18.50; $P < 0.0001$) in the first-line treatment setting, yet the association was not significant in the second-line or later treatment settings [26]. Importantly, nccRCC generally features tumor-infiltrating mononuclear cells and the proportion of their programmed death ligand 1 (PD-L1) expression greatly varies in each subtype: 36% in chromophobe RCC, 60% in papillary RCC, 90% in Xp11.2 translocation RCC, and 100% in collecting duct carcinoma [27]. Therefore, nccRCC tumors are not a homogenous group and each histologic subtype is associated with distinct prognosis.

Immune-Related Adverse Events (irAEs)

Recent studies have observed a positive association between irAEs triggered by ICIs and favorable clinical outcomes, which can in part be explained by bystander effects from activated T cells reflecting an ICI-responsive immune system or by shared epitopes for tumor-associated antigens that cross-react with host organs [28]. There is a systematic review and meta-analysis in patients with various cancer types including mRCC, urothelial cancer, non-small cell lung cancer, and melanoma who were treated with anti-programmed death 1 (PD-1)/PD-L1 agents, which demonstrated that the presence of irAEs was significantly associated with improved objective response rate (ORR), OS, and PFS [29].

In terms of the site affected by irAEs, patients who experienced endocrine irAEs (e.g., thyroiditis) had significantly better oncologic outcomes than those who had non-endocrine irAEs [30]. This interesting phenomenon may be explained by underlying biologic mechanisms that ccRCC has particularly high rate of thyroid receptor mutations in their DNA-binding domains, and that impaired activity of thyroid hormone receptor is involved in the process of carcinogenesis in ccRCC [31, 32]. However, this mechanism is hypothetical and further laboratory and clinical research is warranted to investigate the biologic relationship between endocrine irAEs and clinical outcomes in patients with mRCC treated with ICIs.

Tumor Burden (TB) and Cytoreductive Nephrectomy

TB can easily be assessed from routine radiographic examinations by the sum of diameters of baseline target lesions according to the Response Evaluation Criteria in Solid Tumors guideline [33]. Iacovelli et al. previously demonstrated that TB, was an independent prognostic factor in the post-cytokine era [34].

In terms of the site of metastases from mRCC treated with targeted therapy, there were several studies supporting that specific metastatic sites were linked to poor survival including liver [35], central nervous system [36], and bone [37]. On the other hand, metastases to endocrine organs, such as the pancreas, thyroid, and adrenal gland, were associated with favorable OS according to the results from the IMDC [38]. However, reports on mRCC treated with ICIs are scarce thus far. Ishihara et al. evaluated 62 patients who received nivolumab plus ipilimumab for previously untreated mRCC and demonstrated that both TB and the presence of liver metastasis, were significantly and independently associated with shorter PFS [39]. Further studies for defining ideal threshold for baseline TB, the significance of upfront or differed nephrectomy, and detailed characterization of clinical courses of mRCC with different metastatic sites could help clinicians determine when they should initiate systemic therapy in asymptomatic patients.

Inflammatory and Nutritional Index

Pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 are considered to induce chronic inflammation and subsequent malnutrition involved in cancer progression [40]. From clinical perspectives, there is a growing number of inflammatory biomarkers proposed in patients with mRCC treated with ICI: to name a few, neutrophil-to-lymphocyte ratio (NLR) [41], monocyte-to-lymphocyte ratio (MLR) [42], and C-reactive protein (CRP) [42, 43]. More simply, Ueda, et al. reported that absolute lymphocyte count was more useful than other inflammatory biomarkers such as NLR, MLR, platelet-to-lymphocyte ratio, and CRP [44], as was the case with relative eosinophil change under nivolumab therapy [45].

In addition, several nutritional scoring systems such as modified Glasgow prognostic score, comprising albumin and CRP [46, 47], as well as Controlling Nutritional Status score, consisting of albumin, lymphocytes, and total cholesterol [48], have been proposed as useful risk stratification tools in patients with mRCC treated with ICIs. These scoring systems are considered to reflect impaired anabolism of the host during the development of cachexia even in a low-grade inflammation state [49, 50]. We should, however, be cautious about clinical application of these findings given that established risk models such as the IMDC criteria already contain colinear parameters (e.g., neutrophils and platelets) per se [5], making it unclear whether incorporation of inflammatory and nutritional index to the existing parameters in established models would improve their predictive accuracy.

Body Composition

Obesity is an established risk factor for kidney cancer incidence [51], yet it is also a favorable prognostic factor in patients with mRCC as validated in the IMDC cohort by Albiges et al. [52]. A plausible explanation for this phenomenon is that adiponectin receptor which interacts with adipocytokines can mediate tumor progression via inactivating glycogen synthase kinase-3β/β-catenin and phosphatidylinositol 3-kinase/Akt/nuclear factor-κB pathways in RCC cells at physiological conditions [53]. In clinical settings in the era of ICIs, there are a growing number of studies that support the "obesity paradox" by utilizing body mass index (BMI) as a simple indicator to assess body composition in patients with mRCC [54–56].

Importantly, whether this phenomenon is just an observation of a confounder of other established factors (e.g., the IMDC criteria) is still unclear as the multivariable results of these studies are conflicting. Nonetheless, body composition is an objective indicator of the baseline health status of patients with mRCC unlike PS assessment which has potential problems in objectivity with varied inter-rater agreement [57]. In addition, Martini et al. performed measurement of the density of skeletal muscle, subcutaneous fat, inter-muscular fat, and visceral fat from computed tomography scans prior to ICIs initiation contributed to a better risk stratification in patients with mRCC than BMI and the IMDC criteria [58]. However, radiographic

assessment of muscle/fat mass has the problem in simplicity and thus more convenient tools for body composition measurement are desirable.

Molecular Biomarkers

Despite noted therapeutic advances, treatment resistance remains inevitable [59] and patients remain underserved due to our inability to achieve a granular understanding of the distinct clonal populations at work. Unlike other advanced solid organ malignancies [60–62], a clinically accessible, molecular classification of metastatic ccRCC (mccRCC) remains an unmet medical need. We aim in this section to outline the current state of the art regarding prognostic and predictive biomarkers in mccRCC and potential future directions for this field, as summarized in Fig. 10.2. Currently, all biomarker defined molecular approaches to disease classification in mccRCC remain purely in the research setting, with none ready for clinical prime time.

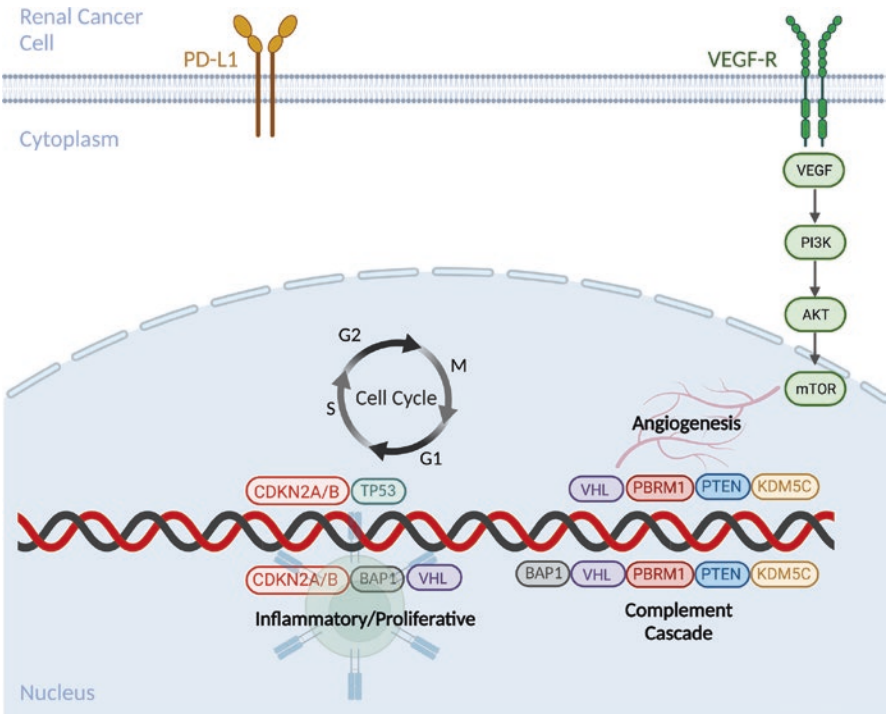

Fig. 10.2 Molecular Prognostic Biomarkers of Interest in ccRCC. (Created by Dr. B. Thankey with BioRender). *BAP1* ubiquitin carboxyl-terminal hydrolase BAP1, *CDKN* cyclin dependent kinase inhibitor, *mTOR* mammalian target of rapamycin, *PI3K* phosphoinositide 3-kinase, *PD-L1* programmed death ligand 1, *PTEN* phosphatase and tensin homolog, *VEGF* vascular endothelial growth factor, *VEGFR* vascular endothelial growth factor receptor, *VHL* Von Hippel–Lindau

PD-1 and PD-L1/2

PD-1 has two ligands, PD-L1 and PD-L2, both of which play an inhibitory role in T cell activation by PD-1 [63]. High PD-1 and PD-L1 expression has been reported to be associated with adverse features including larger tumor size, higher nuclear grade, necrosis, sarcomatoid transformation, c-MET expression, and VEGF expression, while high PD-L2 is similarly associated with c-MET expression and VEGF expression, both associated with poor prognosis in patients with mRCC [64, 65].

On the other hand, there are a relatively small number of studies that investigated PD-L2 expression. Lu et al. compared the expression of PD-L1 and PD-L2 with clinicopathological parameters and revealed that overexpression of PD-L1 and PD-L2 among RCC patients ranged from 6.0 to 70.4% and from 22.4 to 66.2%, respectively, and that PD-L2 possessed a weak prognostic value compared with PD-L1 [66]. We should note that immunohistochemical techniques have been used extensively in these studies; however, there is non-negligible heterogeneity among the definition of cut points, intensity, sample age, tissue quality, intra and intertumoral heterogeneity, and primary antibodies utilized [66]. Therefore, a standardized protocol for the interpretation of PD-L1/2 expression is required for future validation studies.

PBRM1 and BAP1

Initial work on single gene hotspots has focused on PBRM1 and BAP1, both key to chromatin remodeling and the subsequent epigenetic regulation of cell proliferation [67]. It is notable that literature regarding the clonal evolution mccRCC implies distinct evolutionary routes with early PBRM1 loss leading to low grade, well differentiated, highly vascularized angiogenesis dependent tumors and contrastingly BAP1 loss leading to highly proliferative and immune inflamed malignancy [68]. Though this may be a somewhat reductive interpretation, these single genes have been well-characterized in this context. PBRM1 has shown prognostic rather than predictive potential. These mutations are common truncal events, present across all populations of malignant cells when identified [69]. Loss of function of PBRM1 is associated with improved time to treatment failure with VEGFR inhibitors [70] and improved PFS and OS in patients treated with anti-PD-1 or doublet ICIs, compared to patients with intact gene expression [71].

Other critical tumor suppressor genes such as BAP1 have shown inferior PFS and OS in patients treated with the VEGFR inhibitor monotherapy pazopanib in the COMPARZ trial. This led to integration of this gene, alongside the ubiquitous TP53, into the MSKCC scoring criteria to create a composite risk score, involving clinical and genomic stratification. Subsequent model discriminatory ability for prediction of OS, improved, with a *C*-index rising from 0.595 (95% CI 0.557–0.634) to 0.637 (95% CI 0.595–0.679) [72]. This suggests independent prognostic value of these genes in patients treated with VEGFR inhibitors. However, the relevance of BAP1 in mCCRCC in the ICIs era remains to be delineated [73].

Molecular Subtypes

Moving to broader, multi-omics approaches, initial smaller datasets identified an inflammatory, immune-suppressed tumor microenvironment, with upregulated inhibitory PD-L1 and PD-L2 expression on transcriptomic analysis. Unsurprisingly, prior to the widespread use of ICIs, patients with these tumors responded poorly to sunitinib, with a median PFS of 8 months and median OS of only 14 months [74]. This subset, termed ccrcc4 was found to be exclusively IMDC intermediate and poor risk only [75]. Contrastingly, a molecular subtype ccrcc2, favoring a pro-angiogenic signature, was overrepresented in favorable risk disease (77% versus 41%; $P = 0.002$) and experienced improved survival with single agent sunitinib, compared to the other molecular groups ccrcc1 and ccrcc3. The 35 gene panel utilized in this initial unsupervised transcriptomic work has been critical in BIONIKK, the first prospective, genomically matched mccRCC trial.

A larger dataset from the IMmotion151 study appreciated increased resolution of the potential molecular subtypes in this disease. Despite not meeting the primary efficacy endpoint, the IMmotion151 [76] trial has proven a rich source of correlative multi-omic biomarker data, in an attempt to characterize molecularly defined, predictive subgroups [77]. Transcriptomic analysis of 823 (90%) randomized patients, treated with bevacizumab and atezolizumab versus suntinib, identified distinct molecular subtypes, termed clusters. Gene expression signatures first noted in the phase 2 IMmotion 150 [78] trial parsed patients into seven clusters, based on genomic and transcriptomic enrichment for angiogenic, stromal, complement, T-effector, cell cycle, metabolic and small nucleolar RNA (epigenetic) [79] pathways. Clusters enriched for angiogenesis: "angiogenic/stromal (cluster no.1)" and "angiogenic (no.2)," and "complement/omega-oxidation (no.3)" including VEGFR related genes had similar, favorable survival outcomes with both arms, regardless of whether VEGFR antagonism was via VEGFR inhibitors with sunitinib or a monoclonal antibody approach with bevacizumab, plus atezolizumab. Though these clusters had a higher incidence of MSKCC favorable risk patients compared to others outlined, they remained predominantly populated by the broad intermediate risk group, suggesting a potential way forward for integration of clinical and molecular risk stratification.

Upregulation of immune critical T-effector/JAK/STAT/Interferon-α and γ genes, in the clusters termed "T-effector/Proliferative (no.4)" (HR 0.52 95% CI 0.33–0.82) and "Proliferative (no.5)" (HR = 0.47 95% CI 0.27–0.82) exhibited a clear favorable PFS outcome with atezolizumab plus bevacizumab compared to sunitinibA modifiable, anti-tumor checkpoint blockade potentiated immune response was identified in these clusters, with inferior outcomes experienced with sunitinib alone. There identification of a biologically plausible mechanism and parsing of patients into a potentially "immune-sensitive" cohort has led to the development of the OPTIC trial, a phase II study that aims to select the most appropriate first-line combination therapy for patients based on their RNA sequence defined biological cluster [80]. A highly treatment resistant subgroup, "stromal/proliferative (no.6)" had poor mPFS (at most 6.8 months with atezolizumab/bevacizumab). DNA alterations in this cluster are frequently TP53, VHL and CDKN2A/B alongside a high incidence of MSKCC poor clinical risk and likely represent a treatment resistant phenotype.

Relating back to clinically utilized criteria, such as the MSKCC and IMDC, poor risk patients were seen in clusters 1, 2, and 3, but the majority remained intermediate risk. Cox regression looking at each of the seven identified clusters, including MSKCC and IMDC clinical risk group and PD-L1 expression immunohistochemistry showed that the clinical benefit seen in clusters retains independent association with survival, suggesting a path forward for clinical integration of this work.

Future Perspective

Though promising advances have been made in the molecular understanding of mRCC, there remain many unanswered questions regarding the integration of single genes or multi-omic signatures into modern risk criteria. Molecular biomarker approaches are time consuming, cost-prohibitive for the majority of clinicians and patients, and have a long turnaround time. Until robust clinical data is accompanied by streamlined workflows and accessibility, they will remain unfortunately firmly entrenched in the research setting. Furthermore, future trial design based on careful assimilation of clinical risk scores and molecular signatures, with subsequent randomization based on these approaches is required prior to routine clinical use for prognosis and therapy selection. Until that point, the field has much work to do to understand the clonal diversity that exists between different patients mRCC and indeed the multiple clonal populations that likely exist within each patient.

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Predictive Biomarkers in Advanced Renal Cell Carcinoma

11

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Introduction

Though the definition of a biomarkers can vary, they are broadly considered quantifiable characteristics of biological processes that have the potential to influence or predict disease outcomes and treatment responses [1]. In the current era of precision and personalized medicine, biomarkers have become quite common in both the clinical and research setting. However, unlike in other genitourinary malignancies such as prostate, bladder, and testis cancer, biomarkers for renal cell carcinoma (RCC) have historically had a limited use. Indeed, a recent analysis of genomic sequencing data from over 750 RCC tumors found a low prevalence of targetable alterations compared to other malignancy types [2]. Such findings have contributed to the lack of clinically meaningful biomarkers for patients with RCC.

For patients with RCC, the assessment of recurrence risk and response to treatments is largely based on clinical and pathologic features. Various systems have been developed which take into account these factors and offer clinicians and patients with prognostic information, such as the Memorial Sloan Kettering Cancer Center (MSKCC) recurrence nomogram, MSKCC risk score, and International Metastatic RCC Database Consortium (IMDC) risk score for patients with advanced disease [3]. Although useful, such tools rely on variables such as tumor grade, tumor

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necrosis, and performance status which may be subject to inter-observer variability and might not account for individual tumor biology [4].

The advent of novel systemic therapies in the past two decades has caused a paradigm shift in the treatment of advanced and metastatic RCC and has brought upon a renewed focus on the usage of biomarkers. Immune checkpoint inhibitors are now an integral component to the therapeutic armamentarium for this disease process and are often used in combination with other targeted systemic therapies [5]. Despite these advances, survival for patients is still relatively poor. The plethora of treatment choices and an unpredictable disease course with variable responses to these treatments make optimal therapeutic pathways elusive. Thus, there has been a focused effort to identify biomarkers to aid in this endeavor.

This chapter will address the current landscape of predictive biomarkers for advanced RCC. As will be discussed, the scope of work that has been done on this topic is quite broad from histopathologic, to genomic, to microbiome-related biomarkers. While many of the undermentioned topics are investigational and do not yet have any widespread clinical utility, they provide a useful framework for which further research can be based.

PD-L1

The relationship between the body's immune system and cancer development has been well studied. In 2018, the research of James P. Allison and Tasuku Honjo won a Nobel Prize in Physiology or Medicine for elucidating a method by which cancer cells may evade the host immune response. Their research described immune checkpoints, which act as a "brake" in the immune response and can be exploited by tumor cells to promote progression [6]. Programmed death ligand-1 (PD-L1) is a transmembrane glycoprotein that acts as an inhibitor molecule of cytotoxic T cells by binding programmed death protein-1 (PD-1). Tumor cells may express PD-L1 on their surface in order to evade being targeted by the immune system. In multiple studies, the presence of tumor cell PD-L1 expression in RCC is indicative of poor prognosis and adverse clinicopathology features [7–9]. Given this, current immunotherapeutic agents largely target the PD-L1/PD-1 pathway to limit this mechanism of resistance and enhance the T cell response. Immunohistochemical (IHC) expression of PD-L1 has thus been evaluated as a potential biomarker to evaluate and predict the response for such therapies (Table 11.1).

The CheckMate-025 trial for patients who progressed on prior vascular endothelial growth factor (VEGF) therapy showed the superiority of nivolumab over everolimus [10]. In their analysis, nivolumab demonstrated improved overall survival (OS) compared to everolimus in patients with high PD-L1 expression in pretreatment tumor specimens (21.8 vs. 18.8 months, respectively). However, the benefit of nivolumab was observed irrespective of PD-L1 status, as those with PD-L1(−) specimens also had an OS benefit for nivolumab compared to everolimus (27.4 vs. 21.2 months, respectively). CheckMate-214 (ipilimumab plus nivolumab vs. sunitinib) showed improved overall survival and objective response rates among patients

Table 11.1 Outcomes of clinical trials comparing immune checkpoint inhibitors and targeted systemic therapies

Trial	Treatment arms	Median PFS (overall population)	Median PFS (PD-L1+)	Median PFS (PD-L1−)	Overall survival (overall population)	Overall survival (PD-L1+)	Overall survival (PD-L1−)
CheckMate 025 [10]	Nivolumab vs. everolimus (second-line therapy)	4.6 vs. 4.4 months (HR 0.88; 95%CI 0.75–1.03, $p = 0.11$)	NA	NA	Median OS—25.0 vs. 19.6 months (HR 0.73; 95%CI 0.57–0.93, $p = 0.002$)	Median OS—21.8 vs. 18.8 months (HR 0.79; 95% CI 0.53–1.17)	Median OS—27.4 vs. 21.2 months (HR 0.77; 95% CI 0.60–0.97)
CheckMate 214 [11]	Nivolumab + ipilimumab vs. sunitinib	11.6 vs. 8.4 months (HR 0.82; 99.1%CI 0.64–1.05, $p = 0.03$)	22.8 vs. 5.9 months, (HR 0.46; 95% CI 0.31–0.67)	11.0 vs. 10.4 months (HR 1.00; 95%CI 0.80–1.26)	Median OS—NR vs. 26.0 months (HR 0.63; 99.8%CI 0.44–0.89, $p < 0.001$)	Median OS—NR vs. 19.6 months (HR 0.45; 95%CI 0.29–0.71)	Median OS—NR vs. NR (HR 0.73; 95% CI 0.56–0.96)
IMmotion 150 [12]	Atezolizumab + bevacizumab vs. sunitinib	11.7 vs. 8.4 months (HR 1.00; 95%CI 0.69–1.45)	14.7 vs. 7.8 months, (HR 0.64; 95%CI 0.38–1.08, $p = 0.095$)	NA	NA	NA	NA
IMmotion 151 [13]	Atezolizumab + bevacizumab vs. sunitinib	11.2 vs. 8.4 months (HR 0.83; 95%CI 0.70–0.97)	11.2 vs. 7.7 months (HR 0.74; 95%CI 0.57–0.96; $p = 0.0217$)	11.2 vs. 9.5 months (HR 0.89; 95% CI 0.72–1.1)	Median OS—33.6 vs. 34.9 months (HR 0.93; 95% CI 0.76–1.14, $p = 0.4751$)	Median OS—34.0 vs. 32.7 months (HR 0.84; 95%CI 0.62–1.15, $p = 0.2857$)	NA
Keynote 426 [14]	Pembrolizumab + axitinib vs. sunitinib	15.1 vs. 11.1 months (HR 0.69; 95%CI 0.57–0.84, $p < 0.001$)	15.3 vs. 8.9 months (HR 0.62; 95% CI 0.47–0.80)	15.0 vs. 12.5 months (HR 0.87; 95% CI 0.62–1.23)	12-month OS rate—89.9% vs. 78.3% (HR 0.53; 95%CI 0.38–0.74, $p < 0.0001$)	12-month OS rate—90.1% vs. 78.4% (HR 0.54; 95%CI 0.35–0.84)	12-month OS rate—91.5% vs. 78.3% (HR 0.59; 95%CI 0.34–1.03)
JAVELIN Renal 101 [15]	Avelumab + axitinib vs. sunitinib	13.8 vs. 8.4 months (HR 0.69; 95%CI 0.56–0.84, $p < 0.001$)	13.8 vs. 7.2 months (HR 0.61; 95%CI 0.47–0.79, $p < 0.001$)	NA	Median OS—NR vs. NR (HR 0.80; 95% CI 0.62–1.03, $p = 0.039$	Median OS—NR vs. 28.6 (HR 0.83; 95%CI 0.60–1.15, $p = 0.130$)	NA

NA trial data not reported, *NR* not reached (p-values reported when available)

with intermediate- and poor-risk RCC [11]. In patients with less than 1% PD-L1 expression in the tumor specimen, median progression free survival was 11.0 months in the ipilimumab plus nivolumab group compared to 10.4 months in patients with sunitinib. Interestingly, the magnitude of benefit for ipilimumab plus nivolumab was greater in the population with 1% or greater population (22.8 vs. 5.9 months, respectively).

IMmotion-150 was a phase II trial comparing atezolizumab plus or minus bevacizumab vs. sunitinib for metastatic clear cell RCC and showed a higher progression free survival with combination therapy for those with increased PD-L1 expression [12, 16, 17]. The IMmotion-151 phase III trial, built upon the IMmotion-150 trial, again comparing atezolizumab plus bevacizumab combination therapy against sunitinib in clear cell RCC. A progression free survival benefit was analyzed by the extent of PD-L1 status. Indeed, progression free survival favored combination therapy over sunitinib for patients with 1–4% of cells which expressed PD-L1 (HR 0.78, 95%CI 0.57–1.06) and this benefit was increased with increasing PD-L1 expression status [13]. These findings are in line with initial phase 1 data of atezolizumab in patients with metastatic RCC, which revealed a greater overall survival and objective response rate for patients when >1% of tumor cells expressed PD-L1 on IHC [18].

Similar results were seen in KEYNOTE-426, a phase III trial comparing pembrolizumab plus axitinib to sunitinib. Combination therapy improved progression free survival, overall survival, and objective response rate, and this benefit was maintained independent of PD-L1 status [14]. The JAVELIN Renal-101 phase III trial comparing avelumab plus axitinib combination therapy to sunitinib and also showed a progression free survival benefit to avelumab and axitinib in patients with PD-L1 positive tumors (HR 0.61, 95%CI 0.47–0.79, $p < 0.001$), the primary endpoint of the trial [15]. This was also seen in the overall study population which included 31% of patients with PD-L1 negative tumors (HR 0.9, 95%CI 0.56–0.84, $p < 0.001$). Motzer and colleagues conducted deeper molecular analyses of tumor samples from the JAVELIN Renal-101 trial in order to further assess whether PD-L1 expression could be predictive of treatment response [19]. However, even when the threshold for having a PD-L1 positive tumor was raised, the expression status of PD-L1 could not differentiate survival.

A meta-analysis of several of these clinical trials was done, evaluating 4635 patients in total [20]. Although there was an OS benefit for patients who received immune checkpoint inhibitors irrespective of their PD-L1 status, differential expression of PD-L1 on tumor samples was only able to predict a benefit for improved progression free survival. PD-L1 negative patients receiving immune checkpoint inhibitors did not have an observed progression free survival benefit compared to standard of care (HR 0.85; 95%CI 0.82–1.09), whereas PD-L1 positive patients did (HR 0.65; 95%CI 0.56–0.76). This difference between the PD-L1 positive and PD-L1 groups was statistically significant ($p < 0.0001$).

Interestingly, the influence of PD-L1 status on treatment response has also been evaluated in relation to various tyrosine kinase and mTOR inhibitor targeted therapies. Combining data from the CABOSUN (cabozantinib vs. sunitinib) [21] and

METEOR (cabozantinib vs. everolimus) [22] clinical trials for advanced RCC, Flaifel and colleagues found a statistically significant association between tumor PD-L1 expression and overall survival for all patients on multivariable analysis. However, PD-L1 expression was not predictive of response to cabozantinib therapy [23]. Post hoc analysis of the COMPARZ (pazopanib vs. sunitinib) [24] phase 3 clinical trial showed that median overall survival was shortest in patients with higher tumor PD-L1 expression compared to those with low expression as assessed by IHC in both the pazopanib and sunitinib arms (median 15.1 vs. 35.6 and 15.3 vs. 27.8 months, respectively, $p = 0.03$) [25]. Clearly, PD-L1 expression has prognostic value for patients with advanced RCC treated with targeted therapies, but whether it can be used to help guide these treatment choices needs further exploration.

As a whole, results across the multiple clinical trials highlight some of the current limitations of using PD-L1 as a biomarker to predict treatment response. To date, there has been no standardization in the assays or techniques used to assess PD-L1 status in tumor specimens. Additionally, a heterogeneity exists among various studies in the definitions used to define PD-L1 positivity or cutoffs between high/low PD-L1 expression [20]. Better agreement between studies in regards to these parameters will make future comparisons more valid. Although immunotherapeutic agents which target the PD-L1/PD-1 checkpoint axis have transformed the treatment landscape of advanced RCC, the true ability of PD-L1 expression to perform as a predictive biomarker is still unknown and thus there is still no role for the routine testing of PD-L1 status.

Single Gene Mutations

Various germline and somatic mutations have been described in an effort to characterize the genomic landscape of RCC. In this respect, the identification of such genomic alterations and their roles in influencing treatment response are vital in the goal of developing clinically useful biomarkers. As sequencing technology becomes more robust and more commonplace in laboratory and even routine clinical use, this goal is becoming increasingly attainable.

Although many genes may be shown to be altered in tumor samples, great care must be taken to properly validate any new mutation in its role as a predictive biomarker. In papillary RCC, approximately 80% of tumors are associated with mutations of the *MET* gene, which encodes the tyrosine-protein kinase c-Met [26]. Pal and colleagues found that cabozantinib, which has dual VEGF-MET inhibitory activity, significantly improved PFS compared to sunitinib (HR 0.60, 95%CI 0.37–0.97, $p = 0.019$) in a phase II trial of 152 men with papillary RCC [27]. In comparison, the selective MET inhibitors savolitinib and crizotinib did not have any benefit compared to sunitinib. This particular trial did use biomarker data for randomization, however, and promising results in earlier studies of MET inhibiting drugs such as savolitinib in patients with papillary RCC driven by *MET* were initially seen [28]. The phase III SAVOIR trial was therefore designed to determine if savolitinib was a better treatment option for this patient population compared to

sunitinib [29]. Investigators found a numerically, but not statistically significant, higher PFS rate in the savolitinib group compared to sunitinib at 6, 9, and 12 months. However, only 60 patients were randomized after enrollment was terminated early as a result of new data that surprisingly showed *MET* status was not a negative predictor of treatment outcomes on sunitinib. Ultimately, more adequately powered studies will need to be completed in order to more fully clarify the utility of using *MET* alterations in guiding treatment decisions.

VHL

With a loss of heterozygosity at 3p (3p25-3p26) in greater than 90% of clear cell RCC (ccRCC) samples, commonly mutated genes are von Hippel-Lindau (*VHL*), Polybromo1 (*PBRM1*), BRCA associated protein-1 (*BAP1*), and SET domain-containing protein 2 (*SETD2*), among others [16, 30]. One of the foundations for our current molecular understanding of RCC is largely based on Von Hippel-Lindau disease and its role in hereditary RCC which accounts for up to 5% of all kidney cancer cases [31]. The disease is caused by a mutation in the VHL tumor suppressor gene found on chromosome 3p. Loss of the VHL gene causes an overexpression of hypoxia-inducible factor (*HIF*), and *HIF* target genes (e.g., *VEGF* and *TGFα*), which promote angiogenesis, metastasis, and glycolysis of tumor cells [16, 30, 32, 33]. Alterations of *VHL* via genetic or epigenetic mechanisms have been reported in over 90% of tumors with sporadic ccRCC, providing a basis for the use of systemic therapies targeting VEGF in patients with advanced RCC [34]. Furthermore, the lower number of *VHL* alterations seen in non-ccRCC may provide context for the limitations of VEGF-targeted therapies in patients with these tumors [35]. The prognostic impact of *VHL* loss is debatable, as investigations into several cohorts have found no correlation [36, 37], improved outcomes [38, 39], and worse outcomes [40, 41] associated with *VHL* mutations. In a meta-analysis of six studies that included 663 patients with ccRCC, 61.8% of which had an alteration in the *VHL* gene, no correlation with *VHL* alteration and overall survival progression free survival, or overall response rate to VEGF-targeted therapy was found [42].

A novel *HIF-2α* inhibitor, belzutifan, was recently approved to treat patients with RCC and VHL disease [43]. In this phase 2 trial, 61 patients with VHL disease received this treatment with an objective response rate of 49% at a median follow-up time of 21.8 months. Importantly, preliminary phase 1 data indicates a potential role for *HIF-2α* targeting therapy in patients with sporadic advanced clear cell RCC, and thus not just a population with VHL disease [44, 45]. Further work will be done to determine whether identifying *VHL* mutations in tumors can help predict response to this class of treatment.

PBRM1

PBRM1 is a tumor suppressor gene that belongs to the SWItch/Sucrose Non-Fermentable chromatin remodeling complex [46]. *PBRM1* is mutated in approximately 40–50% of ccRCC samples and is the second most common mutation found

overall, next to VHL [47–49]. Studies have analyzed its utility as a prognostic or predictive biomarker, but the results have varied [16, 48, 49].

The Cancer Genome Atlas (TCGA) Research Network conducted a retrospective analysis that included 488 ccRCC samples and concluded that *PBRM1* did not correlate with survival [16]. A different study by Joseph et al. found a higher risk of metastasis (HR 1.46, $p = 0.0011$), but not death (HR 1.083, $p = 0.54$), from RCC with tumors containing a *PBRM1* mutation [50]. The RECORD-3 phase III trial comparing everolimus to sunitinib, however, showed contrasting results [51]. Patients with clear cell RCC and associated mutated *PBRM1* had a longer median progression free survival with everolimus compared to those with wild-type *PBRM1* (12.8 vs. 5.5 months, respectively), though this difference was not seen in the sunitinib arm.

The relationship between *PBRM1* mutations and immunotherapy response in patients with RCC is disputed. Miao et al., performed whole exome sequencing on nearly 100 patients with metastatic RCC who were treated with PD-1 or PD-L1 blocking agents [52]. They found that tumors with loss-of-function mutations of *PBRM1* had a significantly longer overall- and progression free survival, as well as a more sustained reduction in tumor burden. Similar findings were seen by Braun and colleagues when analyzing tissue samples from the CheckMate 025 trial [53]. They identified *PBRM1* mutations in 29% of nivolumab-treated patients and 23% of patients in the everolimus group. Among patients receiving nivolumab, *PBRM1* mutations was associated with an increased progression free survival (HR 0.67; 95%CI 0.47–0.96, $p = 0.03$) and overall survival (HR 0.65; 95%CI 0.44–0.96; $p = 0.03$). This association was not seen in the cohort of patients treated with everolimus.

Alternatively, other studies have not been able to link *PBRM1* mutations and a clinical response to immunotherapy. In the IMmotion150 trial, patients with tumors harboring a *PBRM1* mutation had a significantly longer PFS when receiving VEGF-inhibitor therapy compared to those who received immune checkpoint blockade treatment alone, and no association between *PBRM1* mutations and response to atezolizumab was seen [12]. Hakimi et al. then analyzed an institutional cohort of 189 patients with metastatic clear cell RCC who were treated with immune checkpoint inhibitor therapy [54]. Sixty-one of these patients had a *PBRM1* loss-of-function mutation, and mutations were not associated with time to treatment failure (HR 0.73, $p = 0.11$) or overall survival (HR 1.5, $p = 0.16$). Moreover, even when adjusting for IMDC risk score and line of therapy, *PBRM1* loss-of-function mutations were not predictive of overall survival in a multivariate model (HR1.24; 95%CI 0.69–2.25, $p = 0.47$).

In order to provide a mechanistic understanding of the interaction between *PBRM1* and treatment response, Liu et al. examined a murine RCC model with a *PBRM1* knockout [55]. They found that *PBMR1* loss lowered the immunogenicity of the tumor microenvironment, possibly via a disruption in the IFNγ-induced expression of chemo-attractive signals and a reduction in T cell infiltration. Such a reduction in the immunogenic nature of the tumor microenvironment potentially limits the responsiveness to immune checkpoint blockade due to a lack of antitumor

T cells. Consistent with this, these authors examined three separate RCC patient cohorts, including those from IMmotion150, and demonstrated a significantly lower CD8 T cell population in tumors with *PBRM1* mutations compared to *PBRM1* intact tumors according to IHC intensity. *PBRM1* loss was also associated with a more angiogenic tumor microenvironment in this same analysis. In the RCC patient cohorts, *PBRM1* mutations was associated increased expression of an angiogenesis gene signature, which included genes encoding VEGFs and HIF targets [55]. Hakimi and colleagues further evaluated the impact of *PBRM1* mutations on angiogenesis by analyzing patient and tumor data from the COMPARZ trial and found that tumors with *PBRM1* mutations had higher angiogenesis gene expression [56]. Additionally, they showed that PBRM1 mutations were independently prognostic for overall survival and progression free survival after adjusting for IMDC risk classification. It is, therefore, possible that *PBRM1* has an important role in the regulation of angiogenesis and may provide some explanation for the association of angiogenesis gene expression and TKI response [56, 57].

BAP1

BAP1 is a tumor suppressor gene found on chromosome 3 with chromatin remodeling properties [58]. The gene encodes the *BAP1* protein which binds downstream transcription factors and suppresses cellular proliferation. Mutations in *BAP1* have been found in 10–15% of clear cell RCC samples. According to a TCGA analysis, mutations in *BAP1* were associated with reduced survival [48]. RCC caused by mutations to *BAP1* is considered mutually exclusive from PBRM1, though both are located on chromosome 3 and shares a similar function [16, 58, 59]. Kapur and colleagues retrospectively analyzed 145 patients with clear cell RCC and showed that that the median overall survival was significantly shorter for patients with *BAP1* mutated tumors than those for PBRM1 (4.6 vs. 10.6 years, respectively) [60]. In the analysis of the RECORD-3 study, patients with the *BAP1* mutation had a higher risk of progression in both the everolimus and sunitinib arms [51].

Wang and colleagues sought to evaluate the tumor microenvironment in RCC by leveraging tumor grafts, or patient derived xenografts, to develop a novel tumor microenvironment gene signature [61]. This signature was assessed in 844 RCC samples from TCGA which have available RNA-seq data. Focusing on expression of the tumor microenvironment genes in clear cell RCC patients, two clusters were observed. Further scrutiny of these clusters revealed one that was enriched for Tregs, NK cells, neutrophils, macrophages and other immune-related proteins. This "inflamed subtype" was additionally enriched for mutations in *BAP1*. As some studies suggest that tumors associated with such an inflamed subtype may be more susceptible to immunotherapy, further characterization of the role of *BAP1* in this interaction should be informative.

While these and other genomic alterations have shown some promise as predictive biomarkers in the advanced RCC setting, several limitations to them exist. Voss et al. integrated the Memorial Sloan Kettering Cancer Center (MSKCC) risk model, which uses clinical and laboratory data, with genomic data in order to improve model performance [62]. The tumor mutation status of six genes—*BAP1*, *PBRM1*, *TP53*,

TERT, *KDM5C*, and *SETD2* were gathered from the COMPARZ and RECORD-3 trial. A training cohort identified mutations of *BAP1*, *TP53,* and *PBRM1* as prognostic, and so were added to the original MSKCC risk model. The addition of this genomic data improved the model performance at predicting overall and progression free survival in these patients with advanced and metastatic RCC who were treated with first-line tyrosine kinase inhibitors. This suggests that genomic biomarkers may have the greatest utility when used in combination with clinical data.

DNA Damage Repair Genes

The DNA Damage Repair (DDR) pathways are activated in response to DNA damage, and work to coordinate a series of events to maintain genetic stability and integrity. Many cancer therapies including radiation and chemotherapy work at least in part by inducing cell death via DNA damage. In order to evade such treatments, some malignant cells have been found to dysregulate DDR pathways [63]. Targeting specific DDR pathways has therefore been studied as a therapeutic approach various malignancies such as RCC and DDR genes may be able to be used as a biomarker of treatment response.

In a retrospective analysis of 229 patients with mRCC, 19% of patients had DDR alterations [64]. For patients who received immune checkpoint inhibitor therapy, a deleterious DDR gene alteration was associated with a superior overall survival (log-rank $p = 0.049$), though no association was seen in patients treated with VEGF-TKIs. Additionally, a smaller study by Labriola and colleagues of tumor samples from 34 patients with mRCC treated with immune checkpoint inhibitor therapy found that there was an enrichment of DDR gene mutations in the group that responded to the therapy, further suggesting an association [65]. Larger scale studies are needed to validate these findings.

Clinical trials are currently underway for poly adenosine diphosphate-ribose polymerase (PARP) inhibitors, which block the PARP enzyme from repairing DNA when it becomes damaged, in the mRCC setting (NCT03786796, NCT04068831). Such trials will be informative in whether these novel agent are beneficial for patients with advanced RCC and could further highlight the role of DDR genes as a biomarker.

Novel Biomarkers

Tumor Mutation Burden/Neoantigen Burden

Tumor mutation burden (TMB) refers to the total number of mutations per coding area of the tumor genome while the tumor neoantigen burden (TNB) is the volume of neoantigens in the tumor [66]. Tumor cells with a higher mutational load may stimulate an antitumoral immune response secondary to an increase in these neoantigens [67, 68]. Therefore, it has been hypothesized that there is a more favorable

response to immune checkpoint inhibitors in tumor cells with a larger TMB since they will be more primed for a robust immune response. The TMB/TNB and immunotherapy relationship has been studied in other malignancies with some promising results [69, 70]. A high TNB was associated with significant clinical benefits in patients with non-small cell lung cancer and advanced melanoma treated with immune checkpoint inhibitors [70, 71]. In fact, pembrolizumab was approved by the U.S. Food & Drug Administration (FDA) for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high solid tumors who progressed on first-line options.

Interestingly, mRCC was shown to have the highest proportion of insertion-deletion mutations across 19 different cancers available to be analyzed in the TCGA [72]. TMB is widely variable among the histologic subtypes of RCC, with very low TMB seen in chromophobe compared to clear cell RCC. However, no correlation has been found between TMB and the IMDC or MSKCC risk groups which use clinically-derived data [73, 74]. Furthermore, the utility of TMB as a predictive biomarker for immunotherapy response in advanced RCC is not yet clear. An exploratory analysis of IMmotion150 did not find an association between TMB and efficacy in the atezolizumab treatment groups [12]. Similarly, TMB did not differentiate progression free survival in the avelumab + axitinib arm or sunitinib arm in the JAVELIN Renal 101 trial [19].

Gene Expression Signatures

In other malignancies, gene expression assays have provided reliable and reproducible prognostic information that improve upon traditional clinical parameters and are now part of some treatment guidelines [75–78]. Though similar assays have been explored in RCC, they are not routinely used outside of the research setting. Further work is ongoing to validate their clinical role.

Analyzing samples from the phase 3 COMPARZ trial comparing pazopanib to sunitinib, Hakimi et al. aimed to characterize the molecular characteristics associated with response to treatment and survival [56]. They found four biologically distinct molecular subgroups associated with variations in tyrosine kinase inhibitor efficacy. Given the antiangiogenic effects of TKI therapy, it is not surprising that an association between angiogenesis gene expression and treatment response was seen. Patients who had a higher angiogenesis gene expression demonstrated an improved OS and PFS (HR 0.68 and 0.68, respectively), and this was independent of International Metastatic RCC Database Consortium (IMDC) risk category. Interestingly, the authors also found that tumors with *PBRM1* and *BAP1* mutations correlated to angiogenesis gene expression, which may partly explain the predictive benefit of these gene mutations which were discussed previously in this chapter. These findings are consistent with earlier results from Beuselinck and colleagues, who showed a similar improved response to sunitinib in patients harboring tumors with a pro-angiogenic signature [57]. From this, a novel clinical trial was designed to test the feasibility of allocating treatments to patients with metastatic clear cell

RCC based these tumor molecular classifications [79]. The BIONIKK study was a phase 2 trial in which 202 patients were randomly assigned to treatment with either nivolumab, nivolumab + ipilimumab, or a VEGFR-TKI according to molecular subgroup. Notably, investigators found a higher objective response rate (44%) in the group with a high expression of immunosuppressive checkpoints who received nivolumab than in any prior prospective trial evaluating a single agent anti-PD1 therapy. Additionally, patients with tumors harboring pro-angiogenic features saw an increase in median PFS and objective response rate with a VEGFR-TKI, but only an increase in objective response rate with nivolumab-ipilimumab.

Correlary molecular biomarker analyses of the IMmotion150 study generated three separate subgroups based on the relative expression levels of angiogenesis (angio), immune (T_{eff}), and myeloid inflammation-associated genes [12]. These authors found the association of a high angiogenesis gene signature ($Angio^{High}$) with an improved ORR and PFS within the sunitinib-only treatment arm, though no difference was seen across treatment arms. Furthermore, in the low angiogenesis signature $Angio^{Low}$ group, patients receiving atezolizumab + bevacizumab experienced an improved PFS (HR 0.59; 95% CI 0.45–0.98, $p = 0.042$). The immune-related gene signature was developed based on expression of five different genes involved in T-effector function, IFN-γ response, checkpoint inhibition, and antigen presentation. A high expression ($Teff^{high}$) of this was associated with an improved PFS in the atezolizumab + bevacizumab arm compared to sunitinib (HR 0.55; 95%CI 0.32–0.95, $p = 0.033$). Finally, a high myeloid inflammation gene signature ($Myeloid^{high}$), which has been associated with suppression of antitumor adaptive T-cell response, conferred a worse PFS with atezolizumab monotherapy compared to sunitinib, though this difference was lost when bevacizumab was included [12]. Applying these gene signatures to the patient data from the IMmotion151 study, Motzer et al. found supporting evidence that a $Angio^{high}$ signature was associated with improved PFS in patients receiving sunitinib (HR 0.59; 95%CI 0.47–0.75, $p < 0.01$) [80]. Additionally, PFS was improved in the $Teff^{high}$ (HR 0.76; 95%CI 0.59–0.99, $p = 0.04$) and $Angio^{low}$ (HR 0 l.68; 95%CI 0.52–0.88, $p < 0.01$) groups for patients treated with Atezolizumab + bevacizumab. The OPtimal Treatment by Invoking biologic Clusters in Renal Cell Carcinoma (OPTIC RCC) phase II trial was designed to assess whether the use of these gene expression clusters could be used to select the systemic therapy for patients with advanced RCC. Patients will be assigned to receive nivolumab and cabozantinib if the tumor is driven predominantly by angiogenesis, or ipilimumab and nivolumab if the tumor has high expression of inflammatory and/or proliferation (Teff) pathways. These treatment arms will be compared to historical controls of patients who underwent systemic treatments for advanced RCC agnostic of any expression information, which may provide evidence that these signatures can be used as a predictive biomarker for certain populations.

Reporting on a molecular analysis of baseline tumor samples from the JAVELIN Renal 101 trial comparing avelumab + axitinib to sunitinib, Motzer and colleagues found that an elevated expression of a cluster of immune-related genes was found in patients with a prolonged PFS in the avelumab + axitinib treatment arm [19].

Additionally, they applied this signature to an independent dataset from the JAVELIN Renal 100 study [81], which was the single arm phase 1b study for avelumab + axitinib, a greater PFS was seen in patients with a ≥ median expression of the signature (HR 0.36; 95%CI 0.157–0.805, $p = 0.0097$). Although this 26-gene signature, termed the "Renal 101 Immuno signature," contained genes related to regulators of the adaptive and innate immune responses, cell trafficking, and inflammation, only limited overlap was seen with the IMmotion150 Teff immuno signature.

Neutrophil:Lymphocyte Ratio

Though the exact mechanism is unknown, inflammation is generally recognized as a hallmark of cancer [82]. As such, the Neutrophil to Lymphocyte ratio (NLR) has previously been explored as a biomarker in various malignancies [83, 84]. Recently, it has been investigated as a predictor of response in patients with RCC. Templeton et al. analyzed 1199 men from the IMDC cohort treated with VEGF-targeted therapy showed a shorter OS and PFS if they had a higher NLR at baseline [85]. Additionally, patients with a decline in NLR by week 6 of treatment had improved outcomes. This suggests the NLR could potentially be used as a biomarker in patients receiving VEGF-targeted therapy to predict response and monitor progress over the course of treatment. Over 6000 patients from 25 studies were included in a meta-analysis that showed elevated pretreatment NLR was associated with a poorer OS, PFS, and CSS [86]. Specifically looking at those who underwent immune checkpoint inhibitor therapy, high NLR was again significantly associated with worse OS and PFS (HR 3.92 and 2.20, respectively). These findings are likely representative of the dynamic interaction between the inflammatory response and immune system.

The Human Microbiome

The role of the human microbiome in the development and treatment of genitourinary cancers has recently been appreciated [87]. For advanced RCC, clinical studies have suggested a relationship between the microbiome and systemic treatment efficacy. Routy et al. evaluated 67 patients with advanced RCC who were enrolled in clinical trials for immune checkpoint inhibitors and found that oncologic outcomes for patients who received antibiotics within 2 months of starting the immunotherapy had a decreased progression free survival [88]. Interestingly, an overrepresentation of the bacterial species *Akkermansia muciniphila* was seen in patients with a greater progression free survival, suggesting antibiotic therapy may eradicate this organism and limit the treatment effect. In similar fashion, an analysis of 145 patients who underwent VEGF-TKI therapy for metastatic RCC found that patients who received antibiotics that targeted *Bacteroides* spp. had an improved progression free survival [89]. Collectively, these findings suggest that the microbiome may help modulate

the effects of systemic treatments. Future work will determine whether components of the microbiome are viable biomarkers.

Conclusion

Recent advances in the treatment landscape of advanced RCC has vastly increased the breadth of therapeutic options for patients. As new drugs and drug combinations are developed targeting novel biologic pathways, there is a growing need to identify tumor and patient specific markers to predict treatment response. Such biomarkers will aid in "personalizing" the treatment pathways for patients, which should increase the efficacy of treatments, allow for better prognostication, and limit treatment-associated morbidity. Further studies will need to prospectively validate such biomarkers in the clinical setting. Additionally, careful examinations of the cost effectiveness of these biomarkers are needed to determine whether their inclusion into treatment algorithms is economically feasible.

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First-Line Systemic Treatment Options for Advanced Renal Cell Carcinoma

12

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Abbreviations

axi-ave	Axitinib/avelumab
axi-pembro	Axitinib/pembrolizumab
cabo-nivo	Cabozantinib/nivolumab
ccRCC	Clear cell renal cell carcinoma
c-Kit	Stem cell factor receptor
CI	Confidence interval
CR	Complete response
CSF-1R	Colony-stimulating factor-1 receptor
CTLA-3	Cytotoxic T-lymphocyte-associated protein
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
IFN	Interferon
IL-2	Interleukin-2
IMDC	International Metastatic RCC Database Consortium
ipi-nivo	Ipilimumab/nivolumab
IRAE	Immune-related adverse events
ITT	Intention to treat
IV	Intravenous
len-pembro	Lenvatinib/pembrolizumab

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MSKCC	Memorial Sloan-Kettering Cancer Center
MU	Million international units
NCCN	National Comprehensive Cancer Network
ORR	Overall response rate
OS	Overall survival
PDGFR	Platelet-derived growth factor receptor
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1
PFS	Progression free survival
PR	Partial response
QoL	Quality of life
RCC	Renal cell carcinoma
RET	Ret Proto-Oncogene
RF	Risk factor
TFS	Treatment-free survival
TKI	Tyrosine kinase inhibitor
TRAE	Treatment-related adverse event
US	United states
v.	Versus
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Introduction

The 5-year survival rate for patients with localized kidney cancer has significantly increased over the last decades; however, until recently, prognosis for patients with advanced disease remained poor and kidney cancer remains the most lethal of the common genitourinary malignancies [1]. Furthermore, approximately 20–40% of patients with localized disease eventually develop local and/or distant recurrence [2, 3]. A select patient population may be followed with active surveillance or managed with focal therapies, but the majority of patients with advanced renal cell carcinoma (RCC) will eventually require systemic therapy.

The development of antiangiogenic/molecularly targeted therapies and immune checkpoint inhibitors (ICIs) have significantly expanded systemic treatment options for patients with advanced RCC, particularly those with clear cell histology (ccRCC). Figure 12.1 chronologizes therapeutic developments over the last three decades. Cumulatively, current United States (US) Food and Drug Administration (FDA) approved first-line therapies for ccRCC include cytokine therapies such as high-dose interleukin-2 (IL-2); vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (TKI) monotherapies such as sunitinib, pazopanib, and cabozantinib; the ICI/ICI combination, ipilimumab and nivolumab (ipi-nivo); and multiple TKI/ICI combinations, namely axitinib/pembrolizumab (axi-pembro), axitinib/avelumab (axi-ave), cabozantinib/nivolumab (cabo-nivo), and lenvatinib/pembrolizumab (len-pembro).

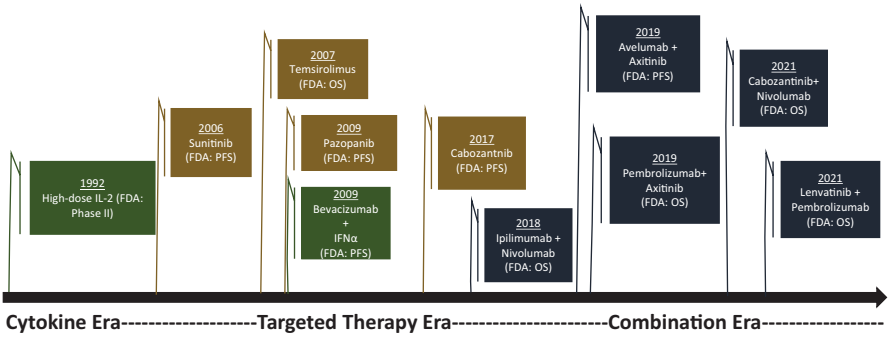

Fig. 12.1 Chronology of FDA approved, first-line therapies for advanced ccRCC. FDA: United States Food and Drug Administration; IFNα: interferon-alpha; IL-2: interleukin-2; OS: overall survival; PFS: progression-free survival

Combination regimens are now standard of care based on superior efficacy, although identifying the optimal combination, particularly ICI/ICI versus TKI/ICI, remains an area of active investigation [4]. This chapter will highlight landmark studies in cytokine, TKI, and combination therapies with a subsequent focus on tailored therapeutic approaches.

The Cytokine Era

Kidney cancer has long been thought of as an immunogenic tumor resistant to cytotoxic chemotherapy [5, 6]. This led to the development of immune-based strategies with a focus on cytokine therapies in the 1980–1990s. Two of the most studied cytokines are IL-2 and interferon (IFN)-α, both considered crucial immune activators [7, 8].

High-Dose IL-2

The US FDA approved high-dose intravenous (IV) bolus IL-2 for the treatment of metastatic RCC in 1992. The approval was based on analyses from 255 patients enrolled into seven phase II clinical trials [9, 10]. Patients received two cycles of high-dose IL-2 (600,000 or 720,000 IU/kg IV infusion over 15 min every 8 h over 5 days for a maximum of 14 consecutive doses per cycle) with 5–9 days of rest in between. The treatment course was repeated every 6–12 weeks for patients with stable or responding disease up to 3 times [9]. The objective response rate (ORR) was modest (14%) but it included ~5% complete responses (CRs) and durable responses [9–12]. High-dose IL-2 essentially unleashes a non-specific, systemic inflammatory response, with associated side effects. Toxicities in these trials were significant, with death in 11 (4%) patients (due to capillary leak syndrome, myocardial infarction, respiratory failure, and/or gastrointestinal toxicities); other

significant, life-threatening toxicities include hypotension (96% overall), arrhythmia (14% overall), myocarditis (1%), and mental status changes (7% grade 4) [4, 9]. However, with standardized modern administration protocols, deaths are rare; in addition, most toxicities are acute and, with the exception of thyroiditis, rarely leave sequalae [13].

Studies evaluating lower dose and subcutaneous administration of IL-2 yielded lower ORR and unfavorable duration of response, suggesting the superiority of high-dose, IV bolus IL-2 and thus its preference for appropriately selected patients with access to such therapy [4, 14]. Prior to the advent of ICIs, high-dose IL-2 was most promising for its long duration of responses. However, given the limited efficacy and significant toxicity, patient selection is key and not all patients are candidates to withstand the toxicities. Nevertheless, given the potential for durable CRs, the limited duration of therapy (maximum of 6 weeks) and the absence of long-term sequalae, this remains an attractive option for some patients.

IFN-α

Interferons (IFNs) are naturally occurring glycoproteins capable of modulating the immune response [15, 16]. They include three subtypes (IFN-α, IFN-β, and IFN-γ), of which IFN-α is the most studied as a therapeutic. IFN-α is associated with low response rates (≤15% ORR and ≤5% CR in most studies) and as monotherapy, was never approved by the FDA for its use in advanced RCC [16–18]. Activity could be boosted to some extent through combinations with chemotherapy (5-fluorouracil or vincristine) or cytokines (IL-2), but these regiments were also never FDA approved [16, 19–23].

The combination of IFN-α plus bevacizumab was more promising. In the phase III, AVOREN trial (NCT00738530), 649 patients with treatment naïve metastatic RCC received IFN-α at 9 million international units [MU] subcutaneously three times a week plus placebo (n = 322) or same dose IFN-α plus bevacizumab at 10 mg/kg every 2 weeks (n = 327) [24]. Significantly higher efficacy was observed in the IFN-α/bevacizumab arm compared to the IFN-α/placebo arm, including a median progression-free survival (PFS) of 10.2 v. 5.4 months (hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.52–0.75; p = 0.0001) and ORR of 30% v. 12%, respectively [24]. OS trended in favor of IFN-α/bevacizumab, although did not reach statistical significance (23.3 v. 21.3 months, HR 0.86, 95% CI 0.72–1.04, p = 0.128). Treatment-related adverse events (TRAEs) were more common in the IFN-α/bevacizumab arm and included hemorrhage (34% v. 9%), hypertension (28% v. 10%), and proteinuria (20% v. 3%) [24]. Similar efficacy and safety results were observed in CALGB 90206 (NCT00072046), an open label, phase III trial of IFN-α/bevacizumab v. IFN-α monotherapy (PFS 8.5 v. 5.2 months, p <0.0001; ORR 25.5% v. 13.1%, p <0.0001; OS favored combination arm but failed to reach statistical significance) [25]. Notably, patients in both trials had access to active post-protocol therapy, including VEGFR-targeting TKIs, which may have confounded the OS analysis. The US FDA approved bevacizumab plus IFN-α for the treatment of

advanced RCC in 2009 [24–26]. However, because of the toxicities, including those from IFN-α, this regimen is rarely used today. What the contribution is of IFN-α and how active bevacizumab alone would be are open questions.

Therapeutic Approach

Currently, neither *high-dose IL-2* nor *IFN-α/bevacizumab* is preferred in the first-line setting, although *high-dose IL-2* may be used in selected patients with excellent performance status, good organ function, favorable risk disease, and/or contraindication to other therapies [4, 27]. IFN-α/bevacizumab is not currently recommended by the National Comprehensive Cancer Network (NCCN) [4]. It is worth noting that VEGF plays an important role in the pathogenesis of peritumoral edema, particularly in the context of primary or metastatic brain tumors. As an anti-VEFG monoclonal antibody, bevacizumab is often used for steroid-refractory, glioblastoma-associated vasogenic edema; its role in reducing RCC metastasis- or radiation necrosis-associated, intracranial edema may be worth considering [28, 29].

The TKI Era and Clinical Prognosis

VEGF is a growth factor crucial to angiogenesis, and its dysregulation plays a significant role in the growth and progression of kidney cancer. In addition to the anti-VEGF monoclonal antibody, bevacizumab, the development of VEGFR TKIs expanded therapeutic possibilities for advanced ccRCC. These include sunitinib, pazopanib, cabozantinib, axitinib, sorafenib, lenvatinib, and tivozanib. mTOR inhibitors, such as temsirolimus and everolimus, were also explored, although have limited role as single agent in advanced RCC in the modern era.

There are two commonly used prognostic models for metastatic RCC: the Memorial Sloan-Kettering Cancer Center (MSKCC) and the International Metastatic RCC Database Consortium (IMDC) model. The MSKCC prognostic model utilizes five clinical factors (Karnofsky performance status <80%, high lactate dehydrogenase, anemia, hypercalcemia, and <1 year from diagnosis to treatment), and the IMDC prognostic model utilizes six clinical factors (anemia, thrombocytosis, neutrophilia, hypercalcemia, Karnofsky performance status <80%, and <1 year from diagnosis to treatment). According to these models, patients are divided into favorable (0 risk factors), intermediate (1–2), or poor (≥3) risk categories [30, 31]. The two models are highly concordant, although the IMDC model may exhibit higher prognostic power, and thus it is preferentially used [32]. In an external validation, IMDC risk groups have significant survival implications in the TKI monotherapy era, with median OS of 43.2 v. 22.5 v. 7.8 months in the favorable, intermediate, and poor risk groups, respectively [31]. As highlighted in later sections, these prognostic models are also increasingly utilized in the combination era to guide treatment selection (i.e., ICI/ICI v. TKI/ICI combinations).

Sunitinib and pazopanib have historically been used as front-line, single agents, while TKIs such as cabozantinib and lenvatinib were initially used in the salvage setting. Evolution of the treatment paradigm has shifted these practices, and this section will detail sunitinib, pazopanib, and cabozantinib as first-line regimens, as these are currently recommended front-line monotherapies under certain circumstances.

Sunitinib

The US FDA approved sunitinib for the treatment of patients with advanced ccRCC across all MSKCC risk groups on January 26, 2006. Sunitinib has activity against platelet-derived growth factor receptor (PDGFR)-α and -β, VEGF receptors (VEGFRs), stem cell factor receptor (c-KIT), FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor-1 receptor (CSF-1R), and Ret Proto-Oncogene (RET) [33]. The efficacy of first-line sunitinib was compared to IFN-α in a randomized, phase III trial of 750 patients with ccRCC in favorable, intermediate, and poor MSKCC risk categories (NCT00098657 and NCT00083889) [34]. Seven hundred fifty patients were randomized to receive either sunitinib (50 mg once daily for 4 weeks in 6-week cycles) or IFN-α (9 MU given subcutaneously 3 times per week) [34]. Sunitinib was associated with significantly higher PFS (11 v. 5 months, HR 0.42, 95% CI 0.32–0.54, p <0.001) and ORR (31% v. 6%, p <0.001 at initial analysis and 47% v. 12%, p <0.001 on long-term follow-up) [34, 35]. OS favored sunitinib although this did not reach statistical significance [34, 35]. The sunitinib-treated cohort also reported significantly better quality of life (QoL), although low-grade fatigue and diarrhea associated with sunitinib can significantly dampen patient QoL [34]. The most common sunitinib-associated grade 3/4 TRAEs included hypertension (12%), fatigue (11%), diarrhea (9%), and palmar-plantar erythrodysesthesia (PPE) (9%) [35]. Sunitinib is usually given in the standard 4:2 week schedule; a 2:1 week schedule may offer better tolerability and could be considered in patients with suboptimal clinical conditions [36].

Pazopanib

Pazopanib became the second US FDA approved TKI for the first-line treatment of advanced ccRCC across all MSKCC risk groups (October 19, 2009). Pazopanib has activity against VEGFRs, PDGFR-α and -β, and c-KIT [37]. In the phase III VEG105192 trial (NCT00334282), pazopanib 800 mg once daily (n = 209) was compared to matching placebo (n = 145, 2:1 randomization) in patients with advanced RCC who were either treatment naïve (54%) or had progressed on one prior cytokine-based systemic therapy (46%) [38, 39]. ORR was 30% with pazopanib compared to 3% with placebo (p <0.001), and PFS was significantly longer with pazopanib in both the overall population (median PFS 9.2 v. 4.2 months, HR 0.46, 95% CI 0.34–0.62; p <0.0001) as well as in treatment-naïve patients (median

PFS 11.1 v. 2.8 months; HR 0.40, 95% CI 0.27–0.60; p <0.0001) [38]. Long-term OS analyses did not reach statistical significance, but were potentially confounded by early and frequent crossover from placebo to pazopanib [38, 40].

First-line sunitinib and pazopanib were compared head-to-head in the phase III, COMPARZ trial (NCT00720941), where 1110 patients with metastatic, ccRCC received sunitinib (n = 553) or pazopanib (n = 557, Table 12.1) at conventional doses [39]. Efficacy was comparable, with pazopanib deemed noninferior to sunitinib with respect to PFS (HR 1.05, 95% CI 0.90–1.2) and OS (HR 0.91, 95% CI 0.76–1.08). Sunitinib had higher incidence of fatigue (63% v. 55%), palmar-plantar erythrodysesthesia (50% v. 29%), and thrombocytopenia (78% v. 41%) while pazopanib had higher incidence of transaminitis (60% v. 43%) [39]. QoL endpoints favored pazopanib in both the COMPARZ and the subsequent PISCES trial (NCT01064310), with 70% of patients preferring pazopanib v. 22% preferring sunitinib (p <0.001); 8% of patients expressed no preference [39, 41].

Cabozantinib

Cabozantinib is a potent multi-kinase inhibitor targeting MET, VEGFRs, AXL, RET, and FLT3 [42]. After the clinical development and approval of cabozantinib in the treatment-refractory setting (from the METEOR study), the phase II CABOSUN trial (NCT01835158) evaluated the efficacy of cabozantinib against sunitinib in patients with treatment-naïve, advanced ccRCC specifically with IMDC intermediate- or poor risk disease (Table 12.1) [43–45]. Cabozantinib showed a statistically significant improvements in PFS and ORR when compared to sunitinib (median PFS 8.6 v. 5.3 months, HR 0.48, 95% CI 0.31–0.74 and ORR 20% v. 9%, respectively). Although OS did not reach statistical significance (26.6 v. 21.2 months, HR 0.80, 95% CI 0.53–1.21), the trial was not powered to detect a difference in OS [43–45]. TRAEs were overall comparable and included fatigue, hypertension,

Table 12.1 Landmark trials evaluating sunitinib, pazopanib, and cabozantinib in advanced renal cell carcinoma (COMPARZ for pazopanib v sunitinib and CABOSUN for sunitinib v cabozantinib)

	Pazopanib	Sunitinib	Cabozantinib
PFS	8.4 v. 9.5 mo; HR 1.05, 95% CI 0.90–1.22		
ORR	31% v. 24%		
OS	28.4 v. 29.3 mo		
	HR 0.92, 95% CI 0.79–1.06; p = 0.24		
AEs	Pazopanib: higher transaminitis		
	Sunitinib: higher fatigue, hand-foot syndrome, and thrombocytopenia		
		CABOSUN trial (sunitinib v. cabozantinib in intermediate/poor risk groups)	
PFS		8.2 v. 5.6 mo; HR 0.48, 95% CI 0.46–0.95; p = 0.012	
ORR		33% v. 12%	
OS		30.3 v. 21.8 mo; HR 0.80, 95% CI 0.50–1.26	

AE adverse event, *Cl* confidence interval, *mo* months, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *v.* versus

diarrhea, transaminitis, and PPE [43, 44]. Based on these results, cabozantinib was approved by the US FDA in 2017 for the treatment of patients with advanced, ccRCC with a preference for intermediate- and poor risk groups [4].

Therapeutic Approach

TKI monotherapy with sunitinib, pazopanib, or cabozantinib can be considered for first-line treatment of advanced ccRCC. However, first-line TKI monotherapy is chosen for a minority of patients, including patients with indolent disease, such as those with glandular metastases, good IMDC risk factors and in the setting of ICI contraindications [4]. Based primarily on the COMPARZ and the CABOSUN studies, sunitinib and pazopanib are the typical options for IMDC favorable risk disease (Table 12.1) [4].

Although TKIs are significantly better than cytokine therapies, efficacy with TKI monotherapy remains modest, with approximate ORRs of 20–30%, median PFS less than 12 months, and median OS less than 30 months [4]. These therapies offer temporizing options but durable responses are seen in only a minority of patients. The introduction of ICIs has subsequently improved these outcomes and revolutionized the overall treatment paradigm for advanced ccRCC.

The ICI/ICI and TKI/ICI Combination Era

Five combination therapies incorporating ICIs are currently approved by the US FDA as first-line treatment options for advanced ccRCC: the dual immune checkpoint inhibitor combination, ipi-nivo (CheckMate-214, NCT02231749), and four TKI/ICI combinations, axi-pembro (KEYNOTE-426, NCT02853331), axi-ave (JAVELIN Renal 101, NCT02684006), cabo-nivo (CheckMate-9ER, NCT03141177), and len-pembro (CLEAR, NCT02811861). Key trial designs, efficacies, and safety signals of these combinations are detailed in Tables 12.2 and 12.3.

ICI/ICI Combination with Ipilimumab and Nivolumab

Seminal discoveries elucidating the many steps of the tumor immune cycle have led to the identification of immune targets and checkpoints with potential for manipulation and therapy development [46]. Upregulation of immune checkpoint proteins on tumor cells such as programmed cell death-ligand 1 (PD-L1) and immune checkpoint receptors on T-cells, such as cytotoxic T-lymphocyte-associated protein (CTLA-4) or programmed cell death-1 (PD-1) leads to immune evasion [47]. Ipilimumab and nivolumab are first-in-class ICIs directed against CTLA-4 and PD-1, respectively. Their complementary activity, and potentially durable antitumor effect has been observed in both preclinical and clinical settings [48].

Table 12.2 Phase III trials evaluating ICI/ICI and TKI/ICI combinations in advanced ccRCC: key trial design and efficacy outcomes

	Ipilimumab/nivolumab [50–53]	Axitinib/ pembrolizumab [59–61]	Axitinib/avelumab [62–64]	Cabozantinib/ nivolumab [65–68]	Lenvatinib/ pembrolizumab[a] [69]
Phase III clinical trial	CheckMate-214 (NCT02231749)	KEYNOTE-426 (NCT02853331)	JAVELIN Renal 101 (NCT02684006)	CheckMate-9ER (NCT03141177)	CLEAR (NCT02811861)
Comparator	Sunitinib				
Inclusion criteria	Advanced or metastatic, clear cell renal cell carcinoma, measurable disease based on RECIST 1.1 criteria, treatment naïve				
IMDC risk group (fav/int/poor), %	Ipi/nivo: 23/61/17 Sun: 23/61/16	Axi/pembro: 32/55/13 Sun: 31/57/12	Axi/avelumab: 21/61/16 Sun: 22/62/16	Cabo/nivo: 23/58/19 Sun: 22/57/21	Len/pembro: 31/59/9 Len/eve: 32/55/12 Sun: 35/54/10
PD-L1+, %[b]	Ipi/nivo: 23 Sun: 25	Axi/pembro: 59 Sun: 62	Axi/ave: 61 Sun: 65	Cabo/nivo: 26 Sun: 25	Len/pembro: 30 Sun: 33
Median follow-up, mo (initial/subsequent/ extended analysis)	25.2/32.4/55/67.7	12.8/30.6/42.8	10.8/19.3	18.1/23.5/32.9	26.6
Efficacy outcomes of ICI/ICI or TKI/ICI combination v. sunitinib[c,d]					
Median PFS, mo (HR, CI, *p*-value)					
ITT	12.3 v. 12.3 (HR = 0.86, 99.1% CI 0.73–1.01; $p = 0.0628$)	[d]**15.7 v. 11.1 (HR = 0.68, 95% CI 0.58–0.80; $p < 0.0001$)**	[d]**PD-L1+ cohort: 13.8 v. 7.0 (HR = 0.62, 95% CI 0.49–0.78; $p < 0.0001$)** ITT (secondary): 13.3 v. 8.0 (HR = 0.69, 95% CI 0.567–0.83; $p < 0.0001$)	**16.6 v. 8.3 (HR = 0.56, 95% CI 0.46–0.68)[p]**	[p]**23.9 v. 9.2 (HR = 0.39. 95% CI 0.32–0.49; $p < 0.001$)**
IMDC favorable	12 v. 29 (HR = 1.60, 95% CI 1.1–2.3)	20.7 v. 17.8 (HR = 0.76, 95% CI 0.56–1.03)	24.0 v. 16.7 (HR 0.63, 95% CI 0.40–0.99)	25 v. 13 (HR = 0.58, 95% CI 0.36–0.93)	HR = 0.41, 95% CI 0.28–0.62
IMDC intermediate/poor	[p]**12 v. 8 (HR = 0.73, 95% CI 0.61–0.87)**	13.8 v. 8.2 (HR = 0.67, 95% CI 0.52–0.80)	Int: 11.6 v. 8.3 (HR 0.76, 95% CI 0.60–0.95) Poor: 6.0 v. 2.9 (HR 0.51, 95% CI 0.34–0.77)	Int: 17 v. 9 (HR = 0.58, 95% CI 0.45–0.76) Poor: 10 v. 4 (HR = 0.36, 95% CI 0.23–0.56)	Int: HR = 0.39, 95% CI 0.29–0.52 Poor: HR = 0.28, 95% CI 0.13–0.60

(continued)

Table 12.2 (continued)

	Ipilimumab/nivolumab [50–53]	Axitinib/ pembrolizumab [59–61]	Axitinib/avelumab [62–64]	Cabozantinib/ nivolumab [65–68]	Lenvatinib/ pembrolizumab[a] [69]
Median OS, mo (HR, CI, *p*-value)					
ITT	55.7 v. 38.4 (HR: 0.72, 95% CI 0.62–0.85; *p* <0.0001)	**[d]45.7 v. 40.1 (HR 0.73, 95% CI 0.60–0.88; *p* <0.001)**	**[d]PD-L1+ cohort: NE v. 28.6 (HR = 0.83, 95% CI, 0.60–1.15; *p* = 1.301)** ITT (secondary): NE v. NE (HR 0.80, 95% CI 0.62–1.03; *p* = 0.0392)	37.7 v. 34.3 (HR = 0.70, 95% CI 0.55–0.90)	NR v. NR (HR = 0.66, 95% CI 0.49–0.88; *p* = 0.005)
Fav	74 v. 68 (HR: 0.94, 95% CI 0.65–1.37)	HR = 1.17, 95% CI 0.76–1.80	NE v. NE (HR 0.81, 95% CI 0.34–1.96)	Fav: HR = 0.94, 95% CI 0.46–1.92	HR = 1.15, 95% CI 0.55–2.40
Int/poor	**[p]47 v. 27 (HR: 0.68, 95% CI 0.58–0.81)**	HR = 0.64, 95% CI 0.52–0.80	Int: 30.0 v. 28.6 (HR 0.86, 95% CI 0.62–1.2) Poor: 21.2 v. 11.0 (HR 0.57, 95% CI 0.36–0.90)	Int: HR = 0.40, 95% CI 0.50–1.08 Poor: HR = 0.45, 95% CI 0.27–0.76	Int: HR = 0.72, 95% CI 0.50–1.05 Poor: HR = 0.30, 95% CI 0.14–0.64
ORR, %				6	
ITT	39 v. 32	60 v. 40	PDL-1+ cohort: 55 v. 27 ITT cohort: 53 v. 27	56 v. 28	71 v. 36
Fav	30 v. 52	69 v. 50	67 v. 40	66 v. 44	–
Int/poor	**[p]42 v. 27**	57 v. 35	Int: 53 v. 27 Poor: 32 v. 13	Int: 56 v. 29 Poor: 38 v. 10	–
CR with combination (ITT/fav/int-poor), %	12/13/11	10/12/9	3.8/–/–	12.4/9/11 (int); 5 (poor)	16.1/–/–
PD with combination (ITT/int-poor/fav), %	17.6/19.3/12.0	11/–/–	12.4/–/–	6.2/–/–	5.4/–/–
Other significant findings	PFS favored ipi/nivo on long-term follow up		OS analysis remains immature at second interim analysis		

Ave avelumab, *axi* axitinib, *cabo* cabozantinib, *CI* confidence interval, *CR* complete response, *eve* everolimus, *fav* favorite IMDC risk group, *HR* hazard ratio, *ICI* immune checkpoint inhibitors, *IMDC* International Metastatic Renal Cell Carcinoma Database Consortium, *int* intermediate IMDC risk group, *ipi* ipilimumab, *ITT* intent-to-treat, *len* lenvatinib, *mo* months, *NE* not estimable, *nivo* nivolumab, *NR* not reached, *ORR* objective response rate, *OS* overall survival, *PD* primary progression, *PD-L1* programmed death-ligand 1, *pembro* pembrolizumab, *PFS* progression-free survival, *poor* poor IMDC risk group, *sun* sunitinib, *TKI* tyrosine kinase inhibitor, *v.* versus

[a] CLEAR study evaluated lenvatinib + pembrolizumab v. lenvatinib + everolimus v. sunitinib. Noted in table are comparisons between lenvatinib + pembrolizumab v. sunitinib

[b] PD-L1 expression ⩾1% is considered positive

[c] Data from latest analyses is included if available, otherwise gathered from initial/interim analyses

[d] Primary endpoint(s) of respective trials are bolded and marked with [P]; for CheckMate-214 study, primary endpoints are PFS, OS, ORR in the intermediate/poor risk group; for JAVELIN Renal 101 study, primary endpoints are PFS and OS in PDL-1+ cohort; for KEYNOTE-426, CheckMate-9ER, and CLEAR studies, primary endpoints are PFS, OS, and/or ORR in the ITT population

Table 12.3 Key safety outcomes of phase III trials evaluating ICI/ICI and TKI/ICI combinations in advanced ccRCC

	Ipilimumab/ nivolumab [50]	Axitinib/ pembrolizumab [59]	Axitinib/avelumab [62]	Cabozantinib/ nivolumab [65]	Lenvatinib/ pembrolizumab [69]
Phase III clinical trial	CheckMate-214 (NCT02231749)	KEYNOTE-426 (NCT02853331)	JAVELIN Renal 101 (NCT02684006)	CheckMate-9ER (NCT03141177)	CLEAR (NCT02811861)
Grade >3 TRAEs	Ipi/nivo: 46% Sun: 63%	Axi/pembro: 62.9% Sun: 58.1%	Axi/ave: 56.7% Sun: 55.4%	Cabo/Nivo: 60.6% Sun: 50.9%	Len/pembro: 71.6% Sun: 58.8%
Dose reduction (R) and/or interruption (I)[a]	*Ipi/Nivo* Ipi: 27% (I) Nivo: 58% (I) Sun: 59% (I), 53% (R)	*Axi/Pembro* Any drug: 69.9% (I) Axi: 20.3% (R) *Sun*: 30.1 (R), 49.9% (I)	*Axi/Ave* Axi: 42.2% (R) *Sun*: 42.6 (R)	*Cabo/Nivo* Cabo: 56.3% (R) Nivo: 71.9% (I) *Sun*: 51.6% (R) 51.9% (I)	*Len/Pembro* Any drug: 78.4% (I) Len: 68.8% (R) *Sun*: 50.3% (R); 53.8% (I)
Discontinuation[a]	*Ipi/Nivo:* 22% *Sun*: 12%	*Axi/Pembro* Any drug: 30.5% Both: 10.7% *Sun*:13.9%	*Axi/Ave* Both: 7.6% *Sun*: 13.4%	*Cabo/Nivo* Any drug: 19.7% Cabo: 7.5% Nivo: 6.6% Both: 5.6% *Sun*:16.9%	*Len/Pembro* Any drug: 37.2% Len: 25.6% Pembro: 28.7% Both: 13.4% *Sun*: 14.4%
Treatment-related death	Ipi/nivo: $n = 8$ Sun: $n = 4$	Axi/pembro: $n = 4$ Sun: $n = 7$	Axi/Ave: $n = 3$ Sun: $n = 1$	Cabo/nivo: $n = 1$ Sun: $n = 2$	Len/pembro: $n = 4$ Sun: $n = 1$
High-dose steroid for IRAEs[b]	35%	–	11.1%	19.1%	–

Ave avelumab, *axi* axitinib, *cabo* cabozantinib, *ipi* ipilimumab, *I* interruption, *IRAE* immune-related adverse event, *len* lenvatinib, *nivo* nivolumab, *pembro* pembrolizumab, *R* reduction, *sun* sunitinib, *TRAE* treatment-related adverse event

[a] Dose reduction, drug interruption, or drug discontinuation due to adverse event of any cause or grade

[b] High-dose steroid is defined at >40 mg of prednisone daily or equivalent

The development of nivolumab in VEGF-refractory patients with metastatic RCC, and the establishment of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg as a feasible combination (v. higher dose ipilimumab at 3 mg/kg with associated higher toxicity) in CheckMate-016 trial (NCT01472081), set the stage for the phase III, CheckMate-214 trial (NCT02231749), which compare ipilimumab 1 mg/kg plus nivolumab 3 mg/kg every 3 weeks for 4 cycles followed by nivolumab 3 mg/kg every 2 weeks against sunitinib 50 mg daily in the standard 4:2 week schedule [49–52]. In total, 1096 patients with treatment-naïve, advanced ccRCC were randomized and stratified for IMDC risk group; co-primary endpoints included PFS, ORR, and OS in the intermediate- and poor risk groups (n = 839) [50]. Secondary endpoints explored these outcomes in the intention to treat (ITT) population as well as in the favorable-risk group [50].

For patients with IMDC *intermediate/poor risk* disease, ipi-nivo demonstrated superior OS and ORR over sunitinib at a median follow-up of 25.2 months (18-month OS rate of 75% v. 60%, HR 0.63, 99.8% CI 0.44–0.89, p <0.001; ORR 42% v. 27%, p <0.001); PFS favored ipi-nivo, although this did not reach statistical significance at initial analysis (11.6 v. 8.4 months, HR = 0.82, 99.1% CI 0.64–1.05; p = 0.03) [50]. Of note, the OS benefit was observed irrespective of PD-L1 expression.

The superior efficacy of ipi-nivo in the intermediate/poor risk remained on extended follow-up analyses at 5 years, including (1) median OS of 47 v. 27 months (HR: 0.68, 95% CI 0.58–0.81) and (2) PFS benefit of 12 v. 8 months (HR = 0.73, 95% CI 0.61–0.87) [53]. The superior efficacy of ipi-nivo was also observed in the ITT population, with median OS of 55.7 v. 38.4 (HR: 0.72, 95% CI 0.62–0.85; p <0.0001) and ORR of 39% v. 32%; PFS was not significantly different (12.3 v. 12.3 (HR = 0.86, 99.1% CI 0.73–1.01; p = 0.0628)) [53]. Additionally, CR was observed in 12%, 13%, and 11%, respectively, and ongoing responses were observed in 65.1%, 56.3%, and 65.2%, respectively, in ITT, favorable, and intermediate/poor risk categories after at least 4–5 years of follow-up [52, 53]. In the ITT population, 30% of patients were free of disease progression at 60 months, and more than 50% of patients in the ITT and IMDC intermediate/poor risk populations were alive after 4 years of minimum follow-up [52].

Importantly, the Checkmate 214 trial highlights a new clinical endpoint of treatment-free survival (TFS). Because the trial was designed so that ipi-nivo would be continued until disease progression or significant toxicity, TFS intervals are generally due to treatment hold for adverse events. TFS intervals can include both time with or time without adverse events, and overall TFS without adverse events were longer for patients treated with ipi-nivo compared to sunitinib. Specifically, in the intermediate/poor risk group at 42 months since randomization, 18% of ipi-nivo treated v. 5% of sunitinib-treated patients are surviving treatment free, respectively, and mean TFS was twice as long after ipi-nivo when compared to sunitinib (6.9 v. 3.1 months) [54].

These prominent, first-in-class results of CheckMate-214 have revolutionized management of metastatic RCC. Ipi-nivo was approved by the US FDA for the treatment of patients with ccRCC and intermediate- or poor- risk features in April

2018. In favorable risk patients, ipi-nivo is an option, but not a preferred first-line regimen [4]. At the most recent 60-month follow-up, OS for both arms is quite similar (median OS for ipi-nivo 74.1 v. 68.4 months for sunitinib; HR 0.94, 95% CI 0.65–1.37, $p = 0.77$), and more data is needed regarding the effect of ipi-nivo combination in the treatment of favorable risk patients [53].

The safety events on Checkmate-214 were similar for either ipi-nivo or sunitinib with grade ≥3 TRAEs occurring in 46% of patients treated with ipi-nivo v. 63% in patients treated with sunitinib [50]. In addition, 22% and 12% of TRAEs led to drug discontinuation, respectively [50].

The most common grade ≥3 TRAEs with ipi-nivo were increased lipase levels (10%), fatigue (4%), and diarrhea (4%). Immune-related adverse events (IRAEs) were also observed. IRAEs are believed to arise from general immunologic enhancement, and can include any organ system. Ipi-nivo now has well-recognized immune-mediated toxicities, of which rash, colitis, and endocrinopathies are the most common but can be manageable, as observed in CheckMate-214. Although rare, fulminant and even fatal toxicities can occur, including but not limited to myocarditis, Guillain–Barre syndrome, and toxic epidermal necrolysis. In CheckMate-214, eight treatment-related deaths in the ipi-nivo arm, although the investigators did not specify which were IRAE-specific [50]. Thirty-five percent of patients experiencing IRAEs received high-dose glucocorticoids (≥40 mg of prednisone per day or equivalent). Most common TRAEs in patients treated with sunitinib included hypertension (16%), fatigue (9%), and PPE; treatment-related deaths occurred in four patients [50].

Thus, the treatment benefits of ipi-nivo include deep and durable responses, treatment-free intervals, the relatively longer follow-up compared to other combination therapies, and the lack of daily AEs associated with TKIs which markedly dampen patient QoL.

TKI and ICI Combinations

Targets of TKIs play important roles in tumor cell proliferation and/or neovascularization, including MET, VEGFR, AXL, and RET. AXL and other targets such as TYRO3 and MER have also been implicated in tumor immune suppression [55, 56]. Preclinical studies and clinical observations suggest that TKIs may promote an immune-permissive environment through inhibition of immune-modulatory targets and enhanced T cell infiltration into the tumor microenvironment [55–57]. However, whether the efficacy of TKI/ICI combinations is additive or synergistic is an area of active investigation, with a lean towards an additive effect, though no definitive conclusion can be drawn at this time [56–58]. Here, we present efficacy data for each combination approved for first-line metastatic RCC treatment and discuss adverse events, which are similar, in aggregate.

Axitinib with Pembrolizumab

The phase III, KEYNOTE-426 trial (NCT02853331) compared first-line axitinib 5 mg orally twice daily plus pembrolizumab 200 mg intravenously every 3 weeks v. sunitinib 50 mg daily 4 weeks every 6 weeks in patients with advanced ccRCC of all IMDC risk groups [59, 60]. Observed benefit on co-primary endpoints of PFS and OS in the ITT population was preserved and at a median follow-up of 30.6 months, the following were reported: median PFS 15.4 v. 11.1 months, HR 0.71, 95% CI 0.60–0.84, p <0.0001; median OS not reached v. 35.7 months, HR 0.68, 95% CI 0.55–0.85, p = 0.0003. In addition, ORRs were 60.4% v. 39.6%, respectively. At a median follow-up of 42.8 months, median PFS rates where 15.7% v. 11.1%, HR 0.68, 95% CI 0.58–0.8, p <0.0001; and median OS rates were 45.7% v. 40.1%, HR 0.73, 95% Cl 0.60–0.88, p <0.001. ORRs were 60.4% v. 39.6% (p <0.0001) [59–61]. The PFS benefit was observed across all risk groups and regardless of PD-L1 expression. The US FDA approved first-line axi-pembro for the treatment of patients with advanced ccRCC across all IMDC risk groups in April 2019.

Axitinib with Avelumab

In patients with advanced ccRCC, first-line axitinib (5 mg orally twice daily) with avelumab (10 mg/kg given intravenously every 2 weeks) (n = 442) was compared to sunitinib (50 mg daily, 4 weeks on/2 weeks off) (n = 444) in the phase III, JAVELIN Renal 101 trial (NCT02684006). Primary endpoints were PFS and OS in patients with *PD-L1 positive tumors* (n = 560/886) [62–64]. PFS was significantly prolonged in the axi-ave arm for both *PD-L1 positive* and ITT population (PD-L1 positive: PFS 13.8 v. 7.2 months, HR 0.61, 95% CI 0.47–0.79, p <0.001; ITT population: 13.8 v. 8.4 months, HR 0.69, 95% CI 0.56–0.84, p <0.001). Results remained stable at subsequent analyses after a minimum follow-up of 13 months [62, 63]. However, OS data remained immature at the time of the second interim analysis [62]. PD-L1 and tumor mutational burden did not differentiate responses to axi-ave versus sunitinib [63]. Based on superior PFS, axi-ave was approved by the US FDA for first-line treatment of advanced ccRCC of all risk groups (in May 2019), but is not a preferred first-line regimen per NCCN guidelines due to immature OS data [4].

Cabozantinib with Nivolumab

Based on the effectiveness of both cabozantinib and nivolumab as monotherapy, the CheckMate-9ER trial (NCT03141177) was designed to evaluate the combination of cabozantinib 40 mg once daily with nivolumab 240 mg every 2 weeks (n = 323) v. sunitinib 50 mg once daily 4 weeks on of every 6-week cycle (n = 328). This phase

III trial enrolled patients with treatment naïve, advanced ccRCC of all IMDC risk groups. Primary endpoint was PFS in the ITT population while secondary efficacy endpoints included OS and ORR [65]. The combination of cabozantinib/nivolumab demonstrated superior efficacy over sunitinib in the ITT population with median PFS of 16.6 v. 8.3 months (HR 0.51, 95% CI, 0.41–0.64, p <0.001), ORR of 55.7% v. 27.1% (p <0.001), and 12-month OS rate of 85.7% v. 75.6% (HR 0.60, 98.89% CI 0.40–0.89, p = 0.001) [65]. The PFS, OS, and ORR benefits of cabo-nivo was generally consistent across IMDC risk groups and independent of PD-L1 expression [65]. At a median follow-up of 23.5 months, median OS was not reached with cabo-nivo but was 29.5 months with sunitinib (p = 0.0034) in the ITT population, and the benefit of cabo-nivo was observed across subgroups [66, 67]. At a median follow-up of 32.9 months, the latest pre-planned analysis showed final median OS of 37.7 months for cabo-nivo v. 34.3 months for sunitinib (HR 0.70, 95% CI 0.55–0.90); PFS and ORR benefit also remained strongly in favor of cabo-nivo (PFS median 16.6 v. 8.3 months, HR 0.56, 95% CI 0.46–0.68; ORR 55.7% v. 28.4%) [68]. The FDA approved first-line cabo-nivo for the treatment of patients with advanced ccRCC across all IMDC risk groups in January 2021. Cabo-nivo therefore is an active—and overall well tolerated/managed—treatment combination in the first-line setting.

Lenvatinib with Pembrolizumab

Len-pembro is the latest ICI-TKI combination to enter the first-line treatment paradigm for advanced ccRCC. The phase III, CLEAR trial (NCT02811861) evaluated len-pembro v. lenvatinib/everolimus v. sunitinib monotherapy [69, 70]. The trial found superiority of lenvatinib 20 mg once daily plus pembrolizumab 200 mg once every 3 weeks (n = 355) over sunitinib 50 mg once daily 4 weeks on every 6-week cycle (n = 357) with median PFS of 23.9 v. 9.2 months (HR 0.39, 95% CI 0.32–0.49, p <0.001), ORR of 71% v. 36.1%, and longer OS (HR 0.66, 95% CI 0.49–0.88, p = 0.005) [69]. PFS benefit was seen across all IMDC risk groups and was not contingent upon PD-L1 expression, organ metastasis, prior nephrectomy, or sarcomatoid component by histology [69, 70]. The FDA approved len-pembro for the treatment of patients with advanced ccRCC across all risk groups in August 2021.

Safety

Toxicity of the aforementioned TKI/ICI combinations was reflective of the TRAEs of the individual drugs, without overt, synergistic toxicity [50–52, 59–67, 69, 70]. Grade ≥3 TRAEs occurred in 50.9–58.8% of patients receiving sunitinib across the 4 TKI/ICI combination trials: most commonly fatigue, hypertension, PPE, diarrhea, and cytopenia [50–52, 59–67, 69, 70]. Grade ≥3 TRAEs occurred in 62.9% of patients receiving axi-pembro, 56.7% of patients receiving axi-ave, 60.6% of patients receiving cabo-nivo, and 71.6% of patients receiving len-pembro with

expected TKI-associated TRAEs (similar to sunitinib) and ICI-associated immune-related adverse events (IRAEs, such as rash, hepatitis, colitis, thyroiditis and other endocrine-related disorders) [50–52, 59–67, 69, 70]. Dose reduction and/or interruption of TKI and dose interruption of ICI were common in TKI/ICI combinations, with discontinuation of both drugs in 10.7% (axi-pembro), 7.6% (axi-ave), 5.6% (cabo-nivo), and 13.4% (len-pembro) of patients in the respective trials. Treatment-related deaths occurred with both TKI/ICI combinations and sunitinib, but were overall low (four or fewer in each of the TKI/ICI cohorts and seven or fewer for sunitinib in each of the trials) with myasthenia gravis and myocarditis as TKI/ICI toxicities occurring more than once. Additional key safety features are detailed in Table 12.3.

Therapeutic Approach

Combination regimens with ICI/ICI (ipi-nivo) or TKI/ICI (axi-pembro, axi-ave, cabo-nivo, and len-pembro) are now standard of care based on their superior efficacy over TKI monotherapy in landmark, phase III trials. However, inherent differences among trials (such as baseline characteristic, endpoints, and statistical analysis) caution against cross-trial comparisons, and lack of head-to-head studies makes selecting optimal combinations a challenge. Several factors should be considered and may offer guidance when selecting first-line therapies for advanced ccRCC.

The IMDC risk model retained its prognostic value in patients with advanced RCC treated with single agent ICI (second-line therapy, median OS not reached v. 26.7 v. 12.1 months in favorable, intermediate, and poor IMDC risk groups, respectively), and was utilized for cohort stratification in the ICI/ICI and TKI/ICI combination trials highlighted above [71]. CheckMate-214 specifically evaluated ipi-nivo in patients with intermediate/poor IMDC risk disease and met its primary endpoints of superior OS and ORR when compared to sunitinib, which was sustained on extended follow-up [50–52]. Additionally, delayed PFS benefit was also observed, with curve separation in favor of ipi-nivo and durable responses (30% of patients without disease progression at 5 years) [52, 53]. These lend strong support for ipi-nivo for the treatment of intermediate/poor risk disease, and this regimen is a preferred regimen per NCCN guidelines [4]. In contrast, KEYNOTE-426, CheckMate-9ER, and CLEAR trials evaluated TKI/ICI combinations across IMDC risk groups, where they showed superior PFS, OS, and/or ORR (Table 12.2). It is worth noting the superiority of TKI/ICI combinations over sunitinib in each of the TKI/ICI trials carried over particularly well in the intermediate/poor risk subgroups (Table 12.2).

The decision between ipi-nivo and one of the three preferred TKI/ICI combinations (axi-pembro, cabo-nivo, or len-pembro) for patients with intermediate/poor risk disease should consider differential advantages. Ipi-nivo has the strongest long-term follow-up data (median 67.7 months), and similar to other ICI-based therapies, efficacy benefits are durable. Furthermore, the regimen has shown long-term OS

superiority against sunitinib. In addition, after the initial 12 weeks of induction/combination therapy, patients go on to nivolumab monotherapy, which is quite tolerable, and some patients come off therapy all-together [52, 54]. In contrast, TKI/ICI combinations could present with both IRAEs and TKI-associated toxicities, with the latter particularly having the potential to dampen patient's QoL.

One disadvantage of ipi-nivo is the relatively high primary progression rate (17.6% in ITT, 19.3% in intermediate/poor risk group) compared to TKI/ICI combinations (5.4–12.4%, Table 12.2). In patients with high disease burden and/or significantly symptomatic disease, TKI/ICI may offer quicker and a greater assurance of relief. Whether the increased efficacy from TKI/ICI combination is a synergistic or an additive effect remains to be determined, but given inasmuch as ~30% of patients fail to receive second-line therapy, the TKI/ICI combination ensure that all patients are exposed to both drug classes, which is of particularly important in symptomatic or high disease burden patients [57].

Choice among the three preferred TKI/ICI combinations will likely depend on clinical and patient factors, as well as shared decision making. Axi-pembro has become a widely used regimen since its approval. Several factors contribute to its broad acceptance, including (1) axitinib's relatively narrow spectrum of targets and short-half life, making it easier to discern axitinib-related toxicities v. IRAEs from pembrolizumab, as well as (2) lower incidence of high grade IRAEs necessitating high-dose glucocorticoid use (11.1–19.1% with TKI/ICI combinations when compared to 35% with ipi-nivo). The axi-pembro combination also leaves other TKIs such as cabozantinib or lenvatinib (in combination with everolimus) for later therapy in the salvage setting. Alternatively, the very low primary progression rate of cabo-nivo and len-pembro when compared to axi-pembro or ipi-nivo should be taken into consideration (6.2% and 5.4%, respectively, v. 12.4% for axi-pembro and 17.6% for ipi-nivo in the ITT population**,** Table 12.2).

Axi-pembro, cabo-nivo, and len-pembro are also recommended regimens in the treatment of patients with IMDC favorable risk disease [4]. Efficacy advantages of TKI/ICI combinations over sunitinib were observed, though less pronounced, in the favorable risk group when compared to the ITT population or intermediate/poor risk groups (Table 12.2). Additionally, it is worth noting that no combination regimen has shown OS benefits over sunitinib in the favorable risk group (Table 12.2).

Ipi-nivo is currently not a preferred combination as exploratory analysis of the favorable risk group in CheckMate-214 favored sunitinib over ipi-nivo in both PFS (15.3 v. 25.1, HR = 2.18, 95% CI 1.29–3.68; p <0.001) and ORR (30% v. 52%) with inconclusive OS observations, although these should be interpreted with caution as the study was not powered to detect these differences in the favorable risk subset [50–52]. For example, first-line pembrolizumab or nivolumab (±salvage ipilimumab), respectively, showed response in favorable risk patients (pembrolizumab: Cohort A of KeyNote 427 trial, ORR 27.5%; nivolumab ± salvage ipilimumab: HCRN GU16-260 trial, ORR 41.4%), respectively [72, 73]. As such, further data is needed to determine the role of ICIs in favorable risk patients.

Some studies suggest favorable risk disease has fewer inflammatory features and more angiogenic drivers than intermediate/poor risk disease, and patients may

derive more benefit from the antiangiogenic, TKI component of the treatment paradigm. McDermott and colleagues' exploratory analysis of the phase II, IMmotion150 trial (NCT02420821) identified gene expression signatures that may correlate with VEGF inhibition v. ICI response [74]. The trial evaluated the efficacy of atezolizumab with or without bevacizumab versus sunitinib in advanced RCC. In the sunitinib cohort, an angiogenic gene expression signature was associated with improved ORR and PFS (ORR 46% v. 9% and PFS HR 0.31, 95% CI 0.18–0.55, respectively) [74]. In turn, bevacizumab/atezolizumab demonstrated improved PFS over sunitinib in patients with tumors of low angiogenesis (PFS: HR 0.59, 95% CI 0.35–0.98) or high T-effector signatures (immune-related marker, PFS: HR 0.55, 95% CI 0.32–0.95) [74]. Motzer and colleagues utilized IMmotion151 trial data (NCT02420821) to transcriptionally profiled 823 pre-treatment tumors from advanced RCC [75]. The study identified seven molecular subsets with distinct angiogenesis, immune, cell cycle, metabolism, and stromal programs, where sunitinib and atezolizumab + bevacizumab showed increased efficacy in high angiogenesis molecular subset, and the atezolizumab + bevacizumab combination also improving clinical benefit in tumors with high T-effector and/or cell cycle transcription [75]. External validation of these molecular subgroups utilizing IMmotion150 trial data (NCT02420821) showed high concordance [75]. Angiogenic v. immune gene signatures have also been evaluated in exploratory analysis of other trials, such as NIVOREN (NCT03013335), JAVELIN Renal 101 (NCT02684006), and CheckMate-214 (NCT02231749), with some promise in the predictive ability of angiogenic signatures for TKI response, but mixed results with immune signatures for ICI response [63, 76–78].

Evaluation of angiogenic v. immune gene signatures of favorable v. intermediate/poor risk groups is worth pursuing prospectively in future studies. Furthermore, favorable risk disease is potentially a heterogenous disease entity not well captured by the IMDC (or MSKCC) risk model(s). For example, ipi-nivo lead to 13% CR and durable PRs in a subset of patients with IMDC favorable risk disease, and whether their disease characteristic is different from the non-responders may offer insights [53]. Thus, additional biological and/or molecular features beyond the clinical features of IMDC (or MSKCC) have been explored previously and should be further characterized [79, 80]. The predictive capabilities of biomarkers such as PD-L1 and tumor mutational burden (TMB) remain inconclusive in kidney cancer. Further deciphering and biomarker discoveries are needed for further patient and optimal treatment selection. These biomarkers are discussed at length in a separate chapter.

Finally, toxicity, tolerability, and QoL should be considered in the first-line treatment decision for patients with advanced RCC. To highlight, ipi-nivo and cabo-nivo demonstrated superior patient reported outcomes/QoL compared to sunitinib in CheckMate-214 and CheckMate-9ER, respectively, particularly on longer follow-up [65, 81–83]. In other TKI/ICI combination trials with available data, QoL seems comparable between combination and sunitinib, although data remains immature [84]. Consideration and attention should be given to the long-term effects of TKI and ICI on both cancer control and the patient as a whole.

Concluding Remarks

In this chapter we briefly reviewed the cytokine and TKI eras with a subsequent focus on ICI/ICI and TKI/ICI combination regimens, which are now the standard of care in the treatment of first line, advanced ccRCC. The critical decision to select the optimal treatment for each patient among these combinations remains a challenge and further predictive biomarkers are needed. Triplet therapy and novel agents such as belzutifan are actively being explored. Ultimately the goal is to extend overall survival with deeper and more durable responses and prolonged treatment-free intervals.

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13 Subsequent Line Systemic Treatment Options for Advanced Renal Cell Carcinoma

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Abbreviations

ADC	Antibody-drug conjugate
AE	Adverse event
ccRCC	Clear cell RCC
CR	Complete response
ENPP3	Ectonucleotide phosphodiesterase-pyrophosphatase 3
FRACTION-RCC	Fast Real-Time Assessment of Combination Therapies in Immuno-Oncology
HIF	Hypoxia Inducible Factor
ICB	Immune Checkpoint Blockade
IL-2	Interleukin 2
mRCC	Metastatic renal cell carcinoma
mTOR	Mammalian target of rapamycin
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
Tela	Telaglenastat
TIM1	T-cell immunoglobulin and mucin domain 1
TKI	Tyrosine kinase inhibitor
VEGFR	Vascular endothelial growth factor receptor
VHL	Von-Hippel Lindau

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Section I: Treatment of Metastatic Renal Cell Carcinoma (mRCC) Prior to the Use of Immune Checkpoint Blockade (ICB) in the Front-Line Setting

Vascular Endothelial Growth Factor (VEGF) Tyrosine Kinase Inhibitors (TKIs) emerged as a cornerstone of therapy in advanced RCC when Motzer et al. reported that sunitinib achieved an objective response rate (ORR) of 31% as compared to 6% for patients receiving interferon [1]. At the same time, sorafenib was the first agent shown to improve progression-free survival (PFS) in the treatment refractory setting, albeit in patients progressing on cytokine therapy, when Escudier et al. showed a prolonged PFS from 2.8 to 5.5 months and increased ORR from 2% to 10% as compared to patients receiving placebo [2]. This paved the way for further clinical trials that investigated other VEGF TKIs in the second-line setting. Motzer et al. showed superiority of second-line axitinib over sorafenib in mRCC with prolongation of PFS (8.3 vs. 5.7 months), but both arms had similar overall survival (OS) [3].

The RECORD-I study established that everolimus, a mammalian target of rapamycin (mTOR) inhibitor, is safe and effective in patients with mRCC progressing after VEGF TKI. Median PFS was 4.9 months versus 1.9 months for those treated with placebo, though no difference in OS was observed between the two arms [4]. Given this data, everolimus was and remains a standard therapy in the post-VEGFR TKI setting, and likewise continues to be used as the comparator arm in pivotal trials [5, 6].

CheckMate 025 was the first randomized trial to explore the role of ICB in advanced RCC. This trial showed that nivolumab was more efficacious and better tolerated than everolimus in the second-line setting post-TKI. Patients treated with nivolumab had a median OS of 25 versus 19.6 months, and an ORR of 25% versus 5% compared to patients in the everolimus arm. Also seen was a lower incidence of grade 3/4 adverse events (AEs): 19% in those receiving nivolumab versus 37% in patients treated with everolimus [7]. This was the first trial to establish a standard role for ICB in RCC. At the same time, results from the phase 3 METEOR trial established the role of cabozantinib, a multikinase inhibitor targeting MET and AXL in addition to VEGF, in the treatment of RCC. In this trial, patients progressing on at least one VEGF targeted therapy had a better OS (21.4 vs. 16.5 months), PFS (7.4 vs. 3.8 months), and ORR (17% vs. 3%) when receiving cabozantinib compared to everolimus [5]. Later, Motzer et al. showed in a randomized phase 2 trial that the combination of lenvatinib and everolimus significantly improved PFS of patients receiving treatment after progression on first-line VEGFR TKI when compared to everolimus alone (median 14.6 vs. 5.5 months) but not when compared to lenvatinib alone (median 7.4 months), and that lenvatinib alone significantly improved PFS compared to everolimus alone [6]. However, these trials were done prior to the use of ICB in the first-line setting. By nature of this design, no patients in Checkmate 025 had received prior ICB, and only 4.8% and 3.2% had received prior ICB in the METEOR and lenvatinib/everolimus trials respectively [5, 6]. Therefore, the management of RCC in the second-line setting after progression on first-line ICB has become an increasingly important area of investigation.

Section II: Status of Therapies Post-ICB in the Front-Line Setting

Combination therapies of ipilimumab plus nivolumab, axitinib plus pembrolizumab, axitinib plus avelumab, cabozantinib plus nivolumab, or lenvatinib plus pembrolizumab are all ICB-based regimens that have been approved for the front-line treatment of mRCC [8–12]. Since most patients now receive ICB in the first line, this has necessitated a shift in second-line treatment strategies. The search is currently ongoing to find the optimal combination of ICB treatments and predictive biomarkers of response that can guide therapy given the minimal data on biomarkers in the second-line setting [13]. However, it is also crucial to consider subsequent therapies that can be utilized in the setting of progression of mRCC post-ICB including TKI, ICB, or a combination of both.

TKI Post-ICB

Retrospective Cohorts

As treatment options rapidly evolved in RCC, clinicians continued to use TKI in the treatment refractory setting independent of the front-line therapy used. Subsequently, multiple retrospective analyses were performed to describe the clinical outcomes of patients with mRCC receiving TKI after progressing on ICB alone or in combination with TKI, providing insights into toxicity and efficacy (Table 13.1). These analyses were limited by variability in the type of ICB provided initially and the TKI utilized subsequently; thus, it is challenging to determine whether one agent is superior to another based on these analyses alone. However, they do provide important evidence that TKIs maintain activity in the post-ICB setting. Efficacy does vary based on preceding therapies, as patients receiving ICB alone in the front-line setting have improved outcomes with VEGF therapy compared to those who received VEGF and ICB, either sequentially or in combination. Importantly, there did not appear to be any new toxicity signals.

Retrospective analyses looking at cabozantinib and lenvatinib/everolimus, two agents shown to improve OS in the VEGF refractory setting, are noteworthy. McGregor et al. reported on 80 patients receiving cabozantinib post-ICB achieving an ORR of 42% when administered after single or combination ICB, and 28% after VEGF-ICB combinations. In that cohort, dose reduction secondary to AE occurred in 45% of patients mainly due to fatigue (27%) [23]. This was supported by Iacovelli et al. reporting on 84 patients with mRCC receiving cabozantinib post-nivolumab achieving an ORR of 52% and a median PFS of 11.5 months, which was further stratified based on early (at third line) or late (at >third line) administration of cabozantinib wherein the median PFS was not reached for the former versus 11.1 months for the latter [24]. Wiele et al. assessed the clinical outcomes of 55 patients with heavily pre-treated mRCC post-ICB and VEGF TKIs (including cabozantinib) who received lenvatinib/everolimus combination and achieved an ORR of 21.8% and a median PFS of 6.2 months, with around 50.9% of patients requiring dose reductions and 7.3% discontinuing treatment due to toxicity [25].

Table 13.1 Retrospective cohorts assessing the efficacy and safety of ICB in patients with mRCC following treatment with VEGF inhibitors

Author	Number of lines of therapy prior to VEGF inhibitor	VEGF inhibitor	ICB alone (N)	ICB/VEGF combination (N)	ORR (ICB alone)	ORR (ICB VEGF)	% D/C for toxicity
Albiges et al. 2015 [14]	≥1	Axitinib (20) Pazopanib (14) Sorafenib (1) Sunitinib (4) Bevacizumab (5)	PD-1/L1 inhibitors (44)	NA	36%	NA	NR
Cao et al. 2020 [15]	≥1	Pazopanib: 2L (182) 3L+ (76)	In 2L setting: Nivolumab (124) Pembrolizumab (22) Nivolumab + Ipilimumab (24) Ipilimumab (5)	NA	NA	NA	11%
Shah et al. 2019 [16]	1	Pazopanib (19) Sunitinib (6) Axitinib (25) Cabozantinib (20)	– Nivolumab or Atezolizumab (12) – Nivolumab + Ipilimumab (33)	PD-L1 inhibitor + Bevacizumab (25)	−50% −44%	33%	27%
Nadal et al. 2016 [17]	≥1	Axitinib (47) Pazopanib (10) Sunitinib (11) Sorafenib (2)	NA (47)	NR (21)	36%	10%	NR
Auvray et al. 2019 [18]	1	Sunitinib (17) Pazopanib (8) Axitinib (6) Cabozantinib (2)	Nivolumab + Ipilimumab (33)	NA	36%	NA	9.1%

Graham et al. 2021 [19]	≥1	Axitinib[a] (83) Cabozantinib (64) Sunitinib (31) Pazopanib (29) Sorafenib (11) Bevacizumab (2)	Nivolumab ± Ipilimumab (220) Other ICB (56)	NA	29.8%	NA	26.3%
Dudani et al. 2020 [20]	1	Axitinib (7) Cabozantinib (11) Pazopanib (11) Sunitinib (24) Lenvatinib + Everolimus (2)	Nivolumab + Ipilimumab (28)	NR (27)	45%	15%	NR
Stukalin et al. 2020 [21]	1	Post-ICB: Sunitinib (39) Cabozantinib (10) Axitinib (4) Pazopanib (20) Lenvatinib/Everolimus (2)	Nivolumab + Ipilimumab (75)	NR (67)	37%	12%	NR
		Post-VEGF/ICB: Sunitinib (39) Cabozantinib (10) Axitinib (4) Pazopanib (20) Lenvatinib/Everolimus (2)					
Ged et al. 2020[b] [22]	1 or 2	Cabozantinib (22) Axitinib (18) Pazopanib (4) Lenvatinib/everolimus (4) Axitinib and dalantercept (2), Sunitinib (1), Sorafenib (1)	NA	Atezolizumab + bevacizumab (34) Avelumab + axitinib(12) Pembrolizumab + lenvatinib (8) Pembrolizumab + pazopanib (2) Pembrolizumab + axitinib (1) Nivolumab + sunitinib (1) Nivolumab + bevacizumab (1)	NA	25%	NR

[a] Only TKI following Nivolumab ± Ipilimumab are documented

[b] Three patients were treated with mTOR inhibitors

Prospective Trials

Several clinical trials have now been performed assessing the role of VEGF TKI following progression on ICB. In a phase 2 trial, Ornstein et al. reported on 40 patients with mRCC receiving axitinib following ICB alone or in combination with bevacizumab or VEGFR TKI, who were followed for a median of 8.7 months and achieved a median PFS of 8.8 months. However, 75% of these patients developed hypertension (60% grade ≥3). Other serious AEs related to therapy were dehydration and diarrhea, occurring in 20% of the cohort [26].

Furthermore, two crucial phase 3 trials shed more light in this space. The ENTRATA trial studied the combination of everolimus with the glutaminase inhibitor telaglenastat (Tela) in patients with mRCC who had progressed following two lines of systemic therapy including a VEGF TKI, and this combination significantly increased PFS compared to everolimus alone (3.8 vs. 1.9 months) [27]. Given early preclinical data that supported the combination of Tela with cabozantinib [28], the randomized phase II CANTATA trial compared this combination to cabozantinib plus placebo among patients with mRCC treated with one or two prior lines of systemic therapy, including ICB or VEGF therapy [29]. This trial did not show a benefit for the addition of Tela to cabozantinib, which yielded a similar PFS of just over 9 months and ORR near 30% in both arms, but it did provide prospective data regarding the role of cabozantinib post-ICB [29]. In an exploratory analysis, the subgroup of patients treated with prior ICB had a longer median PFS in the Tela and cabozantinib arm compared to the placebo and cabozantinib arm (11.1 vs. 9.2 months), although these results did not reach statistical significance. Furthermore, among those in the cabozantinib/placebo arm, median PFS was 9.2 months for post-ICB patients versus 9.5 months for those who did not receive prior ICB, and ORR was 32% and 20% respectively. These data compare favorably to the early evidence from the few post-ICB patients from the METEOR trial of cabozantinib, which reported ORR of 17% and PFS of 7.4 months; however, it is difficult to make comparisons between trials given the small numbers in METEOR analysis and differences in prior therapies. As for safety profiles, the incidence of AEs due to cabozantinib in CANTATA was similar to that seen in the METEOR trial, occurring in 71% of the Tela and cabozantinib and 79% of patients in the placebo and cabozantinib arm. Hypertension (17% and 18%) and diarrhea (15% and 13%) were the most frequently occurring AEs in the two arms, respectively.

The other randomized data for VEGF TKI in the modern era comes from TIVO-3, the first trial to provide prospective data in the third or fourth line [30]. Previously, the phase 3 TIVO-1 trial comparing tivozanib versus sorafenib in the first-line setting for mRCC showed that tivozanib prolonged PFS (11.9 months vs. 9.1 months) but not OS [31]. In the open label randomized phase 3 TIVO-3 trial, patients with metastatic RCC progressing on at least two prior therapies, including at least one VEGF TKI, were randomized to tivozanib or sorafenib. Overall, tivozanib improved PFS compared to sorafenib (5.6 months vs. 3.9 months),

especially if patients belonged to the favorable risk group (median PFS 11.1 months vs. 6 months), and tivozanib was well tolerated [30]. For post-ICB patients, the median PFS was 7.3 months in the tivozanib arm compared to 5.1 months in the sorafenib arm, while median PFS was 5.5 months with tivozanib and 3.7 months with sorafenib in post-VEGF patients. Despite the PFS differences, there was no improvement in OS seen.

Taken together, these data reinforce what was seen in retrospective trials: TKIs have an important role in the refractory mRCC setting independent of front-line therapy.

ICB Post-ICB

Retrospective Cohorts

While initial data reported by Martini et al. showed that patients rechallenged with ICB post-ICB across different cancer types did not respond to treatment, more contemporary datasets have added more data on clinical outcomes in this setting [32]. In mRCC, Ravi et al. retrospectively reviewed patients who had progressed after receiving first-line ICB and were rechallenged with another ICB in the second-line setting, and showed that this strategy resulted in an ORR of 23% with a higher likelihood of response in those who had responded to ICB initially (ORR = 29% in responders vs. 21% in non-responders) [33]. The cohort included 69 patients of whom 27 had received a single-agent ICB and 29 patients received a combination of ICB and targeted therapy in the first-line setting. After discontinuing treatment due to progression or toxicity, the patients received a single-agent ($n = 26$) or dual-agent ($n = 22$) ICB regimen at second line. Furthermore, this approach seems to be safe as grade 3 or higher AEs occurred in 26% and 16% of patients following ICB in the first and second line, respectively. Focusing on the combination of nivolumab and ipilimumab, Gul et al. reported that 20% of 45 patients with mRCC responded to rechallenging with nivolumab and ipilimumab following the use of either prior PD-1 ($n = 34$) or PD-L1 inhibitors ($n = 11$) [34].

Prospective Trials

The best data for the role of nivolumab and ipilimumab following progression on immunotherapy comes from the multi-arm FRACTION-RCC trial, where 15% ($n = 7$) of the 46 patients randomized to the nivolumab and ipilimumab combination arm responded to treatment with a duration of response ranging between 2 and >19 months (5 had an ongoing response at time of cutoff) [35]. Of note, six of the seven responders had received at least two prior lines of therapy. No treatment-related deaths were reported whereas grade 3 or 4 AEs were reported in 13 patients (28.3%), most commonly diarrhea and increased amylase/lipase levels. This is comparable to activity seen in prospective trials exploring an adaptive approach where the addition of ipilimumab for those patients who have a suboptimal response to

nivolumab alone achieved ORRs of 18%, 11%, and 4% in the TITAN-RCC [36], HCRN [37], and OMNIVORE [38] trials, respectively.

ICB-TKI Combination Post-ICB

Taylor et al. reported that among patients with solid tumors progressing post-ICB, those with mRCC achieved the highest ORR (63%) with the combination of lenvatinib and pembrolizumab [39]. This was further validated in the KEYNOTE-146 trial assessing this combination in 143 patients that were stratified into 3 groups: 22 were treatment-naïve, 17 had already received non-ICB treatment, and 104 had already received ICB treatment. ORR was achieved in 16 (73%), 7 (41%), and 58 (55.8%) patients in each group respectively, as assessed by irRECIST after 24 weeks of treatment [40]. From a safety standpoint, 82 patients (57%) had grade 3 AEs and 10 (7%) had grade 4 AEs. Hypertension was the most common grade 3 AE, occurring in 30 (21%) patients across all groups. Treatment-related serious AEs occurred in 36 (25%) patients and three treatment-related deaths occurred due to upper gastrointestinal hemorrhage, sudden death, and pneumonia.

Similarly, the phase Ib/II TiNivo trial enrolled 25 patients who received the combination of ICB-TKI in the second-line setting and achieved an ORR of 62% [41]. Response was similar between treatment naïve and previously treated patients, and side effect profiles were similar to other ICB-TKI combinations, with hypertension being the most reported AE. While the response rate exceeds those seen with TKI monotherapy seen in phase 2 trials of lenvatinib (27%) and tivozanib (18%), the extent of clinical benefit gained by continuing ICB remains unclear [6, 30]. This is being addressed in two ongoing randomized trials: CONTACT-03 (NCT04338269) is testing the combination of atezolizumab and cabozantinib in the second or third line treatment of mRCC following progression on ICB [42] and the TiNivo-2 (NCT04987203) trial assessing the combination of tivozanib and nivolumab versus tivozanib in this same space. In CONTACT-03, treatment will be discontinued if toxicity develops or there is loss of clinical benefit whereas in TiNivo-2, nivolumab will be discontinued in all patients after 2 years as per the study design. These trials will be critical to establishing the role of maintenance ICB. Finally, the response adaptive design PDIGREE trial (NCT03793166) will further explore the role of combination ICB/TKI following ICB albeit not in the treatment refractory space. The trial is enrolling patients with intermediate and poor risk advanced clear cell RCC and all patients will receive the combination nivolumab and ipilimumab. Patients who do not experience a complete response (CR) or progressive disease (PD) by irRECIST will be randomized to nivolumab maintenance alone or nivolumab and cabozantinib whereas those with PD will receive cabozantinib which further sheds light on its role in the post-ICB setting [43].

Current State

The management of RCC after progression on first-line combination therapy with ICB alone or in combination with VEGF continues to evolve, and ongoing trials will be critical to defining the role of maintenance ICB and rechallenge with ICB. As we await this data, treatment in the second-line setting and beyond will be individualized based on agents used in the front-line setting. Retrospective data supports use of TKI in this setting, with prospective trials showing retained efficacy and no new toxicity signals. Ultimately, given the improvement in OS with cabozantinib and lenvatinib/everolimus in the refractory setting, these agents should be considered preferentially if not already used in the front-line setting. Prospective data for tivozanib in third line and beyond supports its role as well, as we wait for novel targets.

Section III: Novel Targets

While there have been considerable advances in the treatment of RCC, there remains a need for novel therapeutic targets. Recent advances in biomedical research have improved our understanding of RCC pathophysiology and uncovered a few such targets, especially those present on immune cells as RCC is regarded as highly-immune inflamed tumors [44]. A wide array of novel targets involving the immune system can be leveraged including novel cytokine therapies, next-generation ICB, and inhibitors of metabolic pathways of the immune microenvironment [45].

While the strategy of inhibiting glutaminase with Tela showed initial promise, there was no improvement in PFS or ORR with addition of Tela to cabozantinib [29]. With the success of antibody-drug conjugates (ADCs) in other genitourinary tumors, such as enfortumab vedotin in urothelial carcinoma [46], several ADCs have been tested in RCC (Table 13.2). Targets under investigation with this treatment modality include T-cell immunoglobulin and mucin domain 1 (TIM1), an immune regulatory glycoprotein expressed on T cells as well as RCC cells [52]. In a phase I clinical trial, CDX-014, an ADC that targets TIM1 showed minimal response and acceptable toxicity among patie. XXnts with advanced refractory RCC [47]. AGS-16C3F is an ADC targeting ectonucleotide phosphodiesterase-pyrophosphatase 3 (ENPP3) that showed promise in phase I clinical trials [53] but unfortunately, a phase 2 trial comparing to axitinib demonstrated PFS of under 3 months [48]. CD27L is another cell surface protein expressed on activated T cells that can be targeted by AMG 172, an ADC which has shown limited clinical activity in relapsed/refractory clear cell RCC (ccRCC), as well as Vorsetuzumab mafodotin (SGN-75) which did not make it beyond phase I clinical trials [49, 50]. Similarly, the phase I trial assessing HKT288 which targets Cadherin-6 was not completed [54].

Table 13.2 ADCs investigated in RCC

Clinical trial number	Phase	ADC	Target
NCT02837991 [47]	I	CDX-014	TIM1
NCT02639182 [48]	II	AGS-16C3F	ENPP3
NCT01497821 [49]	I	AMG 172	CD27L
NCT01015911 [50]	I	SGN-75	CD27L
NCT02947152 [51]	I	HKT288	Cadherin-6

Because molecular studies have revealed that everolimus specifically inhibits the mTOR complex 1 but not complex 2, a novel mTOR inhibitor targeting both mTOR complexes (MTORC) 1 and 2 has also been explored. A randomized, 3-arm phase 2 trial (NCT02724020) exploring the dual MTORC1/2 inhibitor sapanisertib versus sapanisertib with PI3K inhibitor TAK-117 versus everolimus in patients with treatment refractory clear cell RCC showed no benefit to sapanisertib, either alone or in combination with TAK-117, over everolimus. No responses were seen in 32 patients with single-agent sapanisertib while everolimus showed an ORR of 13% ($n = 4$) and better tolerability [55]. In a single arm trial of 38 patients, sapanisertib showed minimal activity in a treatment refractory cohort, including those with variant RCC histologies [56].

The most promising new target in refractory RCC is the Hypoxia Inducible Factor (HIF)-2α pathway. The majority of patients with sporadic ccRCC, the most common subtype of RCC, have defective Von-Hippel Lindau (VHL) protein, loss of which leads to constitutive activity of the HIF-2α transcription factor [57]. MK-6482 (belzutifan), a potent, selective HIF-2α inhibitor, is being tested in phase I and II clinical trials for patients with ccRCC [58–60]. It has been approved for patients with RCC in the setting of VHL disease given data from Jonasch et al. showing ORR of 49% and is being studied in advanced ccRCC [58]. Choueiri et al. reported that belzutifan achieved an ORR of 25% in a phase I clinical trial of 55 heavily pretreated patients with ccRCC that mostly belonged to the poor/intermediate risk groups, of which 62% had received at least 3 prior lines of therapy (80% with prior ICB exposure) [59]. A phase III trial (NCT04195750) is currently underway comparing belzutifan and everolimus after progression on ICB or TKI with up to three lines of therapy [60].

With multiple therapeutic options already available for patients with RCC in the second-line setting, ongoing clinical trials of new agents and unique combinations of existing agents have the potential to add even more treatment possibilities for these patients (Table 13.3). Sequential therapy with second-line ICB treatment for patients with RCC after progressing on ICB in the first-line setting is a valuable option, owing to the diversity of ICB regimens available.

Table 13.3 Ongoing clinical trials enrolling patients with mRCC in the second-line setting. *DOR* duration of response, *DCR* disease-control rate, *DLT* dose-limiting toxicities

Clinical trial number	Phase	Status	Estimated completion date	Intervention	Setting	Estimated enrollment	Primary outcome measures
NCT02996110 [61]	II	Active, recruiting	January 2023	Nivolumab + ipilimumab/ relatlimab/BMS-986205/ BMS-813160	All lines	200	ORR DOR PFS
NCT04338269 [62]	III	Active, recruiting	December 2024	Atezolizumab + cabozantinib	2nd line	500	PFS OS
NCT04195750 [63]	III	Active, recruiting	September 2025	Belzutifan versus everolimus	≥2nd line post-TKI and ICB	736	PFS OS
NCT05012371 [64]	II	Active, not recruiting	April 2023	Lenvatinib + everolimus versus cabozantinib	2nd or 3rd line	90	PFS
NCT04846920 [65]	I	Active, recruiting	July 2025	Escalating doses of belzutifan	≥2nd line	52	Incidence and effect of adverse events and DLT
NCT04714697 [66]	II	Active, not recruiting	February 2025	Cabozantinib	2nd line post-Nivolumab + Ipilimumab or ICB + TKI versus placebo post sequential first-line TKI and 2nd line ICB	201	ORR
NCT03945773 [67]	II	Active, recruiting	January 2023	Cabozantinib	2nd line post-Nivolumab + Ipilimumab or ICB + TKI	250	ORR
NCT04203901 [68]	II	Active, recruiting	March 2022	CMN-001 (autologous dendritic cell therapy) + lenvatinib + everolimus	2nd line	120	OS
NCT03798626 [69]	I	Active, recruiting	April 2025	Gevokizumab + cabozantinib	2nd or 3rd line	60	DLT and PFS

Section IV: Conclusions/Perspective

The evolution of the front-line therapeutic landscape of RCC to include ICB and ICB-based combinations in a short period of time has dramatically improved outcomes for patients presenting with advanced disease. Unfortunately, most of the patients ultimately progress or do not respond to therapy. Furthermore, despite the approval of pembrolizumab in the adjuvant setting, over 20% of the patients still relapse after 2 years, and more data on sequential therapies in the post ICB setting will be crucial to our understanding of how to deploy the many treatment options available most effectively. Unfortunately, as in the front-line space, there are no biomarkers currently available in the treatment refractory setting to guide therapy and choices are often based on tolerability of preceding regimen and toxicity profiles.

Today, there is good evidence in the second-line setting to indicate that single-agent TKIs are active and safe. ICB maintenance may also be considered in this setting pending more definitive data from ongoing studies. Despite the key advances achieved in the field, further studies should be designed to evaluate the effect of various drug combinations in different patient populations. Biomarkers and risk models to predict response to treatment remain a major area of unmet need and would pave the way for precision medicine approaches for RCC in the ICB era.

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Novel Targets in Development for Advanced Renal Cell Carcinoma

14

Bicky Thapa, Ariel Nelson, and Deepak Kilari

Introduction

Despite significant therapeutic advances in the management of advanced renal cell cancer (RCC), the prognosis remains poor, and most patients succumb to their disease. A better understanding of the molecular biology of RCC led to the development of immune checkpoint inhibitors (ICIs) and targeted therapies such as vascular endothelial growth factor tyrosine kinase inhibitors (VEGF TKIs) and mammalian target of rapamycin (mTOR) inhibitors which have dramatically changed the treatment landscape of RCC [1–3]. Unfortunately, resistance is often inevitable and hence the urgent need to better understand the mechanisms of resistance and also develop novel therapeutic targets [4, 5].

Considerable strides have been made in recent years in identifying metabolic and, signaling pathways involved in RCC, as well as novel molecular targets. The understanding of the tumor microenvironment and immunomodulation has also evolved. Currently, several studies are ongoing to evaluate the safety and efficacy of newer agents directed at these novel targets and pathways. This chapter aims to review our current understanding of the pathophysiology, resistance mechanisms and tumor microenvironment in RCC, and discuss potentially new therapeutic approaches in the context of small molecular targets, cellular/signaling pathways, metabolic pathways, epigenetic modulation, and novel immunotherapies.

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Molecular Pathophysiology and Tumor Microenvironment in RCC

RCC is a heterogenous tumor due to genomic diversity within tumor cells and has a highly immune, infiltrated, complex tumor microenvironment [6, 7]. The genomic landscape of clear cell RCC (ccRCC), the most common pathological subtype of RCC, has been well described. Approximately 90% of patients with ccRCC exhibit loss of the short arm of chromosome 3 which contains four tumor suppressor genes namely *VHL*, *PBRM1*, *SETD2*, and *BAP1* [8]. Loss of 3p is considered an initial driver event with a long latency period prior to the development of ccRCC [9]. Furthermore, the loss of function of the von Hippel-Lindau (VHL) gene is an early event in the pathogenesis of RCC and can occur via 3p25 loss, point mutations, insertions, deletions, and silencing via promotor methylation (5–20% of cases) [10]. *VHL* is involved in cell cycle regulation, hypoxia-inducible gene regulation, and extracellular matrix assembly [10]. The most commonly mutated genes include *VHL* (47%), *PBRM1*(40%), *TTN* (14%), *SETD2*(12%), *BAP1*(10%) [11]. Of the identified mutations in ccRCC, missense mutations account for the majority [11]. The gain of chromosome 5q is a frequent genetic event found in ~70% of ccRCC patients [8]. A chromothripsis event is a frequent cause of 3p loss with simultaneous 5q gain [9].

RCC tumors are characterized by extensive vascularization, a result of VEGF and pro angiogenic cytokine production by the tumor cells. Loss of *VHL* function allows hypoxia-inducible factor-1 and -2 (HIF-1 and HIF-2) to accumulate and mediate the cellular response to hypoxia [12]. In ccRCC, increased expression of the HIF gene upregulates proangiogenic pathways and factors such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), placental growth factor (PGF), Epidermal growth factor receptor (EGFR), erythropoietin, interleukin-6 (IL-6), interleukin-8 (IL-8), and transforming growth factor-α [13–15].

Additionally, RCC has low levels of microRNAs namely miR-30-2-3p and miR-30a-3p compared to normal renal parenchyma, which interfere with translation of HIF mRNA and allows the HIF transcripts to be translated [12, 16].

Loss of normal cellular regulatory processes along with somatic alterations in tumor cells results in tumor-specific antigens called neoantigens [17, 18]. Activated $CD8^+$ T cells are known to play a crucial role in the immune response to cancer cells by identifying neoantigens and ccRCC is highly T cell infiltrated with a particularly high number of granzyme A- and perforin-expressing CD8+ cytotoxic T Cells [19]. In addition, RCC tumors have upregulation of antigen presenting machinery (APM) compared to normal renal cell tissue [20]. It has been noted that intra-tumoral antigen presenting cell (APC) dense regions, high levels of $CD8^+$ T cell infiltration, and the upregulation of APM related genes within the tumor are associated with better responses to ICIs [17, 20, 21]. RCC tumors are also infiltrated by myeloid derived suppressor cells (MDSCs) which promote angiogenesis, metastases and also antagonize the effect of cytotoxic T cells and have an immunosuppressive effect [12]. Tumor associated macrophages (TAMs) are also present in abundance in RCC aiding in maintaining an immunosuppressive microenvironment [22].

Current Therapeutic Targets in Advanced ccRCC

Improving upon the current therapeutic landscape for advanced RCC and better understanding mechanisms of resistance can help us develop next generation therapies. To date, most of the FDA approved therapies for management of advanced RCC have focused on targeting the tumor environment, characterized by high levels of immune cell infiltration (immune inflamed) and/or increased expression of VEGF-A [17, 19, 20, 23].

In the 1990s and early 2000s metastatic RCC was managed with cytokines such as interleukin-2 (IL-2) and interferon (IFN), treatments which were associated with significant toxicity and cost. Response rates from monotherapy with IL-2 or IFN were poor ~7% [24]. However, systemic therapy with combination IL-2 and IFN increased the response rate to over 18% [24]. Additionally, high dose IL-2 showed a response rate of approximately 23% with durable response in small subsets of patients [25].

Introduction of agents targeting the VEGF pathway shifted the paradigm of management and improved outcomes in patients with metastatic RCC [26]. In 2005, sorafenib received approval as the first multi-targeted agent for the treatment of advanced RCC [27]. Subsequently, several other VGEF targeted agents were approved for management of advanced RCC such as the humanized anti-VEGF monoclonal antibody bevacizumab and VEGF TKIs, sunitinib, pazopanib, axitinib, cabozantinib, lenvatinib, and most recently tivozanib [28]. In addition, the Akt/mTOR pathway was recognized as a therapeutic target, which expanded the therapeutic options in metastatic RCC. Temsirolimus is a highly selective mTOR inhibitor and was approved as a first-line therapy option in patients with poor prognosis advanced renal cell carcinoma based on the phase III ARCC trial [29]. Everolimus, another mTOR inhibitor, was approved in the second or later line setting as a single agent and more recently in combination with the VEGF TKI lenvatinib [30, 31].

In the last 5 years, the advent of ICIs has changed the therapeutic landscape in patients with advanced RCC. The checkmate 214 study established ipilimumab plus nivolumab as a front-line therapy option in intermediate and poor-risk advanced RCC [32]. Subsequently combinations of ICI plus VEGF TKIs, as also demonstrated a survival benefit as front-line treatment [2, 33–35].

Mechanism of Resistance to Targeted Agents

Elucidating the genomic and transcriptomic profiles of RCC tumors have helped improve the understanding of RCC tumor heterogeneity and the molecular profiles which may contribute to drug resistance. Tyrosine kinase inhibitors targeting VEGF pathways are associated with resistance through various mechanisms which we will summarize below.

AXL and MET are receptor tyrosine kinases whose expression has been associated with resistance to anti-angiogenic agents [36]. Higher c-MET expression is a poor prognostic marker in both clear and non-clear cell RCC [37, 38]. In addition,

increased AXL expression is found in RCC, and a higher level is associated with poor outcomes [39, 40]. Chronic treatment with sunitinib has been associated with increased expression of AXL and MET, leading to the aggressive behavior of the tumor and resistance to sunitinib.

Anti-angiogenic therapy targeting VEGF pathways induces hypoxic cell death however, tumor cells may exhibit "angiogenic switch" which may upregulate existing VEGF pathways or utilize alternate factors allowing escape from anti-VEGF therapy by upregulating and enhancing angiogenesis [5, 41, 42]. Bone marrow derived cells (BMDCs) such as circulating endothelial colony forming cells (ECFCs) have been implicated in resistance to VEGF directed therapies and may play a role in angiogenic switch. When mobilized ECFCs, are released in the peripheral blood and subsequently recruited to the tumor site where they can further proliferate and promote vascular growth in the presence of anti-VEGF therapies [43].

Vessel co-opting, in which tumors utilize or exploit preexisting normal vasculature, and vasculogenic mimicry, in which tumors form non vascular channels for blood flow, have also been described as mechanisms of resistance to anti-angiogenic drugs in solid tumors [44].

Phosphate and tensin homolog (PTEN) is a negative regulator of PI3K/Akt/mTOR pathway. Loss of the tumor suppressor PTEN causes constitutive activation of the Akt/mTOR pathway promoting tumorigenesis [45]. Although PTEN mutation is rare in RCC, low expression of PTEN in RCC is associated with resistance to sunitinb [41, 46]. Mutations in FKBP-12 or the FKB domain of mTOR reduces the affinity of mTOR inhibitors, which potentially results in resistance to systemic treatment [47].

Lysosomal sequestrations, whereby the TKI accumulates within the lysosomal structure and subsequently undergoes exocytosis, has been described as one of the mechanisms for developing resistance to agents targeting VGEF. However, the evidence is controversial [48, 49].

Additionally, single nuclear polymorphisms (SNPs) in genes related to pharmacokinetics and pharmacodynamics of VEGF TKI therapies have been described to play a role in drug efficacy. For example, variations in the *ABCB1* gene, which encodes a drug efflux pump, may result in increased function and therefore increased efflux of drugs and lower drug concentration levels and may decrease progression free survival in patients with metastatic RCC [50, 51].

The epithelial to mesenchymal transition (EMT) is a complex process which involves multiple pathways including the PI3K/AKT/mTOR axis as well as other kinases, interleukins, growth factors and micro-RNAs which ultimately increases tumor cell metastases via migration and invasion [52]. Hammers et al. have previously described that resistance to sunitinib was associated with reversible EMT in a xenograft study [53].

Epigenetic modifications have also been identified as a mechanism of resistance. Micro-RNAs (miRNAs) are noncoding RNAs which have been implicated in tumorigenesis and may be oncogenic or tumor suppressive [54]. Numerous miRNAs have shown to be upregulated in the setting of TKI resistance implicating

miRNAs in resistance mechanisms including Mir-144-3p and Mir-15b and others which have both been linked to sunitinib resistance mechanisms [54, 55].

Mechanism of Resistance to Immunotherapy

An exhaustive review of cancer immunobiology and immunotherapy resistance mechanisms is beyond the scope of this chapter and hence, we will only summarize the key concepts below. Similar to resistance to targeted therapy, immunotherapy resistance mechanisms may be either intrinsic or acquired and may be patient-intrinsic, tumor-intrinsic or existing at the interface of the tumor and the patient, i.e., the tumor microenvironment (TME).

Patient-intrinsic factors such as sex and HLA genotype which are not alterable have been shown to affect PD-L1 expression [56, 57]. PD-L1 signaling is mediated largely in part by interferon gamma (IFNγ) activation and downstream Janus Kinase (JAK) and signal transducer, the activator of transcription (STAT) activation and interferon regulatory factor 1 (IRF1) activation [58]. IFNγ additionally enhances MHC antigen presentation and promotes recruitment of immune cells which are anti proliferative and pro apoptotic [59]. Acquired resistance to immunotherapy has been shown to be present in patients with melanoma who harbor mutations in Janus Kinase 1 (JAK1) and Janus Kinase 2 (JAK2) resulting in impaired IFNγ signaling and may be a mechanism by which resistance occurs in patients with RCC as well [60].

The pro inflammatory conditions of the TME also promote regulatory T cell (Treg) expansion and increase T cell exhaustion; an analysis of RCC from The Cancer Genome Atlas, demonstrated worse outcomes in patients with high proportion of regulatory T cell on tumor immune infiltration analysis [61].

Tumor-intrinsic resistance mechanisms may be related to alterations of tumor response pathways, due to variations in tumor antigen expression, or signaling defects which may lead to changes in the TME making it more immunosuppressive. Defects in antigen presentation including those in the HLA loci or the MHC Class I complex component β2-microglobulin, as well as defects in other antigen processing components, i.e., membrane bound transporter protein TAP1 and TAP2 or immunoproteasome subunits PSMB8 , PSMB9, or PSMB10, have also been shown to be associated with immune checkpoint inhibitor resistance as tumor cells with impaired MHC Class I antigen presentation may permit immune escape [60, 62].

Activation of the WNT–β-catenin signaling pathway, which is an oncogenic signaling pathway, inhibits the initiation of anti-tumor immune responses and immune cell infiltration in the TME and WNT agonists have been shown to promote tumor suppression in melanoma studies [63, 64]. In RCC, high levels of β-catenin are associated with higher stage, nodal involvement, vascular invasion, sarcomatoid differentiation, and poorer prognosis [65]. Multilayer-omics analysis of RCC, including the whole exome, methylome and transcriptome have identified the WNT-β-catenin pathway in kidney cancer pathogenesis and mutations in mediators of β-catenin transcription were present in 18% of RCCs [66].

Role of Gut Microbiota

Gut microbiota composition and its role in anti-tumor responses are evolving across various malignancies. In patients with melanoma, non-small cell lung cancer (NSCLC), and RCC who received antibiotics within 30 days of ICI initiation due to gut dysbiosis, decreased efficacy of the ICI was observed [67–69]. Additionally, in patients with RCC the composition of gut microbiota is influenced by prior TKIs which may result in decreased efficacy of ICI therapy [69]. Stool bacteriomic profiling in metastatic RCC patients on TKI therapies revealed higher levels of Bateroides spp., lower levels of Prevotella spp., and somewhat less abundance of bifidobacterium spp. [70]. A randomized clinical trial in patients with metastatic RCC receiving VEGF TKI treatment, demonstrated modulation of gut microbiota with probiotic supplementation [71]. Besides, the authors also observed clinical benefits in metastatic RCC patients with a specific stool microbiome (*A. muciniphila* and *B. intestinihominis*). On the other hand, species *C. Clostridioforme* and *C. hathewayi* were associated with resistance. The same authors evaluated the role of live bacterial supplementation with CBM588 (bifidogenic live bacteria) with ICI in RCC and noted bacterial supplementation to be associated with significantly longer PFS, higher ORR and no difference in toxicity [72]. Larger studies are warranted for validate these findings and better understand the pathophysiological mechanism between microbiome composition and tumor response.

Novel Targets in RCC

Translational research in advanced RCC is rapidly evolving with the aim to identify novel targets, overcome resistance mechanisms and ultimately improve outcomes for patients with RCC [73]. This section focuses on novel targets in development and is summarized in Tables 14.1 and 14.2.

Cell Cycle Inhibition

Cyclin-Dependent Kinases

The cyclin-dependent kinases 4/6 (CDK 4/6) play a crucial role in regulating the cell cycle process. Proliferative stimuli enhance the expression of D-type cyclins, which activate CDK 4/6 to phosphorylate retinoblastoma (RB) protein [74]. RB protein is a tumor suppressor and is commonly expressed in RCC [75, 76]. Cyclin D-CDK4/6 complex is hyperactivated via several mechanisms/pathways resulting in uncontrolled cell proliferation. Selective inhibition of CDK 4/6 causes G1 arrest of the cell cycle with anti-tumor activity thus CDK 4/6 inhibitors have gained approval for use in solid tumors such as breast cancer [74, 77]. Prior studies have demonstrated increased expression of cyclin D1 in RCC [78, 79]. Additionally, loss of the von Hippel–Lindau protein (pVHL) has been associated with dysregulation of Cyclin D-CDK4/6 pathways [80, 81]. Preclinical studies in a RCC tumor

Table 14.1 Summary of outcome in advanced RCC with novel agents in early phase clinical trials

Author	Targets	Novel agents	Other agents combined with novel agent	Phase of study	Patient population	Previous treatments	Number of patients enrolled	Outcomes
Gut microbiome								
Dizman et al. [72]	Gut microbiome	CBM588	Nivolumab plus Ipilimumab	I	Metastatic RCC	None	30	PFS of 12.7 months who received Nivolumab and Ipilimumab with CBM588 vs. 2.5 months in cohort without CBM588, $p = 0.001$. Response rate of 58% in CBM588 cohort vs. 20%, $p = 006$)
Pili et al. [87]	HDACs	Vorinostat	Bevacizumab	I/II	Metastatic ccRCC	Yes	33	ORR 18%; 1 CR, 5 PR. PFS and OS of 5.7 months
Aggrawal et al. [91]	HDACs	Abexinostat	Pazopanib	I	Advanced solid tumor malignancies including ccRCC	Yes	22 RCC patients	ORR 27% in RCC subset
Molina et al. [90]	HDACs	Vorinostat and isotretinoin	None	I	Advanced RCC	Yes	14	1 PR, 9 SD, median PFS 3.7 months
Courtney et al. [102]	HIF2α	PT2385	None	I	Advanced ccRCC	Yes	51	ORR 14%, CR 2%, SD 52%
Rini et al. [103]	HIF2α	PT2385	Nivolumab	I	Advanced ccRCC	Yes	50	ORR 22%; 1 CR, 10 PR. Median PFS 7.3 months
Papadopoulos et al. [105]	HIF2α	PT2977	None	I	Advanced solid tumors	NR	29; ccRCC-6 patients	1 PR, 4 SD
Choueiri et al. [106]	HIF2α	MK-6482 (Blezutifan)	None	I/II	Advanced ccRCC	Yes	55	ORR 25%, 14 PR, 30 SD
Rosenberg et al. [113]	Nucleolin	AS1411 (DNA aptamer)	None	II	Metastatic ccRCC	Yes	35	Only one patient had an excellent response

(continued)

Table 14.1 (continued)

Author	Targets	Novel agents	Other agents combined with novel agent	Phase of study	Patient population	Previous treatments	Number of patients enrolled	Outcomes
Hamilton et al. [120]	Cadherin6	DS-6000a	None	I	Advanced RCC	Yes	7 RCC, 15 ovarian tumors	2 PR; 1 confirmed in RCC, 9 SD
Sheng et al. [146]	VEGFR/ PDGFR	Vorolanib (X-82, CM082)	Everolimus	I	Advanced ccRCC	Yes	22	Out of 19 patients, the ORR and DCR of 32% and 100%
Parikh et al. [123]	BTK	Ibrutinib	Nivolumab	Ib/II	Advanced RCC	Yes	31	ORR 10.7%; out of 28 patients 1 CR, 2 PR, and 11 SD. Median PFS 2.5 months and median OS of 9.1 months
Meric-Bernstam et al. [126]	Glutaminase	Telaglenstat (CB-839)	Cabozantinib	I	Metastatic RCC (clear cell and papillary histology)	Yes	13	Among 12 patients, ORR of 42% and DCR of 100%
Tannir et al. [127]	Glutaminase	Telaglenstat (CB-839)	Cabozantinib	II, RCT	Metastatic RCC	Yes	444; 221 randomized to CB-839 + cabozantinib	Similar efficacy between CB-839 + cabozantinib vs. placebo + cabozantinib
Diab et al. [180]	IL-2R agonist	Bempegaldesleukin (NKTR-214)	Nivolumab	I	Advanced solid tumors	Yes in 8 RCC enrolled patients	38 (22 with RCC, 11 Melanoma, 5 NSCLC)	1st line RCC (14): ORR of 71.4%, 1 CR, 9 PR, 1 SD. 2nd line immunotherapy naïve RCC (7): ORR of 28.6%, 2 PR, 4 SD
Boni et al. [181]	IL-2	Nemvaleukin alfa (ALKS 4230)	Pembrolizumab	I/II	Advanced solid tumors	Yes	22 RCC patients	1 with PR out of 16 RCC patients
McDermott et al. [182]	CXCR4	Mavorixafor (X4P-001	Axitinib	I/II	Advanced RCC	Yes	65	1 CR, 17 PR, interim PFS 7.4 months
Choueiri et al. [183]	CXCR4	Mavorixafor (X4P-001)	Nivolumab	Ib	Metastatic ccRCC	Yes	9	5 SD, 4 PD

Fong et al. [196]	A2AR	Ciforadenant	Atezolizumab	I	Advanced RCC	Yes	68 (Monotherapy) 33, combination with atezolizumab (35)	Monotherapy (29): Median PFS of 4.1 months, OS of 69% at 16 months. Ciforadenant + Atezolizumab (33): median PFS of 5.8 months, OS of 90% at 25 months
Muselaers et al. [221]	CAIX	lutetium 177–girentuximab	None	II	Metastatic ccRCC	Yes in 7 RCC enrolled patients	14	9 SD

ORR overall response rate, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *DCR* disease control rate, *PFS* progression free survival, *OS* overall survival, *ccRCC* clear cell renal cell carcinoma, *HDACs* histone deacetylases, *HIF2α* hypoxia-inducible factor 2α, *VEGFR* vascular endothelial growth factor receptor, *PDGFR* platelet-derived growth factor receptor, *BTK* Bruton tyrosine kinase, *RCT* randomized clinical trial, *IL* interleukin, *CXCR4* chemokine receptor type 4, *A2AR* adenosine 2A receptor, *CAIX* carbonic anhydrase IX antigen

Table 14.2 Summary of ongoing clinical trials evaluating the safety and efficacy of novel agents in advanced renal cell carcinoma

Novel targets/ pathway	Novel agents	Agents used in combination	Phase	Study NCT registry number
CDK 4/6	Abemaciclib Palbociclib	MK-6482 Sunitinib Avelumab and Axitinib	I/Ib II	NCT04627064 NCT03905889 NCT05176288
HDACs	Abexinostat	Pazopanib	III	NCT03592472
HIF2α	MK-6482 NKT2152	Lenvatinib ± Pembrolizumab None None None Lenvatinib Cabozantinib Lenvatinib and Pembrolizumab None	I II III I III II III II	NCT05030506 NCT04489771 NCT04195750 NCT04846920 NCT04586231 NCT03634540 NCT04736706 NCT05119335
ARO-HIF2	ARO-HIF2 α inhibitor	None	I	NCT04169711
VEGF, PDGFR, c-kit, and FLT-3	Vorolanib	Everolimus	II/III	NCT03095040
AXL	Batiraxcept	Cabozantinib, Nivolumab	I/II	NCT04300140
LAG3	Relatlimab	Nivolumab, Ipilimumab	II	NCT05148546
LAG3	Relatlimab	Nivolumab, Ipilimumab	II	NCT02996110
TIGIT	Tiragolumab	Atezolizumab, SBRT	I	NCT05259319
OX40	Anti-OX40 Antibody PF-04518600	Axitinib	II	NCT03092856
CXCR4	Mavorixafor	Axitinib	I/II	NCT02667886
RIG-I	MK-4621	Pembrolizumab	I I/II	NCT03739138 NCT03065023
CD-70	ALLO-316	None	I	NCT04696731
CAIX	Lutetium 177-girentuximab	Nivolumab	II	NCT05239533
Vaccine	NeoVax DSP-7888	Ipilimumab Nivolumab/Pembrolizumab	I I/II	NCT02950766 NCT03311334
IL-27	SRF388	Pembrolizumab	I	NCT04374877
TME	Recombinant vaccinia virus (JX-594)	Cemiplimab	Ib/IIa	NCT03294083
HERV	HERV-E TCR Transduced Autologous T Cells	None	I	NCT03354390

CDK 4/6 cyclin-dependent kinases 4/6, *HDACs* histone deacetylases, *HIF2α* hypoxia-inducible factor 2α, *VEGFR* vascular endothelial growth factor receptor, *PDGFR* platelet-derived growth factor receptor, *FLT-3* FMS-like tyrosine kinase 3, *IL* interleukin, *CXCR4* chemokine receptor type 4, *A2AR* adenosine 2A receptor, *TIGIT* T cell immunoglobulin and ITIM domain, *LAG3* lymphocyte-activation gene 3, *RIG-I* retinoic acid inducible gene I, *CAIX* carbonic anhydrase IX, *TME* tumor microenvironment, *HERV* human endogenous retroviruses, *HERV* human endogenous retroviruses, *TCR* T cell receptor

xenograft model treated with abemaciclib in combination with sunitinib showed significant anti-tumor activity [82]. Hence CDK 4/6 is a potential target in RCC. A phase I/IB trial is currently actively recruiting patients to evaluate the safety and efficacy of abemaciclib alone or in combination with HIF-2 α inhibitor (MK-6482) in advanced RCC (NCT04627064). Other trials are assessing the safety and efficacy of combinations including abemaciclib plus sunitinib (NCT03905889) and avelumab, palbociclib, and axitinib in advanced RCC (NCT05176288).

Epigenetic Modulation

Histone Deacetylases

Epigenetic aberrations are frequently found in RCC and play key role in tumorigenesis and resistance to TKIs [83, 84]. Histone deacetylases (HDACs) are epigenetic modifiers, and class I HDACs are commonly overexpressed in RCC [85, 86]. Studies demonstrated that HDAC1 and HDAC2 are essential for tumor growth and survival in RCC [86]. In vivo inhibition of HDACs downregulated E-cadherin and platelet-derived growth factor receptor-β (PDGFRβ), reduced tumor growth, and induced apoptosis. HDAC inhibition is associated with decreased expression of HIF1α and HIF2α [87]. Early phase clinical trials demonstrated anti-tumor activity of HDAC inhibitors in ccRCC in combination with VEGF inhibitors [88–90]. Results from the phase I trial using the HDAC inhibitor vorinostat and isotretinoin found the combination to be safe and tolerable with preliminary evidence of disease control in refractory metastatic RCC [91]. Vorinostat with bevacizumab in a phase I/II clinical trial showed the objective response of 18% out of 33 enrolled patients [88]. In another phase I study the combination regimen of the HDAC inhibitor abexinostat plus pazopanib in advanced solid tumor malignancies was well tolerated with anti-tumor activity [92]. In this study the objective response rate of 27% was reported in a subset of patients with RCC, including durable anti-tumor activity in 7 out of 10 patients with pazopanib-refractory RCC [92]. It was noted that better tumor response was seen in patients with increased baseline peripheral blood histone acetylation and *HDAC2* expression. This evidence suggests a potential target for combating resistance to VEGF inhibitors via epigenetic modulations with HDAC inhibitors. Based on the promising results from the phase 1 study [92], a randomized phase 3 clinical trial is ongoing to evaluate the efficacy of abexinostat with pazopanib in patients with ccRCC who are VEGF TKI naive (NCT03592472).

BET Inhibition

Epigenetic proteins could be a potential novel target in RCC. The dysregulation in bromodomain and extra-terminal (BET) proteins can promote malignancy by activating antiproliferative factors and oncogenes [93]. The BET protein family comprises BRD2, BRD3, BRD4, and BRDT and recognize and bind acetylated lysine

residues and are part of the regulatory control of transcription elongation, proliferation, metabolism, cancer stem cells and metastasis [94]. BET inhibitors are small molecules in development which preferentially bind to noncoding critical DNA regions involved in gene transcription [94]. BRD4 upregulation seems to play an important role in cell cycle progression and survival in multiple cancer types. In RCC cell lines its upregulation has been demonstrated and inhibition induced cell cycle arrest [95]. Additionally, BRD gene signature expression has been shown to be associated with aggressive RCC and low overall survival [96]. In the preclinical study with RCC xenograft, BRD2 and BRD4 were overexpressed in RCC tissue [97]. Nitroxoline-derived BET inhibitors showed anti-tumor activity by targeting both BRD2 and BRD4 [97]. Early phase clinical trials of bromodomain inhibitors are ongoing in hematologic malignancies and solid tumors none, however, are RCC specific.

Small Molecules with Therapeutic Potential in Clear Cell RCC

HIF Inhibition

When the VHL gene is mutated/inactivated or under hypoxic conditions, HIF2α forms a heterodimer with aryl hydrocarbon receptor nuclear translocator (ARNT, also called HIF1ß), resulting in the activation of HIF responsive genes [98]. An in vitro study demonstrated the HIF2 α Per-ARNT-Sim-B (PAS-B) domain contains a pocket that can accommodate artificial small molecule ligands [99]. Subsequent studies led to the identification of artificial ligands that allosterically inhibits HIF-2α heterodimerization with ARNT and result in the downregulation of HIF gene expression [100, 101]. This paved the pathway for the development of the first small molecule PT2385, a novel agent which functions as an inhibitor of HIF2α [102]. The first in human, phase-1 dose-escalation trial of PT2385 in previously heavily pretreated ccRCC demonstrated a favorable safety profile and anti-tumor activity with this novel agent [103]. The overall response rate (ORR) was 14% in the entire cohort, with complete response in 2%; stable disease was noted in 52%. Anemia, peripheral edema, and fatigue were the most common treatment-related adverse events. Additionally, the combination of PT2385 with nivolumab in a phase 1 expansion cohort showed promising anti-tumor activity with ORR of 22% and a tolerable toxicity profile in advanced ccRCC [104]. Of note, patients who had therapeutic exposures with PT2385 had better outcomes with a median PFS of 10 months vs. 4.7 months in patients with subtherapeutic exposures.

Variable pharmacokinetics were observed from the early phase trial, which led to the development of second generation HIF2α inhibitor (PT-2977 or MK-6482) with a better pharmacokinetic profile exhibiting superior potency and better drug exposure [105]. A phase I/II trial evaluated the efficacy and safety of second generation HIF2α inhibitor (MK-6482) in patients with advanced ccRCC [106, 107]. In a cohort of 55 patients with advanced ccRCC, an ORR of 24% was observed with MK-6482 [107]. Anemia, fatigue, hypoxia, and nausea were common treatment-emergent adverse events. Therefore MK-6482 as a single agent demonstrated a

favorable safety profile and promising early anti-tumor activity. Currently, several clinical trials in different phases of drug development are ongoing to evaluate the efficacy of MK-6482 as monotherapy or in combination with other agents in patients with advanced RCC (NCT05030506, NCT04627064, NCT04489771, NCT04195750, NCT04846920, NCT04586231, NCT03634540, NCT04736706). Recently, MK-6482 (belzutifan) received FDA approval for the treatment of Von-Hippel Lindau-disease associated RCC, based on a phase 2 clinical trial demonstrating activity of this agent [108].

RNA interference (RNAi) occurs when RNA molecules are involved in suppression of gene expression, and microRNA and small interfering RNA (siRNA) are major players in RNAi. Silencing gene expression of HIF-2α utilizing RNAi is an active area of therapeutic drug development (NCT04169711). In the ccRCC xenograft model, RNAi based therapeutics targeted αvβ3 and αvβ5, which resulted in gene silencing of HIF-2α and anti-tumor activity [109]. ARO-HIF-2α inhibitor is a novel agent which targets αvβ3 in ccRCC. Preliminary results from a phase 1 study of ARO-HIF-2α inhibitor in advanced ccRCC showed a decrease in the expression of HIF-2α with a favorable safety profile [110]. The study also reported disease control in seven patients (1 PR, 6 SD) out of 23 enrolled patients. NKT2152 another novel HIF2α inhibitor is also in early phase clinical trials (NCT05119335).

Targeting transcription factors is another distinctive approach for drug development in advanced ccRCC. HBS1 is a protein mimetic of the C-terminal activation domain of the HIF-1α protein. By selectively binding to the transcription factors p300 and cAMP response element binding protein-binding protein, HBS1 blocks their interaction of HIF-1α and down regulates HIF-1α target genes. In the murine xenograft ccRCC model, HBS1, targeted HIF-1α genes resulting in downregulated expression of hypoxia-inducible genes required for tumor growth [111]. Although this novel therapeutic mechanism is quite attractive; currently, there are no clinical trials investigating synthetic protein mimetic in RCC.

AXL Signaling Inhibition

AXL expression in ccRCC is associated with poor prognosis and resistance to treatment. In a preclinical model of a ccRCC mouse xenograft, inhibition of the AXL signaling pathway by AVB-500 resulted in a decrease in tumor size [112]. AVB-500 (batiraxcept) is a recombinant fusion protein dimer with anti-angiogenic potential which functions by dysregulating the GAS6/AXL signaling pathway [36, 112]. In patients with platinum-resistant recurrent ovarian cancer, a phase 1b study with AVB-500 plus paclitaxel or pegylated liposomal doxorubicin demonstrated encouraging anti-tumor activity with a favorable safety profile [113]. In a phase 1b/2 randomized study of AVB-500 plus cabozantinib versus cabozantinib alone, preliminary results demonstrated promising clinical activity [114]. Currently, NCT04300140 is evaluating AVB-500 in advanced RCC.

Bruton Tyrosine Kinase Inhibition

Ibrutinib is an irreversible bruton tyrosine kinase (BTK) inhibitor with known anti-tumor activity in B cell malignancies and a potent inhibitor of

interleukin-2-inducible kinases (ITK), which provide a therapeutic target by inhibiting T helper 2 cell (Th2) response and favoring T helper 1 cell (Th1) based immune response. Epithelial and endothelial tyrosine kinase (ETK) is a non-receptor tyrosine kinase [115]. In a preclinical study, it was demonstrated that increased expression of ETK in RCC, was associated with tumor cell proliferation, invasion, and migration [116]. Inhibition of ETK/ITK/BTK by ibrutinib may have anti-tumor activity and potentially enhance the efficacy of ICI in advanced RCC [115, 117]. In a Phase Ib/II trial of novel combination with ibrutinib and nivolumab in metastatic RCC, ORR was 10.7% (out of 28 patients, 1 complete response and 2 partial response) and disease control rate of 50% [118]. A Phase 1b/2 study of ibrutinib in combination therapy in selected advanced gastrointestinal and genitourinary tumors is investigating the combination of ibrutinib with everolimus in RCC and has completed enrollment and the results are eagerly awaited (NCT02599324).

Antibody Drug Conjugate Targeting Human Cadherin 6

Human Cadherin 6 (CDH6) is a single transmembrane protein consisting of 790 amino acids classified into the type 2 cadherin family. Human CDH6 is specifically expressed in the brain and kidneys during the development phase and has been reported to systemically decrease in the adult body. CDH6 expression is increased specifically in RCC and ovarian cancer. DS-6000a, a CDH6-targeting antibody drug conjugate (ADC) uses an enzymatically cleavable tetrapeptide-based linker, and a high drug-to-antibody ratio with a novel DNA topoisomerase inhibitor [119] . Preliminary results from an ongoing phase 1 study noted encouraging results [120].

Metabolic Pathways

Glutaminase Inhibition

RCC is characterized by dysregulated metabolism with a high level of glutaminase (GLS) that contributes to tumor proliferation and survival [121]. In the preclinical xenograft RCC tumor model, GLS inhibitor telaglenstat (CB-839) showed synergistic and antiproliferative activity when combined with everolimus or cabozantinib [122]. In a phase I study, novel agent CB-839 in combination with cabozantinib in heavily pretreated metastatic RCC showed a favorable safety profile and promising clinical activity with an ORR of 50% [123]. However, in the randomized clinical trial (CANTANA study), the novel agent telaglenastat failed to improve the clinical efficacy of cabozantinib in heavily treated metastatic RCC [124]. Studies are needed to better understand why glutaminase inhibition did not yield expected outcomes.

IDO-1 Inhibition

Indoleamine 2,3-dioxygenase1 (IDO1) is a rate-limiting enzyme that catalyzes tryptophan conversion to kynurenine [125, 126]. Increased metabolism of tryptophan by IDO1 and production of downstream metabolites promote

immunosuppressive tumor microenvironment by T cell suppression. Overexpression of IDO1 is associated with poor outcomes in patients with advanced malignancies [127]. Epacadostat, an inhibitor of IDO1, decreases the catabolism of tryptophan, resulting in reduced activity of regulatory T cells, upregulation of effector T cell function and natural killer cells, and decreased apoptosis [128]. Epacadostat in combination with ICI demonstrated anti-tumor activity in a preclinical model via upregulation of CD8+ T cells [129]. Epacadostat plus pembrolizumab in phase I/II study in advanced RCC was well tolerated with encouraging clinical activity [130]. Promising anti-tumor activity was observed in other advanced solid tumors with this novel combination well [131]. A phase III study (NCT02752074) with pembrolizumab and epacadostat or placebo in unresectable or metastatic melanoma was negative and subsequently hampered the development of epacadostat. Given the promising mechanism of action, multiple IDO1-targeting therapeutic options (e.g., inhibitors, peptide vaccines, combination with anti-PD1 antibody, PROTACs) for various cancers are currently under investigation.

Novel TKI Therapies

Vorolanib is a novel multi-target TKI that inhibits all VEGF, PDGFR, c-kit, and FLT-3 [132]. Currently approved TKI's are associated with significant toxicity; therefore, the rationale for developing vorolanib is to minimize toxicity with its shorter half and limited tissue accumulation versus existing TKIs, while maintaining efficacy [133]. The preclinical study in the xenograft model demonstrated effective anti-angiogenic and anti-tumor activity with a favorable toxicity profile [134]. In phase 1 clinical study with advanced solid tumors, vorolanib demonstrated clinical efficacy [133]. In a phase 1 clinical trial evaluating vorolanib plus everolimus in advanced RCC which enrolled 22 patients; only 1 patient had dose-limiting toxicity [135]. Out of 19 patients that were evaluable for response, investigators observed an overall response rate (ORR) of 32% and disease control rate (DCR) of 100% [135]. A phase II/III, randomized, double-blind, multi-center study in Chinese patients with advanced RCC is ongoing to evaluate the additional safety and efficacy of vorolanib and everolimus (NCT03095040).

XL092 is a novel oral multi-targeted inhibitor of receptor tyrosine kinases MET, VEGFR2, and TAM kinases (AXL, MER). XL092 as a single agent and in combination with an anti-PD-1 antibody showed anti-tumor activity in xenograft tumor models [136]. Several ongoing trials are evaluating the safety, pharmacokinetics, and preliminary anti-tumor activity of XL092 with ICIs in pts with advanced solid tumors including RCC (NCT03845166, NCT05176483). Preliminary results from STELLAR-001 presented at ESMO 2022 noted that in the 19 patients with clear cell RCC who were heavily pretreated with immunotherapy and/or VEGF TKIs, including 68% who received prior cabozantinib, ORR was 11%, and disease control rate was 95% with single-agent XL092.

Novel Immune-Based Approaches

Immune checkpoint receptors (ICRs) such as CTLA-4 and PD-1/PDL-1/2 play critical roles in maintaining immune hemostasis. Upregulated expression of ICRs results in T cell exhaustion with an ineffective anti-tumor response from effector T cells [137]. Tumor cell mediated upregulation of PD-L1 is associated with tumor cell evasion from the immune system [138, 139]. Although survival outcomes have substantially improved with combination therapy with CTLA-4 and PD-1 inhibitor [1]; primary and acquired resistance is common; hence, it is important to evaluate other ICRs such as TIM-3, LAG-3, TIGIT and others in RCC .

Novel Immune Checkpoint Targets

LAG 3

Lymphocyte-activation gene 3 (LAG3) or CD223 is a transmembrane molecule that is expressed on CD4+ and CD8+ T cells, regulatory T cells, and natural killer (NK) cells [140, 141]. LAG3 is upregulated in chronic viral infection and cancer due to persistent antigen stimulation, resulting in T cell dysfunction due to T cell exhaustion [142, 143]. A preclinical mouse model revealed increased expression of LAG3 and PD-1 on tumor infiltrating lymphocytes (TILs); moreover, anti-tumor activity was observed with dual inhibition of LAG3 and PD-1 [144]. An in vitro study showed increased expression of LAG3 after PD-1 blockade in TILs isolated from RCC patients; furthermore, dual immune checkpoint inhibition of LAG3 and PD-1 led to increased release of INFγ [145]. Prognostically increased expression of PD-1 and LAG3 in the absence of mature dendritic cells was associated with poor outcomes in ccRCC [146]. This evidence suggests the potential anti-tumor activity of the novel dual combination in advanced ccRCC. A phase I trial evaluated a novel agent IMP321 also called Eftilagimod alpha (recombinant soluble LAG-3Ig fusion protein) in patients with advanced RCC [147]. IMP321, an MHC class II agonist induced anti-tumor activity by activating CD8+ T cells and increased long-lived effector memory CD8+ T cells. Relatlimab is a fully humanized antibody that targets LAG3 on T cells. Most recently, a phase III randomized clinical trial in patients with metastatic melanoma, relatlimab in combination with nivolumab, has shown better PFS benefits as compared to nivolumab alone [148]. Relatlimab is an emerging novel agent, and currently, clinical trials are ongoing to evaluate the efficacy in advanced ccRCC (NCT05148546, NCT02996110).

TIM-3

T cell immunoglobulin and mucin domain 3 (TIM-3) is a membrane protein expressed on T cells, Tregs, dendritic cells, natural killer cells, macrophages, and monocytes [149, 150]. TIM3 is overexpressed in TILs and is associated with T cell exhaustion. TIM-3 is commonly expressed in TILs from RCC and higher expression of TIM-3 is known to be associated with poor outcomes [151, 152]. Additionally, co-expression of PD-1 and TIM-3 in TILs aggravates T cell dysfunction resulting in poor clinical outcomes in patients with RCC [153]. Interestingly, increased

expression of TIM-3 on tumor cells was observed to have a better clinical outcome (longer PFS and OS) with anti-PD1 therapy compared to TIM-3 negative tumor cells [154]. In phase I/II clinical trial, MBG453 (humanized monoclonal antibody blocking TIM-3) combined with spartalizumab (an anti-PD-1 monoclonal antibody) showed anti-tumor activity in advanced malignancies [155].

TIGIT

T cell immunoglobulin and ITIM domain (TIGIT) functions as co-inhibitory receptor and is expressed on T cells and NK cells [149, 156]. In preclinical mouse models, dual blockade of PD-L1 and TIGIT demonstrated anti-tumor activity. Early phase clinical trials demonstrated clinical activity of combination treatment with tiragolumab (anti-TIGIT antibody) and atezolizumab in patients with PD-L1 positive NSCLC [157, 158]. A phase I study is underway to assess the efficacy and safety of combination therapy with atezolizumab, tiragolumab and stereotactic body radiation therapy in advanced solid tumors including RCC (NCT05259319).

4-1BB

4-1BB (CD137) also known as TNF receptor superfamily member 9 is co-stimulatory receptor expressed on activated T cells, NK cells, neutrophils, dendritic cells, and monocytes [159, 160]. Increased expression of 4-1BB on TILs was noted with hypoxia via HIF1α pathway [161]. Utomilumab is a novel monoclonal antibody that is 4-1BB agonist. In a phase I clinical trial, utomilumab in combination with pembrolizumab demonstrated encouraging anti-tumor activity with a favorable safety profile in patients with advanced malignancies [162]. ORR of 26% was observed in the entire cohort. Out of 23 patients enrolled, three patients had a diagnosis of RCC; 1 patient attained complete response and 1 patient had partial response [162].

OX40

OX40 (CD 134) is a transmembrane glycoprotein that belongs to TNF receptor superfamily member 4 and is predominantly expressed on T cells [163, 164]. Recent results from a phase I dose-escalation study with Ivuxolimab (OX40 agonist) monotherapy in advanced malignancies demonstrated clinical activity and was well tolerated [165]. A phase II randomized, double clinical trial is ongoing to evaluate the efficacy of axitinib with or without OX40 antibody (PF-04518600) in patients with metastatic RCC (NCT03092856).

Cytokine Therapy

Historically high dose IL-2 was the mainstay of treatment in patients with metastatic RCC; however, treatment was associated with significant toxicities, which restricted further utilization of cytokine therapy. IL-2 activates T cells by binding to IL-2 receptors (IL-2R) that are comprised of IL-2Rα (CD25), IL-2Rβ (CD122), IL-2Ry (CD132) [166, 167]. The binding of IL-2 to IL-2Rβ and IL-2Ry only stimulates effector CD8+ T cells for anti-tumor activity and is associated with less toxicity [166, 168]. Renewed interest in cytokine therapy led to the development of

pegylated engineered IL-2R agonist bempegaldesleukin (NKTR-214), which preferentially binds to IL-2Rβ/Ry as opposed to IL-2Rα [169]. In patients with advanced solid tumors in an early phase trial, combination therapy with bempegaldesleukin and nivolumab demonstrated encouraging anti-tumor activity with an ORR of 59.5% in the entire cohort and a DCR of 83.8% as well as manageable treatment-related side effects [170]. A total of 22 patients with RCC were enrolled (first-line RCC: 14, second line immunotherapy naïve: 8); ORR in the first-line RCC was 71.4% with complete response (CR) in 1 patient and partial response (PR) in nine patients. However, the pre-planned analysis of the phase III PIVOT-09 study evaluating NKTR-214 plus nivolumab in patients with previously untreated advanced RCC demonstrated that the combination regimen failed to meet the pre-specified boundary for statistical significance for objective response rate (ORR) or overall survival compared to a TKI [171].

The ARTISTRY-1, a phase 1/2 study (NCT02799095), explored the safety and efficacy of a novel agent Nemvaleukin alfa (ALKS 4230), that targets IL-2 in patients with advanced solid tumors [172]. In this study, 24 RCC patients were enrolled, and 16 patients were evaluated for response; only 1 patient had PR at the preliminary report.

CXCR4 Inhibition

Alteration in the tumor microenvironment by inhibiting cytokine receptors can enhance anti-tumor immune response. Mavorixafor (X4P-001) is an oral, selective inhibitor of CXCR4 that increases the infiltration of cytotoxic T cells in the tumor microenvironment [17]. Mavorixafor in combination with axitinib in a phase I/II clinical trial (NCT02667886) demonstrated encouraging clinical efficacy with an ORR of 29% (1 CR, 17 PR) [173]. The final results from this study will provide better insight into the efficacy of this combination. Moreover, results from a phase 1b clinical study in metastatic ccRCC who were unresponsive to nivolumab monotherapy exhibited anti-tumor activity with combination therapy with mavorixafor and nivolumab [174]. Out of nine patients enrolled, four had progressive disease, and five had stable disease.

STING Pathway

Stimulator of interferon genes (STING) is an essential pathway in innate immunity for activation of type 1 interferons for defense against different pathogens [175]. Evidence suggests anti-tumor response with activation of STING pathway in TME via antigen presenting cell (APC)-mediated tumor infiltration of T cells [176, 177]. MK-1454 is a novel agent that is agonist of STING; the preliminary results from phase 1 clinical trial (NCT03010176) in patients with advanced solid tumors showed encouraging anti-cancer efficacy with a favorable safety profile in combination with pembrolizumab [178].

Adenosine 2A Receptor (A2AR) Pathway

Adenosine plays a vital role in cancer immune-metabolic pathway by facilitating tumor growth and metastasis [179, 180]. Extracellular ectonucleotidases CD39 and CD73 catalyze ATP to adenosine which activates A2AR in the tumor

microenvironment resulting in derangement in anti-tumor immune response [181, 182]. Moreover, high expression of CD39 and CD73 is associated with poor prognosis across several malignancies [183]. The metabolomic study showed that RCC patients with high baseline adenosine levels had poor PFS and no response to nivolumab [184]. A preclinical study indicated increased expression of adenosine 2b receptor (A2bR) in RCC contributing to tumor progression and A2bR inhibition associated with reduced tumor progression [185]. RCC is known to have high expression of the adenosine genes *ADORARA* (A2AR) and *NT5E* (CD73), providing adenosine-mediated immunosuppression [186]. Ciforadenant is a novel agent which blocks A2AR and shows the anti-tumor activity as a single agent or in combination with Anti-PD-L1 or Anti-CTLA-4 in preclinical studies [187, 188]. In a phase 1 clinical trial, ciforadenant demonstrated anti-tumor activity as monotherapy and in combination with atezolizumab [186]. The study reported improved efficacy with combination therapy; a partial response rate of 11%, a median PFS of 5.8 months, and OS of 90% at 25 months.

IL-27 Inhibition

IL-27 is a pleiotropic cytokine sharing structural resemblances with the IL-6 cytokine family, and it is composed of IL-27p28 chain and Epstein–Barr Virus induced gene 3 (EBI3) protein [189, 190]. IL-27 specifically binds to a heterodimeric receptor expressing IL-27Rα and glycoprotein 130 (gp130) [191], which further activates the JAK-STAT pathway resulting in complex immune-regulatory function [189]. Increased expression of IL-27 is associated with poor prognosis in RCC [192]. SRF388 is an IL-27p28 antibody that downregulates IL-27 signaling by blocking the interaction of IL-27 with *IL-27R*α in immune cells [192]. In vitro studies demonstrated anti-cancer activity of SRF388 [192]. A phase I/1b clinical study evaluating the safety and efficacy of SRF388 in patients with advanced solid tumors *including* RCC is underway (*NCT04374877*).

TGF-β Ligand Inhibition

Transforming growth factor-beta (TGF-β) is a pleotropic cytokine which under normal conditions acts to maintain homeostasis and limit the growth of multiple cell lineages through anti-proliferative and apoptotic responses, and paradoxically also regulates cell invasion, immune responses, and microenvironment modification which can be exploited by cancer cells, thus misregulation of TGF-B can result in tumor development [193]. GC-10008 (fresolimumab) is a fully human monoclonal antibody directed against transforming growth factor (TGF)-beta 1, 2 and 3. A phase 1 study of fresolimumab in patients with malignant melanoma and renal cell carcinoma observed no dose-limiting toxicities with an acceptable safety profile and preliminary evidence of anti-tumor activity (NCT00356460) [194].

CAR-T Therapy

CD70 is highly expressed in RCC with limited normal tissue expression, making it an attractive target for CAR-T therapy. The ongoing Phase 1 TRAVERSE trial is designed to evaluate the safety, tolerability, and activity of ALLO-316 in patients with advanced or metastatic clear cell RCC (NCT04696731).

Vaccine Therapy in RCC

The purpose of vaccine therapy is to induce an immune response against malignant cells and clinical research via vaccine immunotherapeutic approaches in RCC have been ongoing for many years with varied results [195, 196]. IMA901 is a therapeutic multi-peptide vaccine that showed an immune response and better overall survival in phase 1 and 2 clinical trial [197]. Unfortunately, in the phase III IMPRINT study, IMA901 in combination with sunitinib did not show survival benefits compared to sunitinib monotherapy in metastatic RCC [198]. In another pivotal phase III ADAPT clinical trial, Rocapuldencel-T (a personalized monocyte-derived dendritic cell-based vaccine) combined with sunitinib failed to show a survival benefit in patients with metastatic RCC [199]. Notably, an enhanced immune response was observed in about 70% of patients treated with Rocapuldencel-T and was associated with better survival. A phase 2 trial (NCT04203901) is currently evaluating the efficacy of autologous dendritic cell immunotherapy in combination with nivolumab and ipilimumab. Prediction of HLA epitopes is another approach for the development of personalized neoantigen vaccine therapeutics in cancer patients [200]. An ongoing phase I study is assessing the safety and efficacy of a personalized neoantigen vaccine with ipilimumab in RCC (NCT02950766). Additionally, another phase Ib/II study is actively recruiting patients with advanced solid tumors, including RCC, to evaluate the safety and tolerability of Wilm's tumor 1 (WT1) protein-derived peptide vaccine (DSP-7888) with ICI (NCT03311334).

Human endogenous retroviruses (hERV) are transcriptionally silent remnants of past retroviral infections, some of which become aberrantly expressed under hypoxic conditions in RCC are potentially actionable drug targets [201]. An autologous T cell therapy engineered with a T cell receptor (TCR) targeting hERV-E is in phase I development (NCT03354390). In addition, the hypomethylating agent decitabine has been shown to increase hERV expression and activate immune signaling in ccRCC cells, and could also be used to indirectly increase immunogenicity of RCC [202].

Oncolytic Viruses

Oncolytic viruses are therapeutically engineered for selective anti-tumor activity without affecting normal cells [203, 204]. At present talimogene laherparepvec (T-VEC) is the only oncolytic herpesvirus FDA approved for treatment of patients with advanced melanoma [205]. JX-594 (pexastimogene devacirepvec, Pexa-vec) is a thymidine kinase inactivated oncolytic vaccinia virus genetically engineered to express granulocyte macrophage colony stimulating factor [206]. In a phase-2 randomized clinical trial, JX-594 demonstrated anti-tumor activity in patients with hepatocellular carcinoma [207]. In the preclinical study with metastatic orthoptic RCC murine models, JX-594 demonstrated anti-tumor activity by remodeling the TME [208]. Currently, a phase 1b/2a is evaluating safety and efficacy of Pexa-Vec in combination with Cemiplimab in patients with metastatic RCC (NCT03294083).

DNA and RNA Aptamers

DNA and RNA aptamers are short single-stranded DNA and RNA oligonucleotides that can target specific proteins [209]. Aptamers have high specificity to targets and are characterized by low molecular weight, high stability, non-immunogenicity, low toxicity, and instant tissue penetration [210]. AS1411 is a quadruplex DNA aptamer that targets nucleolin which is expressed in many cancers, including RCC [211]. A phase II clinical trial with AS1411 in metastatic RCC showed limited anti-tumor activity; only 1 patient had a response to treatment out of 35 enrolled patients [211]. Internalization of the AS1411-nucleolin complex inhibits DNA synthesis resulting in anti-tumor activity by arresting the S-phase [211]. SW-4 is another potential single stand DNA aptamer that demonstrated high specificity and affinity to RCC 786-O cells in xenograft mice models [212]. The in vitro study showed anti-tumor activity of SW-4b by S-phase cell cycle arrest [212].

Radioimmunotherapy

The carbonic anhydrase IX (CAIX) antigen is known to be overexpressed ubiquitously in clear cell RCC tumor cells but minimally expressed in normal tissues/cells [213, 214]. Girentuximab is a chimeric monoclonal antibody that explicitly targets CAIX [215]. The radiolabeled girentuximab was evaluated in multiple studies as a diagnostic tool with high accuracy in patients with clear cell RCC [216–219]. Unfortunately, no clinical benefit was observed in the randomized clinical trial with adjuvant girentuximab in high-risk clear cell RCC after nephrectomy [220]. In a phase 2 clinical trial, lutetium 177-labeled girentuximab demonstrated clinical response in patients with advanced clear cell RCC [221]. Another phase 2 trial is ongoing to evaluate the safety and efficacy of nivolumab in combination with lutetium 177-labeled girentuximab in advanced clear cell RCC (NCT05239533).

Conclusion

The current chapter describes the significant unmet need of patients with RCC treated within the current therapeutic landscape of VEGF TKI, ICI, and mTOR based therapies. In the last few years many novel targets have been identified in RCC and potential therapeutic agents aimed at these targets as monotherapy and in novel combinations are in different phases of translational development. These new therapeutic mechanisms along with biomarker-based treatment selection have the potential to vastly improve the outcomes of patients with RCC compared to the current treatment landscape and ongoing clinical investigation into these agents should be the utmost priority. Studies evaluating these novel therapies in combination and compared with and in sequences with current standards as well as investigations into novel biomarkers are needed. Hopefully with continued research, we will enter the next era of personalized treatment for patients with RCC.

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Role of Primary and Metastasis-Directed Stereotactic Radiation Therapy for Advanced Renal Cell Carcinoma

15

Michael Christensen and Raquibul Hannan

Introduction

Kidney cancer is a heterogeneous disease associated with variable clinical course and histologic types. Renal cell carcinoma (RCC) originates from the renal cortex and represents 80–85% of primary renal neoplasms. Subtypes of RCC include clear cell (75–85%), papillary (10–15%), chromophobe (5–10%), and other rare subtypes (3–5%) [1]. Approximately 25% of patients with RCC present with regional and distant metastasis at the time of diagnosis [2]. For patients with localized disease, up to 25% of these patients may eventually develop metastasis [2, 3]. RCC has the potential to spread by local invasion through the surrounding tissue, venous drainage, lymphatic spread, or hematogenous dissemination. Surgery has been the primary treatment modality for the management of localized kidney cancer, and historically, systemic therapy for metastatic RCC was limited to cytokine therapies, including high-dose interleukin-2 (IL-2) and interferon. However, due to the considerable toxicity, IL-2 was limited to patients with excellent performance status and few medical comorbidities. In recent years, systemic therapy with immune checkpoint inhibitors (ICI), tyrosine kinase inhibitors (TKI), or a combination of the two, have become the new standard of care for metastatic RCC (mRCC) [4–8].

In addition to surgery and systemic therapy, radiation therapy is an important treatment modality for RCC. Due to a 1996 study of multiple human cancer cell lines that examined radiosensitivity in vitro, RCC was traditionally thought to be radioresistant to conventionally fractionated radiation therapy [9]. Additionally, a clinical trial published in 1987 showed that adjuvant radiation therapy for RCC provided no improvement in local recurrence with severe toxicities, including death [10]. However, RCC has subsequently been shown to be radiosensitive in numerous

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in vivo and in vitro studies, especially when delivered with a higher dose-per-fraction [11, 12]. For instance, one study of an implanted human RCC in a nude mouse model showed effective tumor control when treated with 48 Gy in 3 fractions [11].

Stereotactic ablative body radiation (SAbR) is an emerging treatment paradigm defined by the American Society of Therapeutic Radiology and Oncology guidelines as a "treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body [13]." Potential indications for SAbR include a broad spectrum of tumor types and locations [14]. The safety and efficacy of SAbR to multiple sites is excellent, and it has been assessed prospectively in multiple studies [15–18]. Clinical experience using SAbR or hypofractionated radiotherapy (HFRT) for both intracranial and extracranial RCC metastases showed excellent local control rates between 90% and 98% [19–21]. A Swedish retrospective series of 50 patients with 162 lesions treated with SAbR showed a 90% local control rate with minimum toxicity at a median follow-up time of 37 months [19]. Wang et al. reported a 91% 1-year local control rate post-SAbR in a retrospective series reviewing 175 treated metastatic RCC lesions, with a favorable safety profile including improved outcomes and a biologically effective dose (BED) greater than 115 [22]. Their analysis further revealed that spinal location, re-irradiation and > 1 of prior systemic therapy had higher levels of local failures that can be overcome with higher radiation dose.

Given the excellent local control efficacy and safety profile of SAbR for the treatment of both primary and metastatic RCC, effective integration of this relatively new modality with the emerging systemic therapy landscape for RCC will lead to optimal outcomes for kidney cancer patients. This chapter will discuss the available evidence on the sequencing and integration of SAbR with available local and systemic therapies, highlighting the lack of data and opportunities for future clinical trial development and challenges.

SAbR for Primary RCC

While surgery remains the standard curative treatment for primary RCC, patient characteristics such as inoperability or tumor size may favor observation or other focal treatments. Among these focal treatments is SAbR, which will be the emphasis of this chapter. Several retrospective studies of SAbR for primary RCC are among the earliest to show promising outcomes [20, 23, 24]. The first prospective dose escalation trial of SAbR showed that doses >27 Gy in three fractions did not have any failures and reported an overall local control (LC) of 93.7%. Interestingly, while they noticed a decrease in the SAbR treated lesions indicating tumor cell killing, they did not notice any change in tumor enhancement suggesting that the vasculature in the lesion was not affected by SAbR [25]. A phase 2 trial of 37 primary RCC patients treated with SAbR reported a LC of 100% at a median follow-up of 24 months [26]. They also reported 3% grade 3 toxicity with no grade 4–5 toxicities.

A pooled analysis performed by the International Radiosurgery Oncology Consortium for Kidney (IROCK) published outcomes for 223 patients from nine institutions who had RCC treated with SAbR [27]. In this cohort, the 4-year LC, overall survival (OS), and progression-free survival (PFS) were 97.8%, 70.7%, and 65.4%, respectively. There were only three (1.3%) patients who experienced grade 3/4 bowel toxicity and the mean reduction in estimated glomerular filtration rate (eGFR) was 5.5 mL/min. This study showed that larger tumor size predicted worse PFS, as well as cancer-specific survival (CSS) [27, 28]. An additional pooled analysis reaffirmed these positive results of SAbR for primary RCC [29]. Published in 2020, the authors describe 95 patients deemed not suitable for surgery who had primary tumors greater than 4 cm. Definitive SAbR was effective with 4-year LC of 98.1%, no grade 3–5 toxicities, and had an impact on renal function with an average eGFR decrease of 7.9 mL/min.

Locally Advanced RCC

Standard of care treatment for patients with locally advanced RCC is and has traditionally been radical or partial nephrectomy, as clinically indicated. Adjuvant treatment options have ranged from observation to systemic therapy, both on and off clinical trials. More recently, investigators are exploring an increasingly nuanced approach given a variety of patient factors.

Up to 10% of newly diagnosed patients with RCC have disease that invades the inferior vena cava (IVC). This invasion can surge from the renal vein and travel to the right atrium. The extent of IVC disease can portend a poor prognosis, and if left untreated can lead to venous congestion, Budd-Chiari syndrome, pulmonary embolism, or metastasis. The only curative treatment for locally advanced RCC involving IVC tumor thrombus is surgery, however, there is approximately a 35% rate of high-grade perioperative morbidity, and up to a 13% rate of peri or postoperative mortality [30]. Unfortunately, an increased risk of relapse and metastasis still exists even after curative resection [31]. A 1-year recurrence rate of greater than 40% exists for patients with RCC IVC tumor thrombus. Multiple possible explanations exist for the mechanism of this high rate of recurrence, with one possibility being that the IVC tumor thrombus may invade the IVC wall, resulting in positive surgical margins, ultimately leading to local recurrence. Alternatively, the IVC tumor thrombus may produce tumor emboli, thus causing metastasis.

One alternative adjuvant treatment approach supported by emerging evidence to reduce the risk of RCC recurrence is preoperative SAbR to the RCC IVC tumor thrombus. An initial case report of two patients treated with preoperative SAbR showed no acute or late treatment-related toxicity, as well as a median survival of 20 months at the time of publication [30]. This lead to the design of a safety lead-in phase II clinical trial of neoadjuvant SAbR for RCC IVC tumor thrombus (NCT02473536). The safety lead-in phase of the trial demonstrated that neoadjuvant SAbR of IVC tumor thrombus followed by radical nephrectomy and thrombectomy is feasible and safe, however, the oncologic outcome data is not yet fully

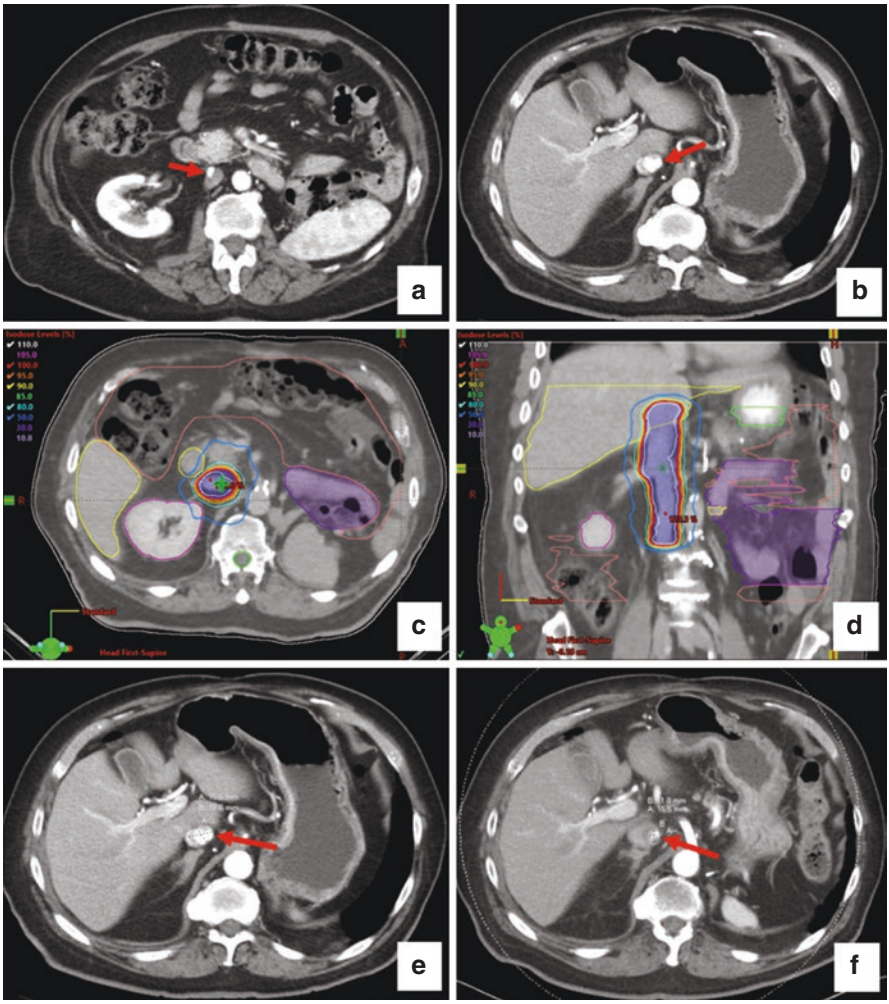

Fig. 15.1 Sample images of a case of a patient with RCC IVC tumor thrombus with adherence of the tumor thrombus to the IVC wall, making resection not possible. The patient was treated with SAbR 36 Gy/3 fractions. (**a**, **b**) Axial abdominal CT with contrast, arrows highlighting arterially enhancing mass in the infra-hepatic IVC consistent with RCC recurrence. (**c**, **d**) Axial and coronal abdominal CT with radiation dose distribution as a percentage of prescription dose. Nearby organs at risk are also contoured—duodenum (yellow), right kidney (pink), liver (yellow), and bowel space (salmon). (**e**) Pre-SAbR tumor thrombus 1.6 × 2.0 cm. (**f**) 6-month post-SAbR tumor thrombus 1.2 × 1.6 cm. *IVC* inferior vena cava, *RCC* renal cell carcinoma, *SAbR* stereotactic ablative radiation therapy

matured [32]. Potential additional indications for SAbR of IVC tumor thrombus include: palliation of Budd-Chiari syndrome, unresectable or recurrent disease after surgery (Fig. 15.1), disease refractory to surgery and systemic therapy, cytoreduction (with systemic therapy) to increase respectability by alleviation of Budd-Chiari/

hepatic venous congestion (which significantly increase surgical mortality), MRI evidence of IVC wall invasion, or a patient eligible for radical nephrectomy but not for tumor thrombectomy. Again, this paradigm is evolving and prospective evidence is currently lacking.

Patients with locally advanced RCC without tumor thrombus may also be unresectable due to the extent of disease, medical inoperability, surgical risks, or simply due to a lack of evidence of clinical benefit as demonstrated by multiple clinical trials [33]. Debulking or consolidative SAbR may have applications in these clinical scenarios. Phase 1 feasibility data is provided by Singh et al. in a small study that treated large kidney tumors neoadjuvantly with SAbR [34]. With the improvement of systemic therapy it is possible for a patient initially diagnosed with metastatic disease to have a near complete response with systemic therapy, with the primary tumor being the only remaining, yet inoperable site of disease where SAbR can be utilized. Ongoing multi-center clinical trials (CYTOSHRINK NCT04090710 and SAMURAI/GU012 NCT05327686) are evaluating this strategy, leveraging potential synergy of SAbR with immunotherapy.

Oligometastatic RCC

Oligometastatic RCC is a broad category of disease where SAbR is effective. Metastatic RCC represents a wide spectrum of disease aggressiveness. For example, patients with International Metastatic Database Consortium (IMDC) poor-risk disease have historically poor outcomes with survival of less than 1 year, while those with favorable-risk disease may have a smoldering progression over many years [35, 36]. Patients may also present with widely disseminated disease or they may exhibit oligometastatic disease. Oligometastatic RCC can be divided into subcategories based on the risk of distant micrometastasis. This can dictate the probability of future progression at distant sites, as well as the speed of progression of the detectable metastases.

The first subcategory are those patients that present with metachronous metastases that develops more than 1 year after resection of the primary kidney tumor. This suggests that the patient's disease is indolent and portends the best prognosis. A subgroup of these patients may represent the "true" oligometastatic state and can be cured with local therapy. For these patients, treatment options include either active surveillance, metastasectomy, SAbR, or systemic therapy [36–41], with a preference for local therapy. The second subcategory are patients with favorable or intermediate IMDC risk. This represents a heterogeneous patient population who will eventually need systemic therapy, however, carefully selected patients can be treated with upfront sequential SAbR that can preserve health-related quality of life as well as available systemic therapy options. Retrospective and prospective studies have both shown disease control in excess of 15 months for these patients with sequential SAbR [38–41]. The third subcategory are patients with a high chance of distant micrometastatic disease, including those with IMDC poor-risk, grade 4 histology, or sarcomatoid component histology. Despite having oligometastatic disease, this

group of patients generally requires up-front systemic therapy, however there may still be a role for consolidation with SAbR to the bulky therapy-resistant metastatic sites. Nevertheless, these patient scenarios provide a framework in which SAbR may be considered as part of the treatment plan.

Active surveillance is a treatment approach for select patients with oligometastatic RCC. A prospective trial of patients with oligometastatic RCC with proven indolent growth of metastases after primary nephrectomy showed that this subset of patients could safely undergo active surveillance for a median of 14.9 months before starting systemic therapy [36].

Metastasectomy is also a treatment option for patients with oligometastatic RCC, but local control, safety, and prospective outcome data are limited [37]. A Japanese retrospective study of 1463 patients in which 20.8% underwent metastasectomy reported prognostic factors for metastatic RCC, including performance status, hemoglobin, lactate dehydrogenase, serum calcium, C-reactive protein, and time from initial visit to metastasis being less than 1 year. Patients with no risk factors had a median survival of 55.3 months compared to 29.6 months for those with 1 to 2 risk factors (1 year OS of 92.8% vs. 76.6%, respectively) [42]. More recently, Tosco et al. investigated the survival impact of prognostic factors in patients with metastatic RCC who underwent metastasectomy [43]. Their results indicated that advanced primary tumor stage, high tumor grade, non-pulmonary metastases, disease-free interval of less than 12 months, and multi-organ metastases were independent factors for survival. Patients with 0 to 1, 2, 3, greater than 4 factors had 2-year cancer-specific survival rates of 95.8%, 89.9%, 65.6%, and 24.7%, respectively [43]. These tools may help clinical decision making for appropriate local therapy patient selection.

SAbR is a promising treatment option for patients with oligometastatic RCC. SAbR has not only shown favorable local control rates of greater than 90%, but can also provide an option for local therapy at an otherwise inoperable location. A phase II prospective trial from Sweden using SAbR in primary and metastatic RCC showed an OS of 32 months with 79% sustained local control rate at a median follow-up of 52 months [20]. A prospective study from the University of Chicago showed that the majority of initial metastatic progression (81%) was limited to less than five sites in oligometastatic RCC patients after treatment with SAbR, and approximately half had either no or limited metastatic progression after a median follow-up of 20.9 months [44]. These experiences suggest aggressive upfront sequential SAbR as an effective local therapy that can potentially control disease progression in patients with limited metastases. Retrospective analyses have supported the use of SAbR for oligometastatic disease due to the ability to defer the start of systemic therapy and possibly extend survival [38]. This has recently become the subject of prospective studies, including one that supported the efficacy and safety of this approach with SAbR [45]. Moreover, this strategy can be employed sequentially in the setting of additional oligometastatic lesions, thus providing durable disease control with subsequent focal SAbR. This approach was described in a retrospective study where 30% of patients received two or more courses of SAbR to additional sites of metastatic disease [38]. A

prospective version of this study confirmed that sequential SAbR in systemic therapy-naïve oligometastatic RCC patients can confer 1-year freedom from systemic therapy in 91.3% of patients [40, 41]. This phase 2 trial also demonstrated a preservation of patient's quality of life using pre- and post- treatment patient-reported quality of life questionnaires. In another prospective feasibility study by Tang et al., SAbR and showed a median PFS of 22.7 months with acceptable toxicity [39]. While the study met its feasibility endpoint, it did not meet its pre-specified efficacy estimate of 71% 1-year PFS and reported a 1-year PFS of 64%. It is important to note that this study allowed pre-treatment with systemic therapy. A phase 3 non-inferiority trial (EA 8211, SOAR) randomizing systemic therapy-naïve oligometastatic RCC patients to be treated with up front sequential SAbR followed by systemic therapy at progression versus systemic therapy up front is currently being designed.

Although the safety of SAbR has been excellent, caution must be exercised in certain scenarios. One such scenario is ultra-central lung metastasis, where given the vascular nature of RCC, rare instances of serious life-threatening hemoptysis or hemothorax have been noticed as a late effect that occurs years after treatment. It is often difficult in these situations to assess the contribution of radiation, tumor recurrence, and systemic therapy as the etiology of the hemoptysis. A second potential cautionary scenario is the use of future systemic therapy which may have side effects that can synergize with the toxicity of current SAbR, leading to a radiation-recall-type side effect.

Oligoprogressive RCC

Individuals with metastatic RCC can develop progression at only a few select sites of disease, deemed oligoprogressive. To date, there has been limited research on patterns of progression. For example, conventionally used criteria for response assessment in clinical trials, such as Response Evaluation Criteria in Solid Tumors (RECIST) criteria, do not distinguish patterns of progression. In clinical practice, the current approach to progression, even if it is only to a few sites, is to switch systemic therapy. This also applies to patients who are otherwise tolerating the ongoing systemic therapy well. However, different modes of progression likely reflect differential disease responsiveness to therapy and biology. Limited progression may indicate overall responsiveness to therapy and may be explained by mutational heterogeneity and clonally propagated branched evolution that fosters tumor adaptation and therapeutic failure through Darwinian selection [46–48]. Different modes of progression may be optimally managed with different approaches, and a change of systemic therapy may be favored for patients with overt progression. The introduction of focal therapies for controlling oligoprogressive sites could be advantageous by increasing the duration of the current therapy and preserving the limited available subsequent therapies. By extending the duration of the current systemic therapy and altering the course of the disease through elimination of resistant metastasis, this approach could also improve survival outcomes. It is

important to keep in mind that subsequent lines of systemic therapy are typically associated with shorter progression-free survival (PFS) intervals, and they are often associated with increased toxicity [49]. Furthermore, local therapy seems unlikely to undermine future systemic therapy, and such an approach may extend patient survival.

Multiple retrospective studies have evaluated SAbR for mRCC, but only a few on oligoprogression [19, 50–56]. A retrospective analysis from Santini et al. found a median PFS of 14 months after evaluating 55 mRCC patients on first line systemic therapy and oligoprogression managed with focal approaches (including SAbR) [51]. In this study, SAbR was used in approximately 46% of patients, and appeared to be effective. Another single-institution retrospective review of 72 patients with mRCC on systemic therapy treated with SAbR to oligoprogressive sites showed similar PFS, regardless of systemic therapy [56]. In a multi-institutional study, Meyer et al. reported 180 patients with mRCC who had been treated with SAbR; of these, 101 patients were treated for oligoprogressive disease [52]. The median local recurrence-free survival, PFS, time to systemic therapy, and OS were 19.3, 8.6, 10.5, and 23.2 months, respectively. UT Southwestern Medical Center performed a retrospective review of SAbR for oligoprogression in mRCC, which showed a median mPFS of 9.2 months [50]. Data on this topic is emerging, with one prospective phase 2 trial showing that SAbR to oligoprogressive sites is able to extend the duration of ongoing systemic therapy by more than 6 months in 70% of patients, with a median duration of SAbR-aided systemic therapy of 24.4 months [57]. All together, prospective studies on SAbR for oligoprogressive RCC are lacking and may be difficult to conduct given concerns and lack of data on side effects of concurrent administration of some of the systemic therapies with SAbR. Few phase 2 trials are ongoing and may provide further insight (GETUG-StORM-01 NCT04299646 and NCT04974671).

SAbR for oligoprogressive mRCC has been shown to be generally well-tolerated, however, toxicity may also be exacerbated by both ICIs and TKIs, and the safety of SAbR in conjunction with systemic therapy continues to be evaluated. SAbR with concurrent ICI/TKI was started with caution due to concerns for potential increased toxicity, but no enhanced toxicity was observed yet, warranting more prospective studies [58–60]. Mohamad et al. evaluated the safety of concurrent ICI and hypofractionated radiotherapy in 59 patients with mRCC, concluding that any grade or greater than grade 3 adverse events did not significantly differ from historical rates of ICI therapy alone [61]. In a phase I trial, Tang et al. treated 55 patients with ipilimumab and either concurrent or sequential SAbR. They reported that 34% rate of grade 3 toxicity which is comparable to treatment with ipilimumab alone [62]. Furthermore, a meta-analysis of 13 prospective randomized trials with concurrent TKI and radiation therapy showed increased grade 3 or greater toxicity [63], with another pooled analysis of 68 prospective trials of ICIs showed that those who received an ICI within 90 days following radiation therapy did not appear to be associated with an increased risk of serious adverse events [64].

CNS and Spine Metastasis

Brain metastases has been reported in up to 17% of patients with RCC [65]. Recently, approved systemic therapies have allowed patients with mRCC to live longer, resulting in an expected increase in incidence for patients with mRCC who develop brain metastases [4, 6–8]. Despite improvements in systemic therapies, the blood–brain barrier poses a persistent challenge to treat RCC brain metastases and is a key contributor to why a local therapy such as surgery or radiation remains necessary [66]. Surgical resection has been a traditional treatment approach for these metastatic tumors, however, surgery may not always be possible due to patient or tumor factors such as medical comorbidities, proximity of eloquent cortex, or the number of intracranial metastases. Classic radiation treatment for intracranial metastases has generally involved whole-brain radiation therapy (WBRT). This paradigm, however, has shifted to prefer stereotactic radio surgery (SRS). SRS is an attractive treatment option because it is a minimally invasive outpatient procedure, can be performed on patients unfit for surgery, and can be used if a lesion is in a location deemed unresectable. Moreover, SRS has been shown to have less neurocognitive toxicity without a survival detriment compared to WBRT with SRS [67]. SRS for RCC-specific brain metastases also allows greater dose-per fraction treatments to combat this traditionally considered radioresistant histology. Local control rates have been excellent and even close to 98% to 100% in certain series [65, 68–71].

Second to pulmonary metastasis, osseous involvement is a common site of metastasis and can occur in up to 27% of patients with mRCC [72]. Of those with osseous metastases secondary to RCC, the spinal column is the most common site [73]. A multi-disciplinary approach is highly recommended for RCC spinal metastasis, as certain clinical factors such as the severity of a patient's pain, neurologic symptoms, presence of spinal cord compression, or associated edema may give priority to one treatment over another [74]. Treatment options include conservative pain management, steroids, surgery, radiotherapy, or a combination of these. RCC patients with isolated spine metastasis or otherwise oligometastatic disease may be considered for curative intent local therapy. SAbR, including single-fraction treatments, for RCC spine metastases has been shown to provide an 83% local control at 1 year, few to no grade 3 or greater toxicity, as well as fast, durable pain relief [75, 76]. If the metastasis has extensively infiltrated the spinal canal, and the proximity of the spinal cord keeps from delivering an ablative radiation dose or safe surgical resection, a multi-modal approach can be taken with neoadjuvant systemic therapy followed by local therapy. In the setting of spinal cord compression or cord abutment of the tumor, if ablative radiation alone is not feasible, a surgical decompression and debulking is performed followed by high-ablative radiation to achieve durable local control. One retrospective review showed that postoperative SAbR following epidural spinal cord decompression provided a 1-year local control greater than 95% [77]. Moreover, osseous metastasis from RCC is lytic and can cause significant cortical destruction, placing patients at increased risk for compression fracture. SAbR can increase the risk of vertebral compression fracture further, and it is therefore recommended to pursue prophylactic kyphoplasty [78]. Surgical

resection for RCC metastasis, which is often vascular, also poses an intraoperative bleeding risk that can be addressed with arterial embolization prior to resection. Consequentially, a multi-disciplinary approach is ideal for the proper management of spinal metastasis from RCC.

Palliation

In addition to various scenarios where SAbR may be indicated for the treatment of RCC with curative, consolidative, and adjuvant intent, multiple palliative indications for RCC irradiation also exits. The most common sites of metastatic disease in patients with RCC have been documented as: lung (45%), bone (30%), lymph node (22%), liver (20%), brain (9%), and adrenal (9%) [79]. Indications for palliative radiation include radiologic evidence of metastatic disease and a corresponding sign or symptom such as pain, spinal cord compression, superior vena cava syndrome, brain metastasis, fracture, prevention of fracture in the weight bearing bones, bleeding, as well as others. Hematuria is a frequent presenting symptom for metastatic RCC that can be palliated with radiation therapy [80]. Given RCC's radioresistance to conventional fractionation, hypofractionation schemes favoring a higher dose per fraction are preferred and a regimen of 20 Gy in 5 fractions is preferred over the 30 Gy in 10 fractions. Whenever possible, applicable dose escalation should be considered with intensity-modulated radiation therapy or SAbR.

Conclusion

SAbR is both an established and emerging treatment option with curative or palliative intent, ranging from early inoperable RCC to oligometastatic RCC to widely metastatic RCC. Given SAbR's safety and efficacy for both primary and metastatic RCC, the onus is on the physician to successfully integrate this modality with the available and emerging local and systemic therapies in order to maximize outcomes for RCC patients. While a number of clinical trials are ongoing, many more are required to provide high-level prospective evidence regarding integration of SAbR for the management of primary and metastatic RCC.

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Systemic Therapies for Advanced Non-Clear Cell Renal Cell Carcinoma

16

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Introduction

Renal Cell Carcinoma (RCC) is the most common primary tumor of the kidney in adults and accounts for nearly 90% of all renal malignancies. In the USA, an estimated 79,000 patients were diagnosed with RCC with nearly 14,000 associated deaths [1]. Worldwide, RCC has an incidence approaching 400,000 cases per year and is among the 10 most common cancers in the USA [2]. Additionally, the incidence of RCC continues to increase by 2–3% annually, at least in part due to the increased utilization of cross-sectional imaging in all fields of medicine [3].

RCC comprises a heterogeneous group of tumors. From the initial classification of two subtypes in 1952—clear cell and granular cell—the classification of kidney cancer has evolved to recognize a large variety of histological subtypes according to the World Health Organization (WHO), and over 50 genetically distinct tumor subtypes have been proposed [4–6]. Although clear cell RCC is the most commonly identified subtype, accounting for 70–90% of newly diagnosed renal tumors [7, 8], non-clear cell variants are important to recognize since differences in disease biology can limit susceptibility or confer resistance to therapies used for clear cell RCC. Indeed, while localized clear cell renal cell carcinoma is more likely to present with more advanced T stage, higher nuclear grade, and metastatic disease [9], the prognosis for advanced non-clear cell RCC variants appears to be less favorable despite the advent of newer kidney cancer-directed therapies [10].

The term "non-clear cell RCC" has been commonly used in the literature over the past two decades to describe a wide variety of renal tumors and is primarily a term of convenience. More recently, the term has fallen out of favor as a better

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understanding of the histologic, genetic, and clinical diversity underlying these tumors has led to better characterization and classification of distinct subtypes previously captured under this rubric. Identification of the genetic drivers associated with distinct subtypes of non-clear cell variants is necessary to provide appropriate treatment strategies in both the localized and advanced disease settings. Our understanding of the genetic alterations associated with non-clear cell variants has been supported by the study of hereditary forms of RCC, which account for 4–8% of RCCs [11]. While treatment of localized disease is covered elsewhere, herein we describe some key principles and recent advances governing the management of a variety of advanced non-clear cell RCC variants with a focus on genetic alterations, targeted therapies, and clinical trials supporting disease-specific treatment strategies.

Papillary Renal Cell Carcinoma

Papillary RCC (pRCC) is the second most common form of RCC, making up 10–15% of renal epithelial tumors. Although divided into two subtypes according to the 2016 WHO classification (Type I and Type II), pRCC is now known to represent a more heterogeneous group of tumors [12]. Based on comprehensive molecular profiling of 161 samples by The Cancer Genome Atlas, at least four distinct molecular subtypes have been recognized (C1, C2a, C2b, and C2c). Subgroup C1 is largely comprised of type I pRCC and is associated with *MET* alterations or gain of chromosomes 7 and 17 (70–80% of pRCC cases). Type 2 pRCC tumors are associated with alterations in a variety of genes including NFE2L2, CDKN2A, SETD2, BAP1, and PBRM1; additionally, tumors classified in subgroup C2c were characterized by a CPG island methylator phenotype characteristic of tumors with fumarate hydratase (FH) deficiency [13].

Based on their activity in clear cell RCC, several clinical trials were undertaken to evaluate the efficacy of therapies directed at VEGF and mTOR pathways in advanced pRCC, including single arm studies of pazopanib, sunitinib, and everolimus. Not surprisingly, these studies demonstrated modest activity, with lower objective response rates and survival outcomes than were seen in clear cell RCC [14–18] (Table 16.1).

The *MET* gene encodes for the MET tyrosine kinase (TK) receptor, which is normally activated by its ligand, hepatocyte growth factor (HGF). The HGF/MET pathway is involved in regulating a variety of cellular functions varying from proliferation, motility, and differentiation in normal cells to invasion, angiogenesis, antiapoptosis, and metastasis in cancer cells [19]. Activating mutations of the *MET* proto-oncogene (located on chromosome 7q) are seen in both sporadic and hereditary (Hereditary Papillary RCC, HPRC) forms of Type 1 pRCC. While activating *MET* mutations are considered the primary driver of pRCC associated with HPRC, such alterations are present in only ~15% of sporadic Type I pRCC cases [20–22]. Since genes encoding both MET and HGF are located on chromosome 7, copy number variations involving this chromosome (i.e., gain of chromosome 7) or focal amplification of these genes have been hypothesized to lead to activation of the Met pathway. The *MET* pathway has thus been an attractive target for therapeutic intervention in Type I pRCC.

Table 16.1 Active trials evaluating novel therapeutic strategies in advanced papillary renal cell carcinoma

Identification	Title	Agent(s)	Estimated completion	Status
NCT05665361	Palbociclib and Sasanlimab for the treatment of advanced clear cell renal cell carcinoma (ccRCC) or papillary renal cell carcinoma (pRCC)	• Palbociclib • Sasanlimab	June 2025	Not yet recruiting
NCT05043090	Savolitinib plus Durvalumab versus Sunitinib and Durvalumab monotherapy in MET-driven, Unresectable and locally advanced or metastatic PRCC (SAMETA)	• Savolitinib • Durvalumab • Sunitinib	September 2026	Recruiting
NCT05096390	Axitinib +/− Pembrolizumab in first line treatment of mPRCC (PAXIPEM)	• Axitinib • Pembrolizumab	December 2025	Recruiting
NCT05411081	Testing Cabozantinib with or without Atezolizumab in patients with advanced papillary kidney cancer, PAPMET2 trial	• Cabozantinib • Atezolizumab	July 2027	Recruiting
NCT05287945	Study of Orellanine in metastatic clear cell or papillary renal cell carcinoma	• Orellanine	April 2025	Not yet recruiting
NCT04981509	Testing of bevacizumab, Erlotinib, and Atezolizumab for advanced stage kidney cancer	• Bevacizumab • Erlotinib • Atezolizumab	December 2024	Recruiting
NCT03685448	ANZUP—non-clear cell post immunotherapy CABozantinib (UNICAB) (UNICAB)	• Cabozantinib	April 2024	Recruiting
NCT05122546	CBM588 in combination with Nivolumab and Cabozantinib for the treatment of advanced or metastatic kidney cancer	• Cabozantinib • Nivolumab • Claustridium butyricum	November 2023	Recruiting
NCT04413123	Cabozantinib in combo with NIVO + IPI in advanced NCCRCC	• Cabozantinib • Ipilimumab • Nivolumab	December 2025	Recruiting
NCT04603365	Pamiparib and Temozolomide for the treatment of hereditary Leiomyomatosis and renal cell cancer	• Pamiparib • Temozolomide	August 2024	Recruiting

(continued)

Table 16.1 (continued)

Identification	Title	Agent(s)	Estimated completion	Status
NCT03866382	Testing the effectiveness of two immunotherapy drugs (Nivolumab and Ipilimumab) with one anti-cancer targeted drug (Cabozantinib) for rare genitourinary tumors	• Cabozantinib • Ipilimumab • Nivolumab	February 2024	Recruiting
NCT03635892	A study of Nivolumab in combination with Cabozantinib in patients with non-clear cell renal cell carcinoma	• Cabozantinib • Nivolumab	August 2023	Recruiting
NCT04071223	Testing the addition of a new anti-cancer drug, Radium-223 dichloride, to the usual treatment (Cabozantinib) for advanced renal cell cancer that has spread to the bone, the RadiCaL study	• Cabozantinib • Radium 223	October 2024	Recruiting

Evaluating MET-Directed Therapies in pRCC

Several trials have investigated the efficacy of MET-directed agents in advanced pRCC. A phase II trial investigated the use of foretinib, the first TKI with activity against MET available for clinical evaluation, in patients with pRCC. Although only modest activity was noted in the overall cohort (ORR 13.5%, median PFS 9.3 months, $n = 74$), a planned subgroup analysis demonstrated that patients with activating MET alterations ($n = 10$) were highly sensitive to this agent (ORR 50%) [23]. A subsequent study that evaluated crizotinib, a dual MET and ALK inhibitor, in 23 patients with pRCC (4 *MET* positive, 16 *MET* negative, and 3 unknown *MET* status) also demonstrated preferential activity in patients with activating *MET* alterations [24]. Similarly, a single arm study of savolitinib in 109 patients with pRCC demonstrated an objective response rate of 18% in patients with activating MET alterations versus 0% in patients without [25].

The first randomized trial comparing a MET TKI to sunitinib was reported in 2020; in the SAVOIR trial, subjects with "MET-driven" metastatic pRCC (defined as any tumor demonstrating gain in chromosome 7, MET amplification, pathogenic MET kinase domain variants, or HGF alterations) were randomized to receive either savolitinib or sunitinib. Although the PFS, OS, and ORR were numerically higher for the savolitinib group, the findings were not statistically significant. Median PFS was 7.0 months in the savolitinib group versus 5.6 months in the sunitinib group. The trial was halted early due to results from a concurrent molecular epidemiology study suggesting that MET activation did not confer worse outcomes for patients with pRCC on

sunitinib, and therefore the trial would be unlikely to detect a difference between treatment groups [26]. In a multi-arm randomized phase II trial (PAPMET) comparing sunitinib to the MET kinase inhibitors cabozantinib, crizotinib, or savolitinib, improved progression free survival was noted in patients randomized to the cabozantinib arm compared to sunitinib (9.0 months vs. 5.6 months, $p = 0.019$), while the crizotinib and savolitinib arms were closed after a pre-specified futility analysis [27]. Subjects in the PAPMET trial were not selected based on MET status; however, MET status is being assessed retrospectively and efforts to explore correlation with outcomes is ongoing.

Immune Checkpoint Inhibitors

Recent studies have demonstrated the efficacy and safety of immune checkpoint inhibitors (ICIs) in advanced non-clear cell RCC variants. A single arm Phase II study evaluated the efficacy of first line pembrolizumab monotherapy in patients with a variety of advanced non-clear cell RCC variants. For patients with papillary histology, ORR, PFS, and OS were 28.8%, 5.5 months, and 31.5 months, respectively [28]. Atkins et al. reported outcomes of a phase II trial of nivolumab with salvage nivolumab/ipilimumab for patients with treatment-naïve advanced non-clear cell RCC. Among 19 patients in the cohort with pRCC, only 1 (5%) demonstrated an objective response by RECIST criteria (abstract only) [29]. In a phase IIIb trial examining the safety and efficacy of nivolumab in previously treated advanced non-clear cell RCC, Vogelzang et al. reported partial response and stable disease in 2/24 (8.3%) and 9/24 (37.5%) patients with pRCC, respectively, as well as no grade 3–5 immune-mediated adverse events [30]. Tykodi et al. reported outcomes from a subgroup of patients with advanced non-clear cell RCC from Checkmate 920, a multicohort, phase 3b/4 clinical trial of nivolumab plus ipilimumab treatment in predominantly US community-based patients with previously untreated advanced RCC. Among 18 patients with pRCC, 1 (5%) achieved a complete response and 4 (22%) achieved a partial response [31].

While the overall efficacy of ICI monotherapy was modest, these studies opened the door to combination therapy with targeted agents. In a recently published phase II trial, Lee et al. reported outcomes in patients treated with a combination of cabozantinib and nivolumab in advanced non-clear cell RCC patients with 0–1 prior systemic therapies (excluding prior ICIs). The subjects were segregated into two cohorts by histology: cohort 1 (papillary, unclassified without papillary features, and sarcomatoid) and cohort 2 (chromophobe RCC). When stratified by histology, objective responses were observed in 15/32 (47%) patients with pRCC, including all five patients with fumarate hydratase (FH)-deficient RCC. Although response rates were not reported specifically for pRCC, cohort 1 (consisting of 80% pRCC) demonstrated a median PFS of 12.5 months and a median duration of response of 13.6 months [32]. A second phase II study evaluated a combination of an ICI (durvalumab) and a MET inhibitor (savolitinib) in a cohort of 41 largely IMDC favorable and intermediate risk patients with metastatic pRCC (CALYPSO trial). In a mixed cohort of treatment-naïve and previously treated patients, the authors noted an ORR of 27%, and a median PFS of 4.9 months. A total of 17 (41%) patients were

identified as having MET-driven disease, and the ORR in this subgroup of patients was 53% (cPR in 9/17 patients). Additionally, median PFS and OS in patients with MET-driven tumors were 12 months and 27.4 months, respectively. PFS was substantially longer for patients with MET-driven than non-MET-driven tumors [33].

In preliminary results from the phase II KEYNOTE-B61 study of pembrolizumab in combination with lenvantinib, a multiple kinase inhibitor targeting VEGFR1, VEGFR2, and VEGFR3 kinases, a subgroup of 51 treatment-naïve patients with pRCC demonstrated an ORR of 52.9%, suggesting that this doublet may be active in some patients with pRCC [34].

Non-MET-Directed Combination Therapies

A multicenter phase II trial of atezolizumab, a monoclonal antibody targeting programmed death-ligand 1 (PD-L1), and bevacizumab, an anti-VEGF antibody, evaluated the activity of this combination in patients with advanced non-clear cell RCC or clear cell RCC with at least 20% sarcomatoid differentiation. Twelve of 42 patients (35%) had papillary histology. The majority of patients (65%) were treatment naïve, and none had received bevacizumab or ICIs prior to enrollment. After a median follow-up period of 13.5 months, the ORR was 26% amongst all patients with non-clear cell histology. Although further outcomes were not stratified by histology, the majority of patients with pRCC demonstrated some degree of tumor shrinkage during treatment [35].

Other combination therapies that have been explored include a phase II trial of bevacizumab and everolimus in advanced treatment-naïve non-clear cell RCC, with noteworthy activity identified in 5 patients with papillary histology (ORR of 43%, median PFS of 12.9 months, and OS of 28.2 months) [36]. Based on these results, the trial protocol was amended to allow an expansion of 20 additional patients with predominantly papillary histology. Although most patients were determined to have unclassified RCC with papillary and no clear cell features ($n = 24$, 61%), 14/39 (36%) had pRCC and one patient had translocation-associated RCC with papillary features. The investigators observed an ORR of 35% for the entire cohort; 43% for unclassified RCC with papillary features and 23% for pRCC. With a median follow-up of 17.6 months, median OS was 33.9% [37]. Lastly, a phase II trial evaluating the combination lenvantinib and everolimus showed promising anti-tumor activity in a cohort of 31 patients with non-clear cell RCC (ORR of 26%), although activity in the subgroup of 20 patients with advanced pRCC was much more modest (ORR 15%) [38].

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)

Historically, kidney cancer associated with HLRCC was classified histologically as a Type II pRCC variant; however, the WHO 2016 classification system recognized HLRCC-associated RCC as a distinct entity [6]. HLRCC is characterized by a pathogenic germline alteration in the gene encoding fumarate hydratase (FH), a

Krebs cycle enzyme which catalyzes the conversion of fumarate to malate [39]. The mutation is inherited in an autosomal dominant fashion, but expression of the phenotype requires loss of the second allele via a somatic event. Loss of FH activity leads to accumulation of its substrate, fumarate, with several consequential cellular alterations ensuing. Post-translational modification of several intracellular proteins by fumarate (a process known as succination) leads to altered function of the affected proteins. Inactivation of the DNA polymerase POLG and other proteins critical for mitochondrial DNA replication and fidelity contributes to mitochondrial dysfunction and abrogation of ATP synthesis via oxidative phosphorylation resulting from disruption of the mitochondrial electron transport chain. FH-deficient cells consequently exhibit metabolic reprogramming, with reliance on aerobic glycolysis, a more primitive and less efficient process for ATP synthesis, in order to meet cellular bioenergetic needs (Warburg Effect). Fumarate accumulation also leads to impaired activity of HIF prolyl hydroxylase, resulting in aberrant activity of the hypoxia response pathway and consequent upregulation of a number of proangiogenic and growth factors [40, 41].

Until recently, there were no studies specifically evaluating systemic therapy approaches in patients with advanced HLRCC-associated RCC and patients typically received agents with activity in clear cell RCC, with modest efficacy. However, further understanding of the mechanisms underlying FH-associated tumorigenesis has allowed identification of rational targeted therapeutic strategies in this aggressive disease [42]. A phase II study at the National Cancer Institute evaluated the combination of bevacizumab (a monoclonal antibody targeting VEGF-A) and erlotinib (an EGFR inhibitor) in two parallel, independent cohorts: those with HLRCC-associated pRCC and those with sporadic pRCC. The combination demonstrated activity in patients with HLRCC, with an objective response noted in 27/42 patients (ORR 64%), and a median PFS of 21.1 months. In patient with sporadic pRCC, 15/41 patients demonstrated an objective response (ORR 37%), with a median PFS of 8.7 months [43]. Based on these results, the combination of bevacizumab and erlotinib has been included in the NCCN guidelines as a preferred treatment regimen for patients with advanced HLRCC and an option for those advanced sporadic pRCC.

Chromophobe RCC

Chromophobe renal cell carcinoma (chRCC) accounts for 5–7% of all RCCs. Localized chRCC has generally been associated with a favorable prognosis compared to clear cell and pRCC; however, a subset of chRCC patients present with advanced disease with or without sarcomatoid differentiation [44, 45]. chRCC may present sporadically or as part of an inherited syndrome, such as Birt-Hogg-Dube (BHD) syndrome. In the latter instance, the characteristic histology is hybrid oncocytoma/chromophobe presentation, although pure or predominantly chromophobe tumors have also been described [46]. Genetically, chRCC is often characterized by multiple chromosomal copy number alterations, and in patients with BHD are associated with pathogenic alterations in the *FLCN* gene [47, 48].

Systemic Therapies for chRCC

Due to the relative rarity of metastatic chromophobe RCC, data evaluating systemic therapy options in this entity are scant. Early studies were comprised largely of retrospective series evaluating the efficacy of VEGFR TKIs and mTOR inhibitors within this subtype. For example, a retrospective multi-institutional study reported outcomes of targeted therapies (VEGF TKIs or mTOR inhibitors) for patients with metastatic chRCC. Within this heterogeneous cohort, among 50 patients treated with anti-angiogenic targeted therapies, median time to treatment failure (TTF) was 8.7 months and OS was 22.9 months versus 1.9 months and 3.2 months among 11 patients treated with mTOR inhibitors [49]. In a more recent retrospective study of 112 patients with advanced non-clear cell RCC treated with cabozantinib, a subgroup of 10 patients with chromophobe RCC had an observed ORR of 30%, with median TTF of 5.7 months and 12 month overall survival estimated at 60% (95% CI 16–87) [50].

Few prospective studies have evaluated systemic therapies specifically for patients with advanced chRCC, but patients with this diagnosis are usually included as part of non-clear cell variant cohorts. The ASPEN trial, a randomized phase II study comparing the efficacy of everolimus to sunitinib in patients with advanced non-clear cell RCC variants, included 16 patients with chRCC (10 in the sunitinib arm, 6 in the everolimus arm). ORR was 10% in the sunitinib arm and 33% in the everolimus arm. Median PFS was numerically greater in the everolimus arm (11.5 vs. 5.5 months) but not statistically significant [17]. The similarly designed ESPN trial included six patients in each arm (sunitinib versus everolimus) and the investigators observed favorable outcomes for chRCC compared to other subtypes (median OS 31.6 months with sunitinib and 25.1 months with everolimus, consistent with prior retrospective data) [10, 18].

Data for the activity, or lack thereof, of ICIs in chromophobe RCC are largely derived from subgroup analysis of prospective trials in patients with non-clear cell variants. In the Keynote 427 trial of pembrolizumab monotherapy for advanced variant histology RCC, a subgroup of 21 patients with chRCC demonstrated a disease control rate (DCR, or the sum of patients with complete response, partial response, or stable disease for at least 6 months) of 33.3%. The median PFS was 3.9 months and median OS 23.5 months [28]. Seven patients were included in a phase II trial of combination cabozantinib/nivolumab, the majority of whom (5/7) were treatment naïve (two patients had received prior VEGF TKI therapy). Although the DCR was reported to be 71%, no patients demonstrated partial or complete response (ORR 0%); five patients had stable disease. Because of the small size of the cohort, the median PFS was not calculable [32].

Anti-tumor activity of the combination of lenvantanib and everolimus was observed in a phase II trial evaluating this regimen in 31 patients with advanced or metastatic non-clear cell RCC. In the nine patients with treatment-naïve advanced chRCC, the investigators reported a DCR of 78% with partial response noted in 44% [38]. A more recent phase II trial evaluating the efficacy of lenvantanib in combination with pembrolizumab as first line therapy in an assortment of non-clear cell

variants reported a DCR of 73.3% and ORR of 13.3% among 15 patients with advanced chRCC [34].

An effective treatment approach that is widely accepted as a reasonable standard in patients with chRCC remains elusive. A better understanding of the molecular drivers of these tumors is needed to enable the design of rational treatment strategies.

MIT Family Translocation RCC

Microphthalmia-associated transcription factor family translocation RCC (MITF-tRCC) is a rare subtype of renal cell carcinoma initially recognized by the WHO in 2004 as Xp11 translocation RCC [51]. The MIT family of transcription factors has since been recognized to include TFE3, TFEB, TFEC, and Mitf, of which TFE3 (Xp11) rearrangement and TFEB (6p21) alteration have been recognized as distinct molecularly defined RCC subtypes by the WHO in 2022 [52, 53]. Although MITF-tRCC is conventionally thought to represent 1–5% of RCC diagnoses, it is believed that the true incidence is greater as these tumors are often misdiagnosed as clear cell, papillary, or other RCC variants due to overlapping morphologic characteristics and immunohistochemistry profile; the need for fluorescent in-situ hybridization (FISH) or NGS/RNA-Seq molecular typing for definitive diagnosis poses additional diagnostic challenges [54]. Traditionally thought to primarily affect children and young adults, more cases of MITF-tRCC are being identified in adults, likely due to increased awareness among pathologists and clinicians, as well as inclusion in pathology guidelines [55, 56]. The clinical course of MITF-tRCC is variable, but can be associated with an aggressive phenotype including early nodal metastases [57]. Some fusions, such as the ASPSCR1-TFE3 t(X;17)(p11;q25) translocation, have been associated with advanced stage at presentation, while others may portend a relatively indolent course [58].

Systemic Therapies for MITF-tRCC

Given the rarity of this entity, limited data beyond those from small subgroups within larger trials and retrospective studies is available to inform management of advanced disease. Retrospective studies have evaluated the response to targeted agents for MITF-tRCC, with modest results. In a consortium review of 23 patients <45 years of age with metastatic MITF-tRCC treated with an assortment of therapies, including sunitinib, sorafenib, cytokines, and mTOR inhibitors, those treated with TKIs had the best response. Median PFS for first line sunitinib therapy was 8.2 months, while all three patients receiving sunitinib as second line or later therapy demonstrated a partial response with median PFS 11 months. Of 7 patients receiving an mTOR inhibitor in the second line or later setting, only 1 had a partial response while six had stable disease [59]. In a multicenter cohort study, Chanza et al. identified 17 patients with Xp11.2 translocation histology treated with cabozantinib, observing an ORR of 29% and median time to treatment failure of 8.3

months [50]. In the largest series to date, Thouvenin et al. reported outcomes of 52 patients with MITF-tRCC treated with cabozantinib, largely with IMDC intermediate risk disease (67%). They observed an ORR of 17.3%, with two complete responses and seven partial responses. Median PFS was 6.8 months and median OS 18.3 months with a median follow-up of 25.1 months [60].

ICIs, in particular in combination with TKIs, show some promise and merit additional study. Boileve et al. retrospectively reviewed 24 patients receiving ICI therapy in the second line or later, among whom 4 (16.7%) had a partial response and 3 (12.5%) had stable disease [61]. In the IMmotion151 trial, a randomized study comparing outcomes of sunitinib versus atezolizumab/bevacizumab, the six patients with MITF-tRCC in the sunitinib arm had modest outcomes (PFS 3.5 months) compared to 9 in the atezolizumab/bevacizumab arm (PFS 15.8 months) [62]. Indeed, case reports have described long term response with atezolizumab/bevacizumab [63].

Limited prospective data is available from subgroup analysis of larger studies. The ESPN trial included seven patients with MITF-tRCC (4 receiving everolimus and 3 receiving sunitinib). Median PFS in the everolimus and sunitinib groups was 3.0 months and 6.1 months, and median OS was 8.1 months and 16.2 months, respectively [18]. Two patients were enrolled in a prospective phase II trial of combination nivolumab/cabozantinib for non-clear cell RCC, of whom one had an objective (partial) response [32]. Five patients with MITF-tRCC were enrolled in the phase II study of combination atezolizumab/bevacizumab, of whom at least 1 had a partial response [35]. Among five patients enrolled in a prospective trial of first line pembrolizumab/lenvantinib, ORR and DCR were 60% and 80%, respectively [34].

With a paucity of available prospective data, no clear guidelines have been established for the treatment MITF-tRCC. An ongoing study dedicated to treatment of advanced MITF-tRCC (NCT03595124) comparing ICI monotherapy (nivolumab) with combination ICI/TKI (nivolumab/axitinib) might provide much needed prospective data but additional preclinical and clinical studies are clearly needed.

Succinate Dehydrogenase Deficient RCC

Succinate dehydrogenase (SDH) is a tetrameric enzymatic complex comprised of four genetically distinct subunits (SDHA, SDHB, SDHC, and SDHD). The complex is assembled in the mitochondria to shuttle reducing equivalents along the electron transport chain as well as oxidate succinate to fumarate within the Kreb's cycle. Disruption in the function of the SDH complex leads to intracellular accumulation of succinate and can cause redirection of metabolic activity to aerobic glycolysis. Emerging evidence implicates HIF upregulation and deficient homologous recombination DNA repair occurring as a result of these changes, in tumorigenesis [64–66].

Mutations in the SDHB gene are the most commonly reported genetic alterations in SDH-deficient RCC, though alterations in the other three subunits have been reported [67]. While germline SDH mutations are more commonly associated with development of paragangliomas of the head, neck, and retroperitoneum, as well as pediatric gastrointestinal stromal tumors, lifetime risk of RCC in SDHB mutation carriers is

approximated to be 14%. SDH-deficient RCC is a rare entity, estimated to account for between 0.05 and 0.2% of RCC cases and often associated with younger age at diagnosis and an aggressive clinical course even with small primary tumors [68, 69].

There is a paucity of data to support recommendations for systematic treatment of metastatic SDH-deficient RCC. Therapeutic agents such as VEGFR inhibitors have been proposed in the metastatic setting but not formally evaluated in clinical trials. Ongoing trials include a phase 2 trial of Talazoparib (PARP inhibitor) and Avelumab (NCT04068831), as well as a phase 2 trial of Cabozantinib and Nivolumab combination therapy (NCT03635892).

Medullary Renal Cell Carcinoma

Renal Medullary Carcinoma (RMC) is a distinct, rare entity first described in 1995 and estimated to account for <0.5% of kidney cancers. RMC is typically identified in young male patients of African descent with sickle hemaglobinopathies and associated with the loss of *SMARCB1*, a tumor suppressor gene, leading to deregulation of the SWItch/Sucrose Non-Fermentable (SWI/SNF) complex [70, 71]. Medullary RCC is associated with an aggressive clinical course and portends a poor prognosis, with disease often metastatic at the time of diagnosis and a median overall survival of 13 months [72–74]. Because of the high rate of early recurrence after nephrectomy for clinically localized disease, is has been recommended to treat nearly all patients with RMC with upfront systemic therapy, including those with localized disease at presentation [75].

RMC is generally considered resistant to traditional targeted and anti-angiogenic therapies [76]. However, treatment with platinum-based cytotoxic therapy has shown some efficacy (with a reported response rate of 29%) and remains the recommended front-line therapy [74]. Given the poor response rates with cytotoxic chemotherapy, there is significant interest in alternative systemic therapy approaches for RMC. SMARCB1 inactivation has been shown to induce significant upregulation of protein anabolism, which may introduce susceptibility to proteosome inhibitors [77]. Indeed, one case report noted a durable complete response to single agent bortezomib, and an additional case series of three patients further noted a complete response to combination bortezomib with cytotoxic therapy lasting >12 months for 2 patients and > 7 years for one [78, 79]. Ongoing trials aim to further explore the role of proteosome inhibitors in combination with cytotoxic therapies (NCT03587662), as well as the potential for immunotherapy agents for RMC (NCT03274258).

Other Rare Variants

As the classification of RCC variants continues to evolve, rare morphologically or molecularly defined subtypes continue to be recognized. Conversely, some subtypes thought to be more frequent, such as collecting duct carcinoma (CDC), are thought to be misclassified tumors of newly recognized subtypes, such as RMC, FH-deficient

RCC, or NF2-deficient pRCC [4, 80]. As such, without sufficient data to guide therapies for rare subtypes, systemic treatment strategies must also continue to adapt based on improved understanding of the disease-specific molecular basis of tumorigenesis.

For some rare entities, such as CDC, minimal data exists to guide therapies. A phase II trial of gemcitabine and cisplatin in 23 patients showed an ORR of 26% with median PFS of 7.1 months and median OS of 10.5 months, leading to this combination therapy becoming the preferred treatment strategy for CDC [81]. A combination phase II trial of gemcitabine and cisplatin with bevacizumab was closed due to unacceptable toxicity at interim analysis [82]. A more recent trial of first line cabozantinib in 23 patients with metastatic CDC showed promising efficacy, with an ORR of 35% and median PFS of 6 months [83].

Conclusion

The term "non-clear cell RCC" has traditionally been used to encompass a wide spectrum of histologically, biologically, and clinically distinct subtypes of kidney cancer. As our understanding of these diverse entities has evolved, newer and more effective mechanism-based strategies directed against individual subtypes have emerged. An understanding of the genetic and consequent molecular mechanisms underlying tumor biology and clinical course have greatly informed systemic treatment strategies and provided opportunities to evaluate tailored approaches in patients with rare RCC subtypes.

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Approach to Special Populations with Advanced Renal Cell Carcinoma

17

Shuchi Gulati and Yan Jiang

Introduction

Renal cell carcinoma (RCC) accounts for approximately 90% of all malignant kidney diseases. It comprises a heterogeneous histologic subtype of malignant neoplasms arising from the nephron. Clear cell RCC is the most frequent (80–90%) histological subtype, followed by papillary and chromophobe carcinoma with an overall proportion of 10–15% and 4–5% respectively [1]. The underlying pathogenesis, genomic characteristics, clinical course, propensity of metastases, and susceptibility to conventional therapy vary widely among different subtypes.

In general, RCC is highly resistant to chemotherapy. The evolving knowledge of molecular and immunological characteristics of the tumor significantly advanced systemic therapy over the past two decades. Until 2006, immunotherapy with cytokines, IFN-a, and aldesleukin (human recombinant interleukin-2 [IL-2]), represented the primary treatment of advanced RCC [2]. The discovery of essential signaling pathways involving vascular endothelial growth factor receptor (VEGFR), mammalian target of rapamycin (mTOR) made multi-target tyrosine kinase inhibitors (TKIs) and mTOR inhibitors the standard-of-care (SOC) treatment for metastatic RCC (mRCC). The first immune checkpoint inhibitor (ICI), nivolumab, was approved by the Food and Drug Administration (FDA) in 2015, which started the era of ICI- based treatments for mRCC [3].

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Subsequently, TKIs and ICIs alone or in various combinations have become the SOC for mRCC; their efficacy and safety have been proven in multiple clinical trials [4–7].

Special populations such as patients with brain metastases (BrMs), autoimmune diseases, dialysis patients, patients with a history of organ transplant, and pregnant patients, are usually excluded from clinical trials [8]. Due to their small number and unique features, limited data is available to guide SOC recommendations. The goal of this chapter is to summarize the evidence from limited clinical trials and available case reports/retrospective studies in these special populations to aid clinicians in treatment decision-making.

Special Considerations in Patients with Metastatic RCC Presenting with Brain Metastasis

BrMs occur in 8–10% of patients with mRCC and the frequency varies by histology (more common in clear cell vs. papillary or non-chromophobe) [9, 10]. With a median survival often less than 1 year, patients with brain metastasis tend to have worse prognoses (compared to patients with lung, lymph nodes, adrenal and pancreatic metastasis) [10]. Additionally, BrMs are often associated with severe clinical symptoms such as confusion, headaches, seizures, and altered behavior, hence portending a high degree of morbidity and mortality. In the pre-ICI era, several prognostic scores were proposed that include evaluation of clinical characteristics (age, Karnofsky performance score, number of brain metastases, time interval between initial mRCC diagnosis and BrMs occurrence) and radiologic characteristics of the metastatic lesions (cumulative intracranial tumor volume) [11–14]. The use of these scores is not rampant in clinical practice, however, and decisions for management are made on a case-by-case basis. These scores have also not been validated in the ICI era.

Role of Local Therapy

For patients with solitary localized and symptomatic BrMs with no or controlled extracranial metastasis, neurosurgery has been the gold standard local treatment regardless of primary malignancy, especially for patients younger than 60 years of age [15]. Surgery has the advantage of rapid control of life-threatening symptoms and providing tissue for diagnosis and molecular analysis. Surgery, however, may not be feasible or sufficient for achieving local control, and primary or postsurgical radiotherapy is considered for local control [16, 17]. In recent years, stereotactic radiosurgery (SRS) is being incorporated in RCC-associated BrMs management with 1-year local control rates as high as 94% [18]. In a retrospective cohort of 216 RCC patients with BrMs, local control at 1 year was reported to be similar for patients undergoing surgical resection compared to SRS [83.6% and 75.6%, respectively ($p = 0.55$)] and were significantly poor for patients that underwent

whole-brain radiation therapy (WBRT) or observation (at 53.3% and 36.4%, respectively) [19]. While the common notion is that for multiple brain metastases (≥ 4) and large tumors (>3 cm in size) WBRT may still be the preferred treatment modality, a multi-centered, prospective observational study with 1194 patients of BrMs (3% (n = 36) with mRCC), SRS by an experienced radiation oncologist was shown to be safe and effective to treat up to ten brain lesions [20]. The use of specific modalities thus depends on the expertise of the radiation oncologist and the ability to minimize cognitive impairment with techniques such as hippocampal avoidance [21, 22].

Role of Systemic Therapy

Patients with BrMs have historically been excluded from prospective clinical trials due to the need for urgent local therapy. As the use of targeted drugs and immunotherapy has become rampant in patients with mRCC, data is now becoming available on the efficacy of these treatments in patients with BrMs which will be described in the next section.

Targeted Therapy

Most information regarding the efficacy of targeted therapies in mRCC patients with BrMs has been derived from retrospective studies, expanded access programs (EAPs), and prospective single-arm studies.

The role of sunitinib in patients with brain metastases was first described as part of the sunitinib global metastatic RCC EAP. Of the 321 patients with brain metastases, 213 (66%) were evaluable for efficacy. The overall response rate (ORR) was reported at 12% and 52% of patients were reported to have stable disease for at least 3 months, leading to a clinical benefit rate of 64% [23]. These results were, however, challenged in a phase-2 trial of 16 patients with mRCC with untreated brain metastases, where treatment with sunitinib did not elicit any intracranial responses [24].

More recently, an international retrospective study on 88 mRCC patients with BrMs treated between January 2014 and October 2020 with the multi-kinase inhibitor cabozantinib was described [25]. The study had two cohorts—one including patients with progressing brain metastases without concomitant brain-directed local therapy and the second with stable or progressing brain metastases concomitantly being treated by brain-directed local therapy [25]. The first cohort experienced an objective intracranial response rate of 55% (95% CI: 36%–73%) (with three complete responses (CR) and 14 partial responses (PR)) while the second cohort was reported to have an objective intracranial response rate of 47% (95% CI: 33%-61%) (with 1 CRs and 24 PRs). Adverse events were in line with those previously reported in trials utilizing cabozantinib with fatigue (77%) and diarrhea (46%) being the most common. Based on this data, cabozantinib can be proposed as a safe and effective treatment option for RCC patients with BrMs until prospective data from ongoing clinical trials such as CABRAMET are available [26].

Immunotherapy

Despite recent evidence suggesting the efficacy and safety of ICIs in patients with mRCC, their benefit is undefined in those with BrMs due to the exclusion of patients with active brain metastasis universally from large clinical trials. While previously the central nervous system (CNS) was considered an "immune-excluded" environment; recent studies have shown the CNS to have a distinct immune milieu, and hence the role of immunotherapy is likely to expand in patients with BrMs.

The Italian EAP with nivolumab is among one of the initial studies reporting on the clinical activity of ICIs in BrMs secondary to mRCC. The study enrolled 389 mRCC patients, of which 32 (8%) had asymptomatic brain metastases (not requiring radiotherapy or high-dose steroids). The disease control rate was 53.1% and 53% in patients with or without BrMs, respectively with similar treatment-related adverse events (AEs) in the two groups [27]. The French phase-II study, GETUG-AFU 26 NIVOREN also reported the efficacy of nivolumab in 73 patients with mRCC and BrMs (after progression on previous TKIs) [28]. The results were described for two cohorts (one cohort of patients with previously untreated brain metastases, and the second cohort of patients whose brain metastases had previously been treated). In patients with untreated brain metastasis (cohort 1), intracranial ORR was 12% with a median PFS of 2.7 months (95% CI: 2.3 to 4.6 months). Median PFS in the second cohort was 4.8 months (95% CI: 3.0 to 8.0 months). However, importantly, no objective responses were seen in patients with multiple brain lesions as well as in lesions >1 cm in size. While the pivotal phase-III trial CheckMate 214 (that compared ipilimumab and nivolumab with sunitinib) excluded patients with brain metastasis [4], CheckMate 920 (a phase-IIIb/IV) trial combining treatment with ipilimumab and nivolumab reported 28 mRCC patients with non-active brain metastases. This study reported an ORR of 28.6% (95% CI: 13.2–48.7) in these patients with adverse events consistent with those reported in previous trials using the combination [29], thus pointing to the efficacy of the combination.

Other phase- III ICI/TKI combination trials such as Keynote 426 (comparing pembrolizumab + axitinib vs. sunitinib), IMmotion 151 (comparing atezolizumab + bevacizumab vs. sunitinib), CheckMate 9ER (comparing nivolumab + cabozantinib vs. sunitinib), and CLEAR (comparing lenvatinib + everolimus/pembrolizumab vs. sunitinib), excluded patients with active and untreated brain metastasis. The subset analysis on outcomes of patients with treated brain metastasis has not been reported from these studies yet [5, 7, 30, 31]. JAVELIN Renal 101 (phase-III trial comparing avelumab + axitinib vs. sunitinib) [32] reported its post-hoc analysis on 23 patients with asymptomatic BrMs in each arm [33]. Patients on avelumab + axitinib had a PFS of 4.9 months (95% CI: 1.6-5.7) vs. 2.8 months (95% CI: 2.3-5.6) for patients treated with sunitinib (HR: 0.90; 95% CI: 0.43-1.88). Among patients without brain metastasis at enrollment, eight patients in the avelumab + axitinib arm and ten in the sunitinib arm developed new BrMs while on the study (cumulative incidence rate at 18 months of 2% (95% CI: 0.6-3.3) vs. 3% (95% CI: 1.1-4.8), respectively. While none of these results were statistically significant, they do suggest that the combination of avelumab + axitinib could lend to activity in mRCC patients with BrMs.

In addition to clinical trials, real-world studies are available to discern the role of ICIs in BrMs. Examples include a case series of 19 patients with BrMs treated with nivolumab + ipilimumab where an ORR of 42% was reported (no CRs) [34]. IMDC recently published results from a comparison between nivolumab vs. cabozantinib for second-line treatment of mRCC with BrMs [35]. The cohort included ten patients with BrMs in the nivolumab cohort and one patient in the cabozantinib cohort. The overall survival and time to treatment failure were comparable to data from the previous phase-III Checkmate-025 and METEOR trials, respectively [3, 36]. Further specifics about patients with BrMs were not provided, likely due to a small number of patients in the cohort.

Overall, both targeted therapies and ICI-based regimens appear to be safe in patients with mRCC and BrMs as summarized in Table 17.1. In addition, there are several ongoing trials in this realm, using targeted therapies and ICIs alone as well as in combination with radiation therapy, and are presented in Table 17.2.

Special Considerations in Patients with Metastatic RCC with End-Stage Renal Disease (ESRD) on Hemodialysis

Previous studies have shown an increased incidence of RCC in patients with ESRD and those on dialysis [39]. Patients receiving >10 years of dialysis seem to have an increased risk of sarcomatoid dedifferentiation, which correlates with worse outcomes [40]. Furthermore, 2.7–4.7% of RCC patients are at risk of progressing to dialysis or transplantation after nephrectomy [41]. Concrete data on the safety of use of current drugs in these patients is lacking as most clinical trials exclude patients with a low GFR, significantly elevated creatinine, or on dialysis. However, in clinical practice, encounters with mRCC patients on dialysis are not uncommon. Here we describe the scarce literature which comes predominantly as experience from case reports/series and retrospective studies. It is important to emphasize that package inserts for most of these drugs, including TKIs and ICIs do not recommend dose adjustment based on renal impairment, and the common belief is that therapies can be safely and effectively used in patients on dialysis as shown in multiple case reports and case series (Table 17.3). Specific information regarding patients on dialysis is not available for all drugs.

Tyrosine Kinase Inhibitors (TKIs)

TKIs undergo predominantly hepatic metabolism by the CYP3A4 enzymes, are nondialyzable, and are predominantly eliminated in the feces [84]. Sunitinib is the most studied TKI in dialysis patients. There is no FDA-recommended starting dose adjustment for sunitinib in patients with ESRD on hemodialysis. However, despite no elimination of the drug by dialysis [84], subsequent systemic exposure has been found to be lower by 47% and a gradual increase in dose is recommended as tolerated by the patient [85]. The main concern about adverse events in this patient

Table 17.1 Efficacy of ICIs and/or TKIs in mRCC with BrMs in previous studies and clinical trials

Study/Trial (Ref)	Type of study	Drug and mechanism	Line of therapy	N	Outcomes		
					Median PFS	Median OS	Other
Gore et al. [23]	EAP	Sunitinib (VEGFR)	≥ 1	321	5.6 mos (vs. 10.9 mos overall) (95% CI: 10.3–11.2)	9.2 mos (vs. 18.4 months overall) (95% CI: 17.4–19.2)	ORR 12% CBR 64%
Chevreau et al. [24]	Prospective phase-II trial	Sunitinib (VEGFR)	1–4 median	17		6.3 months (95% CI: 2.1–7.9)	ORR 0% CBR (stable disease) 31%
Hirsch et al. [37]	Retrospective	Cabozantinib (VEGFR)	≥ 1	Cohort A: 33 (without concomitant local therapy)	Median TTF: 8.9 mos (95% CI: 5.9–12.3)	15 months (95% CI: 9.0–30.0)	ORR 55% (95% CI: 36–73%) (3 CRs; 14 PRs)
				Cohort B: 55 (with concomitant brain-directed therapy)	Median TTF: 9.7 mos (95% CI: 6.0–13.2)	16.0 months (95% CI: 12.0–21.9)	ORR 47% (95% CI: 33–61%) including (1 CR; 24 PRs)
Bracarda et al. [27]	Italian EAP	Nivolumab (anti-PD-1)	≥ 2	32			DCR 53%
GETUG-AFU 26 NIVOREN [28]	Prospective phase-II trial	Nivolumab (anti-PD-1)	≥ 2	Cohort A: 39 (without concomitant brain-directed therapy)	2.7 mos (95% CI: 2.3-4.6)	66.7% (95% CI: 49.6-79.1)	ORR 11.8% (95% CI: 3.3-27.5)
				Cohort B: 34 (with pretreated BrMs)	2.6 mos (95% CI: 2.3 to 4.0)	58.8% (95% CI: 40.6- 73.2%)	Not reported
JAVELIN renal 101 [33]	Phase-III trial	Avelumab+ axitinib (anti-PD-L1 + VEFGR	1st line	23	4.9 mos (95% CI: 1.6- 5.7)		Not reported
		Sunitinib (VEGFR)		23	2.8 ms (95% CI: 2.3- 5.6)		

Checkmate 920 [29]	Phase IIIb/IV	Nivolumab + Ipilimumab (anti-PD-L1 + CTL-4)	1st line	28	9.0 mos (95% CI: 2.9–12.0)	NR	ORR 32% (95% CI: 14.9–53.5)
Brown et al. [34]	Retrospective	Nivolumab + Ipilimumab (anti-PD-L1 + CTL-4)	≥ 1	19	7.6 mos (95% CI: 5.6 to 14.9)	NR	ORR 73% No CRs

ICI immune checkpoint inhibitors, *TKIs* tyrosine kinase inhibitors, *BrMs* brain metastasis, *EAP* expanded access programs, *VEGFR* vascular endothelial growth factor receptor, *PD-1* programmed death-1, *PD-L1* programmed death ligand-1, *mos* months, *CI* confidence intervals, progression-free survival, *OS* overall survival, *ORR* overall response rate, *CBR* clinical benefit rate, *CR* complete response, *PR* partial response, *TTF* time to treatment failure, *DCR* disease control rate

Table 17.2 Ongoing clinical trials in mRCC with brain metastasis

Trial (NCT) [38]	Phase	Systemic therapy	Local therapy	Cohorts	N	Primary Endpoint	Status	Comments
NCT03967522 (CABRAMET trial)	II	Cabozantinib	None	mRCC	77	Non progression rate in brain metastases at 3 months	Recruiting	AEs, PFS, OS up to 54 mo as secondary endpoint
NCT02978404	II	Nivolumab	Radiosurgery	mRCC mNSCLC mSCLC mMelanoma	60	Intracranial PFS at 1 year	Active, not recruiting	Actual enrollment of 26 patients has occurred so far
NCT05048212	II	Nivolumab + Ipilimumab + cabozantinib	None	mRCC	40	Intracranial PFS	Not yet recruiting	Time frame: Through study completion, an average of 1 year
NCT04955743	II	Pembrolizumab+ Lenvatinib	None	mRCC mMelanoma	56	BMRR up to 2 years	Not yet recruiting	The study will exclude symptomatic brain metastasis
NCT02886585	II	Pembrolizumab	None	Several including mRCC	102	Intracranial ORR, OS and extracranial ORR	Recruiting	
NCT04187872 (TORCH trial)	I	Pembrolizumab	Laser interstitial ThermotHerapy (LITT)	Several including mRCC	16	Immune effect	Recruiting	Phase-1 study to look at safety and immune effects of LITT plus pembrolizumab

mRCC metastatic renal cell carcinoma, *AEs* adverse events, *PFS* progression-free survival, *OS* overall survival, *mo* months, *mNSCLC* metastatic non-small cell lung cancer, *mSCLC* metastatic small cell lung cancer, *BMRR* brain metastasis response rate, *ORR* overall response rate

Table 17.3 Summary of cases reports and case series reporting on the safety and efficacy of targeted therapies and ICIs in mRCC patients on dialysis align with those reported in clinical trials with no concerns about toxicity

Drug	Dose	Dialyzable	Elimination	N	Grade 3-5 toxicities (No. of pts)
Sunitinib [42–61]	12.5–50 PO mg daily, 4/6 weeks	No	Feces: 61% Urine: 16%	68	**Cardiovascular** Acute CHF/pulmonary edema (3) Hypertension (3) **Hematologic:** Anemia (2) Bleeding (2) Thrombocytopenia (4) Leucopenia (1) **General:** Fatigue/ asthenia (6) Anorexia (1) **Gastrointestinal:** Diarrhea (1) Pancreatic enzyme elevation (2) Vomiting (1) Mucositis (1) **Skin:** Hand-foot syndrome (2)
Sorafenib [42, 43, 49, 62–67]	100–800 mg PO daily	No	Feces: 77% Urine: 19%	55	**Cardiovascular** Left ventricular dysfunction (2) Syncope (1) Cardiac ischemia (2) Hypertension (9) **Hematologic:** Anemia (11) Bleeding (4) **General:** Fatigue/ asthenia (5) Anorexia (2) **Gastrointestinal:** Diarrhea (11) Nausea (1) Gastritis (1) Liver dysfunction (3) Mucositis (1) **Skin:** Hand-foot syndrome (4) **Pulmonary** Pneumonitis (2) Dyspnea (1) **Infection/ sepsis (2)**

(continued)

Table 17.3 (continued)

Drug	Dose	Dialyzable	Elimination	N	Grade 3-5 toxicities (No. of pts)
Axitinib [50, 53, 68–70]	4–14 mg PO daily		Feces: 41% Urine: 27%	13	**Cardiovascular:** Hypertension (1) **General:** Fatigue (1) **Gastrointestinal:** Cholangitis (1)
Pazopanib [43, 49, 71, 72]	200–800 mg PO daily	No	Feces: Majority Urine: <4%	13	**Cardiovascular:** Hypertension (1) **Hepatic:** Hepatic dysfunction (2) **General:** Headache (1) Fatigue (2)
Cabozantinib	PO	Unknown	Feces: 54% Urine: 27%	NA	NA
Lenvatinib	PO	No	Feces: 64% Urine: 25%	NA	NA
Everolimus [43, 44, 49, 53, 63, 73, 74]	5–10 mg PO daily		Feces: 80% Urine: 5%	28	**Cardiovascular toxicity (1)** **Hematologic:** Thrombocytopenia (1) Anemia (1) **Skin:** Rash (1) **Gastrointestinal:** Pancreatic enzyme elevation (1) **General:** Decreased performance status (1) Hyperglycemia (1)
Temsirolimus [43, 63, 75, 76]	20–25 mg/week; IV		Feces: 78% Urine: 4.6%	17	**Hematologic:** Thrombocytopenia (2) Anemia (1) **General:** Asthenia (1)
Nivolumab [45, 46, 48, 77–81]	3 mg/kg or 240 mg Q2W or 480 mg monthly IV		Intracellular catabolism	17	**Gastrointestinal:** Diarrhea (1) General: Asthenia (1) Anorexia (1)
Ipilimumab+ Nivolumab [82, 83]	Ipilimumab (1 mg/kg) + Nivolumab (240 mg) IV every 3 weeks		Intracellular catabolism	2	None reported

ICIs immune checkpoint inhibitors, *mRCC* metastatic renal cell carcinoma, *No*. number, *PO* per oral, *IV* intravenous, *NA* not applicable

population is that of high blood pressure and hematologic issues such as anemia which would require close monitoring [84]. A case series of 24 patients with mRCC (16 patients treated with sunitinib and 8 patients treated with sorafenib) however, found both TKIs to be safe in patients on dialysis with no unexpected adverse outcomes [42]. Similar case series have described the safety and efficacy of axitinib in mRCC patients on dialysis. A case series involving eight patients reported outcomes similar to previously published data for axitinib and also reported that the dose was able to be increased to 5 mg twice daily in six of the eight patients [68]. Pharmacokinetic studies in hemodialysis patients have shown that the dialyzer does not clear off sunitinib, sorafenib, pazopanib, or axitinib from plasma, and hence these drugs can be administered independent of the timing of dialysis [62, 69, 71, 86]. There is limited experience with cabozantinib in patients on hemodialysis, however, the FDA label does not suggest a dose adjustment is necessary for this drug.

Overall, clinicians do need to be cognizant that patients on hemodialysis and chronic kidney disease are at a higher risk of cardiovascular comorbidities, and hence should be monitored closely. Once started on TKIs, these patients should be under close surveillance of dose-limiting AEs such as high blood pressure and dose reduction may be required as appropriate. However, being on dialysis does not prohibit the use of these drugs and their administration does not need to be timed with dialysis.

mTOR Inhibitors

Similar to TKIs, mTOR inhibitors (temsirolimus and everolimus) are metabolized primarily in the liver, and in pharmacokinetic analyses, clearance has not been shown to be affected by mild-to-moderate renal dysfunction [87]. There is no requirement to adjust the dose of these agents in patients on dialysis as these drugs also do not enter the dialysate [73, 75]. The outcomes and AEs in mRCC on dialysis, when treated with mTOR inhibitors, have been shown to be comparable to non-dialysis patients and hence deemed safe in this population [74, 88].

Immune Checkpoint Inhibitors (ICIs)

Even though the use of ICIs has become common in the mRCC space, there is a scarcity of data to support the safety of these agents in patients on dialysis. PK analysis of PD-1 inhibitor, nivolumab in other solid tumors show clearance and exposure of nivolumab to be the same between patients with and without renal dysfunction [89]. Other ICIs have not been studied in this context, however, based on case series [77–79, 90] with nivolumab in patients with mRCC with end-stage renal dysfunction or for those on dialysis, the outcomes, and adverse events are comparable to non-dialysis patients. Thus, while ICIs are considered safe in patients on dialysis, further larger studies are required to make definitive recommendations.

Special Considerations in Patients with Metastatic RCC with Autoimmune Diseases

Both the activity and toxicity of ICIs largely stem from the release of tumor- or host-specific cytotoxic-T cells. Therefore, patients with pre-existing autoimmune diseases, are at high risk of major concerns regarding the safe use of ICIs and hence have traditionally been excluded from ICI clinical trials. Additionally, patients with autoimmune diseases often require immunosuppressive treatment, such as high-dose corticosteroids, which may additionally compromise efficacy [91]. Direct evidence of the safety of ICI use in patients with mRCC with pre-existing autoimmune diseases is extremely limited. Experience and data have been extrapolated from studies involving other tumor types where ICIs are widely used such as melanoma, non-small cell lung cancer, and urothelial cancer. One of the first studies to describe the efficacy and overall toxicity of ICIs in this population was a retrospective review of 119 patients with advanced melanoma from 13 academic centers [92]. The patients included in this study were treated with anti-PD-1 antibodies (pembrolizumab or nivolumab) and either had pre-existing autoimmune disorders or had developed significant toxicity with prior ipilimumab use (67 patients). In patients with pre-existing autoimmune disorders, 38% of patients had a flare requiring immunosuppression. However, only 4% of patients had to discontinue treatment due to the flare. In patients who had a history of immune-related AEs (irAE) with prior ipilimumab exposure, 3% of patients had a recurrence of the same irAEs and 34% developed new irAEs, and 12% of patients had to discontinue treatment. No treatment-related deaths were reported in either arm. Thus, in melanoma patients even with a pre-existing autoimmune disorder, anti-PD-1 therapy-induced mild immune toxicity which was manageable and did not require cessation of therapy; thus allowing for the continuation of therapies and achievement of clinical response. Another retrospective study that included 56 patients with non-small cell lung cancer with an underlying autoimmune disorder, who received a PD-(L)1 inhibitor reported the autoimmune disorders' incidence similar to that reported in clinical trials where patients with autoimmune issues had been excluded and none of these were reported to be severe or such that required permanent discontinuation of the ICI agent [93]. A systematic review included 123 patients (from 49 publications) with pre-existing autoimmune disorders; of which 2.4% of patients had mRCC reported data on the use of ICIs [94]. Adverse events, including exacerbation of pre-existing autoimmune issues, de novo irAEs, or both, were seen in 75% of the patients. AEs improved in >50% of patients without having to discontinue the ICIs. However, three patients were reported to have died from the AEs; thus speaking to the seriousness of these events.

In light of this data, prospective studies are now evaluating the issue of safety of ICI-based therapies in patients with autoimmune disorders. A subgroup analysis of the international SAUL study, which explored the safety and efficacy of atezolizumab in patients with underlying autoimmune issues and urothelial carcinomas; reported an increased rate of irAEs (~11% incidence), which was comparable to that reported in previous retrospective studies and no treatment-related deaths or

AEs necessitating treatment discontinuation were reported in those with and without autoimmune disorders [95]. Efficacy was similar in both groups as well. Another prospective study, the phase-1b AIM-Nivo trial is currently enrolling patients to assess the safety of nivolumab in patients with underlying dermatomyositis, systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, multiple sclerosis [96].

Results from these prospective studies should inform clinicians about the safe use of ICIs in patients with autoimmune disorders. Overall, as of now, when choosing systemic treatment for mRCC patients with pre-existing autoimmune disorders, there are multifactorial considerations. First, the effectiveness of monotherapy versus combination therapy should be evaluated based on the patient's risk stratification. Those with underlying severe autoimmune issues may not be appropriate candidates for CTLA-4 inhibitors and even PD-1(L1) inhibitors. TKI monotherapy should be considered in such cases. Second, the type of issue is of critical importance. Currently available reports suggest that rheumatological disorders flare most frequently (44%), psoriasis flares also appear common (43%), while thyroid autoimmune flares seem less frequent (13%); fortunately, all are easily managed with standard treatments [92, 97]. On the other hand, inflammatory bowel disease (IBD) flares, in particular following CTLA-4 targeting, can result in significant clinical deterioration and morbidity, and vigilance is warranted as also stands true for neurological autoimmune disorder flares (such as myasthenia gravis and multiple sclerosis), which need close monitoring [92].

In summary, pre-existing mild-to-moderate autoimmune disorders do not explicitly prohibit ICI treatment, and many patients who experience no or mild flares, may not be required to discontinue their ICI and may not need corticosteroid initiation. Those who do experience irAEs/flares can often successfully be managed with standard therapeutic algorithms. However, there are many areas where experience is lacking, and future clinical trials will provide additional answers to these conundrums.

Special Considerations in Patients with Metastatic RCC with Solid Organ Transplant

The population of patients with solid organ transplants, especially kidney transplants is particularly interesting because, there is an increased risk of developing cancer in the native as well as the transplanted kidney, especially in patients who have been on dialysis for a prolonged period [98, 99]. Once solid organ transplant patients develop cancer, they should be managed per standard of care, however particular attention should be paid to the risk of transplant rejection with the administration of ICIs. In a systematic review of 64 solid organ transplant cases and case series, treatment with ICIs led to an overall graft rejection rate of ~40% [100]. In another retrospective study, where 69 kidney transplant recipients were treated with ICIs, 42% developed acute rejection and 19% of patients lost their allograft (compared to only 5% of the stage-matched cancer patients who were not treated with an

ICI) [101]. Other systematic reviews have shown similar rates of allograft rejections (~40% for kidney transplants, and seemed to be higher as compared to other solid organs) with a median time to rejection of 21–24 days from the start of ICI therapy [102, 103].

The main risk factors for graft rejection are yet to be defined, but anti-PD-1/PD-L1 therapies (rather than anti-CTLA-4 drugs) and the need for a reduction of the dose of immunosuppressants conferred a higher risk of rejection [104]. It is unclear as to which immunosuppressive treatment adequately reduces rejection risk without significantly reducing ICI activity. Peri-infusional prednisone and mechanistic target of rapamycin (mTOR) inhibitors may aid allograft preservation, but the experience is limited, and prospective studies are needed [101]. Because dialysis is an option following renal transplant failure, treatment with ICI is feasible in this setting if patients fully understand the risks and implications of possible renal failure. However, if the patient is not prepared to accept the risk of graft rejection and dialysis, ICI-based therapy should not be used.

Special Considerations in Pregnant Patients with Metastatic RCC

Cancer can affect 1 in 1000 pregnant patients, the most common types being breast cancer, melanoma, cervical cancer, and lymphomas [105]. Urological cancers are rare, with RCCs being the most commonly reported renal neoplasm during pregnancy [105]. No consensus or guideline has been proposed or verified in pregnant patients with RCC. Management of RCC during pregnancy depends on the stage of disease and may be further influenced by the trimester of pregnancy at diagnosis. In general, for localized RCC (stage I or II), surgical intervention should be avoided in the first trimester, which can be postponed until after the second trimester or after confirming fetal lung maturity [106]. If possible, term delivery (after 37 weeks) is the goal as a preterm delivery places the child at risk for impaired neurocognitive outcome [107]. In cases that delivery is planned by cesarean section, simultaneous oncological surgery can be planned [108]. A case series of 29 kidney cancer cases diagnosed and managed surgically during pregnancy showed that 79% of patients achieved complete remission and all patients underwent surgery after 35 weeks of gestation, except for one twin pregnancy that needed to be induced at 32 weeks. For locally advanced stage III or IV tumors found in any trimester, on the other hand, a thoughtful discussion needs to be had regarding fetal and maternal risk to decide on the optimal treatment plans. As far as systemic therapies are concerned, there is a paucity of data regarding the safety of exposure to TKIs and ICIs during pregnancy, data being mostly derived from case reports and or animal studies. In general, exposure to TKIs in the first trimester is best avoided due to its association with spontaneous abortions and congenital malformations [109]. Anti-PD (L)-1 drugs at this time, are categorized as pregnancy category D by the FDA whereas anti-CTLA-4, ipilimumab is pregnancy category C (due to the less clear role of the CTLA-4 axis in fetal immune tolerance) [110]. While not directly teratogenic, these drugs can

reverse the maternal immune tolerance to the fetus and lead to worse pregnancy outcomes such as miscarriage, prematurity, and low birth weight; and their use is not recommended in pregnant women [110]. If the use of these drugs is absolutely warranted, close monitoring of the mother and the fetus is required.

When faced with a pregnant patient with RCC, clinical decision-making must consider both the outcome for the pregnant patient and the unborn child, which is challenging and requires a multidisciplinary approach. Future clinical trials are required to assess the safety of systemic therapies in pregnant patients as well.

Conclusion

In recent years, several advancements have been made in the field of kidney cancer. Despite increasing awareness, representation of special populations of patients with cancer, such as those discussed in this chapter is lacking in clinical trials. Additionally, patients of older age, certain ethnic groups, those with poor performance status, with HIV, other viral illnesses are not being included in trials. As a result, there is a paucity of data on how best to manage these patients and to align with the Food and Drug Administration (FDA)'s guidance for industry partners to enhance the diversity of clinical trial populations [111]. With an increase in awareness, we can encourage investigators to design trials that would help answer questions pertaining to the best management strategies for populations of special interest in mRCC, which is currently an area of unmet need.

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Integration of Palliative Care into the Renal Cancer Treatment Paradigm

18

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Introduction

In the USA, an estimated 79,000 new cases and over 13,900 deaths due to kidney and renal pelvis cancer are projected to occur in 2022 [1]. Over 90% of kidney cancer cases are due to renal cell carcinoma (RCC). About 75–80% of cases are due to clear cell histology (ccRCC), while the remainder is referred to as nonclear cell RCC (nccRCC). About 30% of patients initially present with metastatic RCC and another third of patients will have cancer recurrence with distant metastases after extirpative surgery [2, 3].

Palliative care is specialized medical care delivered by a multidisciplinary team of physicians, nurses, social workers, and other specialists that addresses multiple domains of care [4]. These domains include physical, psychological, social, spiritual, cultural, ethical, and legal aspects of care for patients [5]. Palliative care focuses on symptom management as well as provides expert communications with

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patients, caregivers, and clinicians. Borne out of the hospice movement, research shows that earlier integration of palliative care into routine cancer care has improved patient centered outcomes including quality of life, symptoms, and overall survival [6–8]. There are several models of delivery, including the provider-based model and the issues-based model [4]. The provider-based model defines the term "primary palliative care" as the care provided by patient's primary team, in this case, oncology team. For patients with complex care needs, this primary oncology team can refer patients to "secondary or subspecialty palliative care" [4].

This chapter will first briefly outline current treatment paradigms for RCC, then it will seek to examine palliative care and the role it can play in RCC management, including evidence for various palliative care interventions based on randomized studies. Next, this chapter will discuss current obstacles and challenges concerning the broader adoption and integration of palliative care provision, and lastly, this chapter will discuss potential next steps, including potential steps to take to design and implement integrated service and clinical trials of integrated services to improve care of the patient with RCC.

Treatment Paradigms for RCC

The treatment and management strategies for ccRCC have evolved significantly over the last decade. A larger focus on active surveillance and nephron-sparing surgery for small renal masses has improved the morbidity and mortality associated with kidney surgery. Furthermore, the development of minimally invasive approaches, such as laparoscopy and robot-assisted procedures, has further improved operative outcomes and management of renal masses.

Significant biological developments have led to the identification of key pathways that are important for ccRCC tumor biology. Therapeutics initially focused on inhibiting the mammalian target of rapamycin (mTOR) and vascular endothelial growth factor (VEGF) pathways, but more recently, the discovery of immune checkpoint receptors has led to the development and approval of combination of immune checkpoint inhibitor therapies for treating locally advanced and metastatic ccRCC as highlighted in earlier chapters [9]. As the data matures, we may see that more than 10% of patients who were deemed incurable a decade ago may be able to be off all therapies and live a normal life, and to be cured of their cancer, even in the metastatic setting. The advances in clinical trials have also increased the number of therapy choices that can be offered to patients with metastatic cancer in the first, second, and even third-line setting.

These advances have also translated into potentially preventing recurrence of cancer. Immune checkpoint inhibitor pembrolizumab has been shown to decrease recurrence of cancer in patients with high risk of recurrence. In the study, high risk of recurrence was defined as those patients with pathological findings of pT2 stage with nuclear grade 4 or sarcomatoid differentiation, ≥pT3, nodal disease, or needing nephrectomy and metastasectomy [10]. Several other clinical trials are also evaluating the role of adjuvant therapy for patients at high risk of recurrence [11, 12].

As a result of the therapeutic advances in ccRCC, there has been significant increase in survival as well as potential for long-term complete remission and potential cure, where patients can live without any therapies [10].

While ccRCC has seen an exponential increase in treatment options, nccRCC remains difficult to treat. Advances have been limited given the lower incidence of nccRCC and fewer clinical trial successes. nccRCC contains a higher mutational burden, making it difficult to identify a specific aberrant pathway that can be targeted [13]. As a result, current National Comprehensive Cancer Network guidelines recommend treatment with sunitinib, a VEGF inhibitor, or cabozantinib, multikinase receptor inhibitor, or enrollment in clinical trials [14].

Current Treatment Paradigms for Integration of Palliative Care

This section will seek to examine current paradigms in delivering palliative care interventions. One can divide palliative care interventions into various categories: local interventions or systemic interventions; or interventions in the setting of localized disease or metastatic disease, palliative care versus hospice care and primary vs. subspecialty palliative care. In most solid tumors, treatment intent for localized disease is considered curative and in metastatic disease, palliative. Of course, as outlined above, that paradigm may be shifting in RCC with newer systemic therapy choices where even patients with metastatic disease can be considered to have curative disease making the latter distinction of localized and metastatic disease blurry.

Palliative Intervention: Local or Systemic Interventions

Palliative interventions can take the form of local interventions or systemic interventions. Local interventions focus primarily on mitigation of symptoms at the site of suffering, such as in the case of a local nerve block that reduces or eliminates pain symptoms in a particular area of the body. Local therapy can also take the form of invasive or non-invasive interventions aimed at preventing or alleviating issues, such as obstruction that may arise in the genitourinary (GU), gastrointestinal, respiratory, or biliary system. In renal cell carcinoma, for example, ureteral stenosis secondary to external mass compression or fibrosis secondary to radiation or chemotherapy treatment can frequently be treated with stents, improving patients' quality of life and alleviating suffering [15]. Local bleeding in GU tract or other metastatic site including lung and brain can be treated with non-invasive intervention such as radiation or invasive interventions such as interventional urologic, pulmonary, or neurosurgical procedures. Other examples in RCC include frequent metastasis to the lungs, which can cause bronchial obstruction that can be treated with invasive procedure such as bronchial stenting or non-invasive radiation therapy [16]. In contrast, systemic interventions concern broader approaches to symptom relief, such as the delivery of therapies that reduce symptoms such as

pain, dyspnea, nausea, constipation, weakness, fatigue, mood changes that cause patient suffering [17].

Palliative Interventions: In the Curative or Non-curative Setting

In most solid tumors, treatments for early-stage diseases are considered curative and late stage or recurrent are considered non-curative or palliative. In the curative setting, the goal of care is to cure the cancer by eliminating disease completely. Patients may require surgery, radiation, systemic therapies or a combination of therapies to achieve the goal. It also requires taking the risk of an increase in patient discomfort with side effects of these therapies. These can be physical and emotional symptoms as well as loss of function post intervention either temporarily or permanently. Palliative care intervention can potentially work in conjunction with curative therapies, and help primary oncology team improve overall patient symptoms including pain and function [18].

In solid tumors with non-curative setting, sometimes referred to as palliative setting, the goal of care is to help prolong quality of life for the individual patient. Since quality of life is individual, it requires patient input regarding their goals for their life and how they prefer to live their life. In this setting, palliative care interventions can include symptom relief from cancer and cancer therapies including side effects of therapies. Palliative care interventions can also include help with communications and decision making on specific therapies.

Palliative Interventions: Continuum of Palliative Care and Hospice

When patients have decided to forgo focusing on their cancer and thus focus of care is entirely on symptoms, the delivery of care is transitioned to a hospice team. In the USA, hospice care is an insurance benefit that requires a certification from physicians of limited life expectancy. The key difference is that disease-directed measures, such as systemic therapies, are discontinued. Thus as shown in Fig. 18.1, palliative care can be initiated at any time during a patient's illness trajectory and can be delivered in conjunction with curative or palliative intent therapies and hospice is appropriate when focus is only on symptoms or palliation [19].

This transition from focus on disease to focus on symptoms only, or hospice, has been challenging in the U.S. Multiple studies have suggested that there is delayed referral to involve palliative care and hospice teams [20]. Contrary to common public perception regarding hospice care that shortens life expectancy, some studies have shown that hospice patients may actually have an increased survival rate [21]. In a study of cancer and non-cancer patients, early incorporation of hospice care in patients with serious disease found that on average across a wide range of illnesses, patients entering hospice early are seen to have increased quality of life and even survive an average of 29 days longer than those not entering hospice early in the

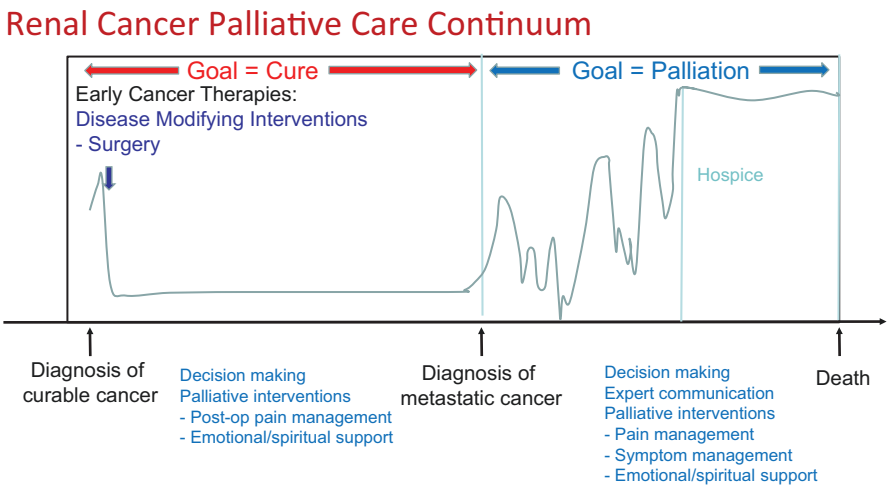

Fig. 18.1 Integration of palliative interventions throughout the course of management of kidney cancer, from diagnosis and curative treatment focus to palliative focus and hospice

course of illness. These impacts were most pronounced in patients with congestive heart failure, lung cancer, and pancreatic cancer [21].

Based on published models of integration of palliative care, and above definitions, we propose a model of palliative care in continuum of kidney cancer treatment in Fig. 18.1 [4].

Palliative Interventions: Primary or Subspecialized Palliative Care

Palliative care can be provided by primary medical teams (either primary oncology teams consisting of urologist, medical oncologist, radiation oncologist or hospitalists) or in conjunction with a subspecialty palliative care consultation team [4, 22]. Typically, primary palliative care is provided by primary medical teams and usually encompasses basic symptom management, advanced directive discussions, and conversations regarding illness trajectory and prognosis and goals of care. In contrast, subspecialty palliative care concerns palliative care provided by specialist multidisciplinary palliative care team consisting of physicians, nurses, social workers, chaplains, pharmacists, physical therapists, and health aides [4].

Current Evidence for Palliative Care Integration in Genitourinary Cancers

Despite the abundance of evidence supporting the use of palliative care in patients with advanced cancer, relatively little research has been conducted that examines the effect of palliative care integration in patients with advanced genitourinary cancers, and RCC specifically.

Of all the large, randomized studies of early integration of palliative care into routine oncological care, limited number of these studies had patients with GU malignancies. ENABLE III randomized controlled trial of early versus delayed integration of palliative care into the treatment of patients with advanced cancer found that patients with earlier integration of palliative care had increased median survival rates at 1 year. In this intervention, patients had an initial palliative care physician visit followed by 6 weekly nurse-led phone coaching sessions and monthly phone follow up monitoring. There were only 8% of patients with genitourinary cancer comprised of seven patients in the intervention arm and 9 patients in the control arm [6].

A cluster randomized study of early integration study of palliative care had 4 out of 24 oncologist practicing GU oncology. In patient participation, 27/228 in the intervention arm and 51/233 control in the standard oncological care arm had GU malignancies [8]. This study intervention consisted of at least monthly specialty palliative care visit that included structured assessment of symptoms and routine assessment of goals of care, patient and family support needs, patient and family psychological distress and coping and discussion of advanced care planning. Intervention also included access to palliative care team if hospitalized and offer of home visits and coordination with family physician. The study found improvement in quality of life assessments at 4 months. In another study of outpatient oncology palliative care clinic found had 5% of intervention and 9% of control group had patients with GU cancer [23].

In a large European trial of early integration of palliative care into oncological care that found improved quality of life, had 6% of patients in intervention and 11% of patients in control group had GU cancers [24]. In this study, patients were enrolled within 12 weeks of diagnosis of incurable cancer, and intervention was early and systematic integration of palliative care team that included medical specialists, psychologists, social workers, dieticians, and specialized nursing. Patients in control arm had access to the intervention resources on an ad-hoc basis. Study found that at 12 weeks, quality of life was improved in the intervention arm despite patients in control arm having access to the same resources and having been offered psychological support. Thus, there are very limited number of GU patients and thus there are even smaller number of patients with RCC.

This lack of prospective evidence of integration in GU cancers is also corroborated by retrospective data on utilization of palliative care in management of RCC. A retrospective analysis of National Cancer Database (NCDB) suggested that less than 20% of patients with advanced RCC are coded to have received palliative care, with both advanced age and minority status associated with reduced likelihood of

palliative care use [25]. This was corroborated by the studies in other GU malignancies such as bladder and prostate cancer [26].

There is limited emerging and encouraging evidence of integration of palliative care in GU cancer including RCC. Rabow et al. (2015) examined the effects of integrating palliative care with cystectomy in patients with muscle-invasive bladder cancer, in comparison with cystectomy with standard care, alone. Palliative care intervention was defined as the provision of a palliative care consult with anticipatory guidance regarding management of likely symptoms, offering a handbook with guidance on symptom management, giving a compact disc with meditation programming, the provision of in-hospital palliative care visits, and the conducting of monthly teleconferences with palliative care providers to review symptoms and suggested remedies. Patients were then asked to complete symptom surveys at 2, 4, and 6 months post-operatively. The authors find that the intervention arm had improved depression and anxiety scoring over the 6-month intervention, compared to an increase in both in the control arm. The intervention arm also saw relative improvements in fatigue symptoms and quality of life scoring [27]. Huen et al. (2019) examined the effect of integrating a palliative care clinic with a urology clinic on advanced urological cancer patients' health-related quality of life, and found that patients undergoing the combined care modalities saw no decrease in quality of life, despite a significant proportion of patients suffering disease progression and death during the monitoring period [28].

Obstacles and Challenges to Integration of Palliative Care

Since there is no specific data on obstacles and challenges to integration of palliative care in to routine RCC care, the potential obstacles and challenges to integration of palliative care are derived from experience of integration across entire cancer care continuum. According to World Health Organization, only about 14% of patients who need palliative care receive it [29]. Numerous challenges, barriers to integration of palliative care exists. Some authors have presented a model of classifying barriers into structural, provider, and patient-family barriers [20].

Structural Barriers

In addition to the data from the WHO which includes low- and middle-income countries, there are limited resources for integration of palliative care into routine oncological care in North America as well. A survey of US National Cancer Center (NCI) designated cancer center and non-NCI designated cancer executives showed that 95% of NCI and 40% of non-NCI centers had outpatient palliative care program [30]. Thus, a large number of patients do not have access to outpatient palliative care where most patients receive their care. In the survey, the existence of outpatient program overestimates availability of palliative care services when patient desires, for example on the same day as their visit with their oncologist.

Resources in rural and other areas outside of the NCI and non-NCI designated cancer centers represent another structural barrier where patients do not have access to providers with expertise in palliative care [31]. Oncology workforce survey shows that about 80% of oncologists practice in non-academic setting [32]. Providers have also provided feedback on concerns for copays and reimbursements for palliative care [20].

Provider Barriers

Review of literature of oncologists barriers has showed multiple barriers to palliative care integration, including association of palliative care with hospice and thus death, and lack of exposure in training and lack of understanding of local resources and expertise leading to delayed referral [20]. A survey of the American Society for Radiation Oncologists (ASTRO) in 2015 showed that most did not receive any additional training in palliative care outside of their residency program and felt least confident in preparing advanced care planning or end of life care. They also felt time constraints and concern for upsetting medical oncology colleagues were barriers to referring to palliative care [33]. Similar surveys do not exist for urologists.

Patient Barriers

In addition to some of the structural barriers, such as readily-available palliative care resources, patients also report an association of palliative care with hospice and despite evidence of improvement in quality of life, there is decrease uptake of palliative care [31]. Patient concerns about copayments and cost of additional visit is another potential barrier to palliative care.

Combined Barriers

Though not traditionally defined as barrier, patient–provider emotions and inaccurate prognostic understanding can be a barrier to palliative care integration.

Patients suffering from advanced disease are bound to experience myriad emotions as they progress through the course of their illnesses. At times, patients may experience overwhelming feelings of dread of expected future developments, fear, or anxiety, and at other times, patients may experience sadness and grief at the loss of time with family or the lack of ability to experience events with loved ones. Patients may also experience rebounding feelings of joy or happiness as they recall times with family that they find meaningful or when symptom management strategies are successful. Understanding these emotions and the impact they can have on patient quality of life and decision making abilities is critical to the delivery of effective palliative care. In a report evaluating expression of emotion in both patients and their families undergoing discussions regarding palliative care, 69% of

conversations features some expression of emotional distress. Most common emotion were anxiety and fear followed by sadness, anger and frustration [34].

Oncologists are not free from the influence of emotion in conduct of routine oncological care including palliative care discussions. The delivery of bad news concerning prognosis, treatment options, and availability of effective measures to treat symptoms of advanced disease can be emotionally draining for providers. These provider impacts can be further heightened when providers have established a long-term patient–provider relationship through the course of chronic disease, or when providers have developed acquaintance and relationship with family or support structure members. This was demonstrated in a study where longer oncologists had known the patient, less accurate their prognosis became [35].

As patients and providers are reluctant to seek help from palliative care team, unless there are symptoms or no further cancer directed therapies, having an inaccurate understanding of the prognosis may be a big factor in delayed palliative care referral. In a large multi-center study, there was discordance between oncologist and patient prognostic understanding. In patients where oncologist had expectation of fewer than 6 months to live, only 5% of patients had an accurate understanding about the incurability of their disease and the timeframe for medical decline. Furthermore, only 38% of patients reported having ever discussed longevity expectation with their oncologist [36].

This challenge is heightened in the era of immunotherapy. As highlighted elsewhere in this book, newer immunotherapy can offer potential for cure even in patients who were thought to have incurable disease just a decade ago. A study of patients with advanced GU cancers, approximately 23% of patients believed that they had curable disease when the actual statistics is less than 10% [37]. Of note, the authors find that anxiety scores are lower in patients with accurate expectations regarding outcomes of immunotherapy, and no differences in quality of life scores or depression were noted (despite the expectation of worse disease outcome in the subset of patients with accurate understanding of disease prognosis) [37].

Incomplete or inaccurate understanding of prognosis can impact patients' decision to proceed with aggressive medical measures near end of life. In a study of patients with advanced non-small cell lung cancer treated prior to immunotherapy, found at baseline, nearly 32% of patients expected that their metastatic disease was curable, and 69% reported that elimination of all cancer was a reasonable goal of treatment. The patients were then divided into groups receiving early palliative care consultations on a monthly basis and those undergoing standard oncological care. At follow-up, a greater percentage of the early palliative care intervention arm was noted to have cultivated an accurate understanding of prognosis (82.5% vs. 59.6%). Furthermore, the authors find that patients having an accurate understanding of disease prognosis and undergoing palliative care treatment were least likely to opt for aggressive IV chemotherapy treatment within 60 days of death [38].

A systemic review examining the data concerning the efficacy of various interventions in improvement in prognostic understanding in patients with life-limiting illness identified nine unique interventions [39]. These interventions included decision aids as parts of medical consultation, communication training for patients and providers, early palliative care integration with oncology care, and structured goals

of care discussions led by social workers, it was still estimated that inaccurate prognostic understandings were had by 31–95% of patients [39].

Thus, despite evidence of improvement in patient's quality of life and even longevity, there are structural, patient, physician, and combined barriers to integration of palliative care into routine oncological and specifically RCC care [31].

Opportunities for Integration and Enhancement of Palliative Care in RCC

As there is no specific data on barriers to integration of palliative care in RCC, we present potential opportunities for both patients with RCC and other cancer for implementation of palliative care research and integration of palliative care into routine oncological care.

Structural Considerations

Given the patient and provider barrier of naming of the service, in the national survey of NCI and non-NCI designated cancer centers, 35% of NCI designated cancer centers and 30% of non-NCI designated cancer centers changed their name to "supportive care" from "palliative care" [30]. Thus, when designing integration programs, having stakeholder input including local patients and providers may help successful implementation.

Many of the interventions included phone follow-ups by nursing reducing potential need for in-person visit which may overcome some of the patient and structural barriers such as access to palliative care in rural areas [6, 8].

Provider Consideration

In terms of provider skills, any of the RCC providers, including urologists, medical oncologists, or radiation oncologists, can provide primary palliative care as long as they have the appropriate skill set. Communication skills is an important skill set and there is data for need and benefit of communication skills intervention in medical oncologists training. Medical oncologists are primary oncology care providers for most patients with metastatic RCC. Since there has been recognition that the delivery of adequate and effective palliative care requires substantial provider knowledge of palliative care techniques and communication skills, there has been focus on training oncologists in these skills. Communication skills were the first to be focused on with implementation of the SPIKES protocol in Oncotalk [40].

Oncotalk was a research study that successfully trained approximately 10% of trainees in US fellowship programs from 2002 to 2007 [41]. Later, faculty training for communication skills, Oncotalk Teach, was implemented with the hope to disseminate the principles throughout training programs [42]. Surveys of radiation

oncologists suggest that most do not pursue further communications or palliative care skills outside of residency training programs [33]. Thus, there is a need for systematic integration of programs similar to Oncotalk (now VitalTalk) in training of all three primary oncology disciplines: urology, radiation oncology and medical oncology.

In addition to communication skills, there are other important skills in palliative care delivery including symptom assessment and management, management of emotional symptoms and patient centered decision making. A survey of oncology fellows in 2004 showed that they spent minimal time obtaining a palliative care skillset and fellows desired more training in pain management, psychosocial care, and communication skills [43]. Importantly, when exposed to a palliative care rotation, fellows reported improved attitudes and knowledge in all PC domains [44]. Therefore, an opportunity exists to improve training in all RCC practitioners: including medical oncologists, urologists, and radiation oncologists for increased training in basic palliative care skills to provide primary palliative care and to recognize the need for subspecialty palliative care. Recently, there has been a call to increase further integration of palliative care in oncology training [45].

Having skills will not be enough to improve integration nor enhance patient care. This is evident from retrospective data highlighted above suggesting low palliative care interventions despite national guidelines for palliative care integration. Survey of medical oncologists suggests that they would refer patients for specific symptoms and not for goals of care conversation as they feel they can and should be providing that as primary palliative care [20]. A potential model to overcome this barrier may be the embedded palliative care clinic in Biological Therapy Center [46]. In this model, patients visiting medical oncologists completed battery of quality of life and symptoms assessment survey and there was automatic referral to palliative care for certain threshold score. This streamlined referral and avoided the potential provider barrier. Thus from a program development and implementation perspective, a survey of patient needs and survey and competency of practitioners may help devise a plan for screening and referral and provide individual plan for each practitioner.

Special attention should be paid to urologists who play a critical role in many patients' care. Many patients present with localized disease and have a long term and trusting relationship with their urologists. Urologists can provide primary palliative care both in early and in late stages of RCC treatment. Urologists and urological oncologists can play roles in explaining renal cancer diagnoses and prognosis, and they can help in explaining both systemic and localized effects of treatment. They can also educate patients on specific urological system complications that may be expected with disease progression. In addition to this, urologists can offer interventions such as tumor debulking procedures or ureteral stent insertions to assist in alleviation of ureteral stenoses, due to increase in tumor size or due to localized radiation therapy [15]. Urologist can also ask for secondary palliative care when they need assistance in specific symptoms or decision making. For example, a frail patient with locally advanced disease may benefit from a secondary palliative care team with expertise in evaluation of frail patients and decision making. The patient and family can work with palliative care team and urologist to develop a patient centered decision. Similarly, a medical oncologist can request secondary

palliative care consultation when a patient has radicular pain and requires potential intervention from a subspecialty palliative care team.

In addition to changes to clinical delivery of palliative care, to ensure appropriate quality assurance, a mechanism to measure palliative care interventions appropriately is needed. Currently, data on palliative care utilization is predominantly captured by institutional data or administrative databases, like the National Cancer Database (NCDB) and Surveillance Epidemiology and End Results-Medicare (SEER-Medicare) linked database. SEER-Medicare links a cancer registry with Medicare claims data to understand how services are rendered to elderly patients with cancer diagnoses. The NCDB is also a cancer registry that codes how palliative interventions are used for patients with cancer diagnoses. While these databases provide a snapshot of how palliative care is used for patients with RCC, NCDB does not code for primary or subspecialty palliative care consultations, do-not-resuscitate (DNR) status, spiritual counseling, or patient related outcomes and SEER-Medicare is made up of patients that are older than 65 years and does not capture vulnerable patients that may be uninsured or have other types of insurances.

How palliative care interventions are coded remains a major obstacle for understanding how palliative care is utilized. For example, a physician can offer a patient chemotherapy for palliative intent, but a lack of documentation or inappropriate coding may lead to not coding the use of chemotherapy as a palliative intervention. Incorporating patient-reported outcomes into these administrative databases remains a top priority [47]. For a subset of oncologic patients, quality of life and psychological outcomes are likely more important than clinical outcomes like survival.

There is a dire need to update these administrative databases for modern times. Several actionable items need to be implemented for this to occur. Creating standards for coding palliative interventions is important for decoding palliative care use. Capturing data elements that are pertinent for understanding palliative care use, such as changes in DNR status, the use of palliative care services, and quality of life outcomes. Furthermore, technological advancements such as machine learning and electronic medical records can be harnessed to capture patient-reported outcomes. Finally, stakeholders need to be represented when discussing any of these changes so that culturally competent and inclusive modifications can be made.

Given palliative care can be offered by both primary and subspecialty palliative care teams, for both implementation as well as purposes of documentation and coding, we provide an example of some specific tasks that primary or subspecialty team can perform for patients to meet their needs. An example of potential palliative care interventions during a patient's journey is highlighted in Table 18.1.

Ultimately, there is a need to build evidence of integration of early palliative care with evaluation of patient symptoms, quality of life, and decision making leading to the delivery of care that is aligned with patient goals of care. Studies that have shown survival benefit with early palliative care integration do not provide us with a mechanism of why these patients benefited. Studying the mechanism of how patients benefit in terms of quality of life, psychological symptoms, and longevity may help advance care for all patients.

Table 18.1 Example of patient symptoms that may require palliation in a RCC patient's journey

Examples of patient needs In localized disease	Provider skills required
Understanding of diagnosis	Medical knowledge; Ability to effectively communicate knowledge
Informed decision making	Ability to elicit patients' desires to utilize in shared decision making
Goal-aligned treatment	Ability to assess patient goals and discuss how each treatment option could impact patient goals
Post-operative pain	Familiarity and knowledge of pharmacological and non-pharmacological modalities to alleviate pain
Surveillance-related anxiety	Ascertain and evaluate the key sources of patient anxiety, communicate and interpret test results that are meaningful to patients
Family discussion/support	Facilitate patient and caregiver communication about diagnosis and prognosis
Examples of patient needs in metastatic disease	*Provider skillset*
Emotional symptoms—Anxiety, depression etc.	Evaluate and address patient's emotional symptoms due to cancer, cancer treatment
Understanding Prognosis	Communication skills to elicit patient understanding and then providing patient information in empathic manner
Uncertainty/life expectancy	Elicit and manage emotions related to uncertainty Plan for uncertainty
Goals of care discussion/shared decision making	Elicit patient and family perspective Engage patient and family in discussion about patient's goals Provide information on various options and help devise a plan that maximized likelihood of meeting patient's goals
Physical symptoms—Pain, nausea, rash, diarrhea, shortness of breath, fatigue etc.	Knowledge on evaluation and management of each of the symptoms Seek assistance when needed

One area of study might involve isolating the specific mechanisms by which earlier integration of palliative care team impacts patients' understanding of their illnesses and guides shared decision making. Specifically, when both primary oncology teams and specialist palliative care teams are involved in patient care, what role does each team play in various tasks of shared decision making may be beneficial [48]. As shown in the shared decision making model, patients need to understand their goals, values, and preferences; they need to understand their therapy choices and risk and benefit of each and then with the help of the oncologist make an informed decision. Over time, the decision can be changed if the expected outcomes are not met. As a component of this study, the utility of having a separate palliative care team (distinct from the primary oncology team) can be assessed in terms of which team or a combination facilitates each of the above steps to produce a patient centered decision and ultimately leads to optimal patient centered care. Determination of specific roles

played by each of the team and mechanisms of benefit would then guide further future research into precisely when these mechanisms are best applied in integration of palliative care, either by a primary oncology team or by a specialist palliative care team.

Conclusion

RCC may be an ideal disease to study this mechanism as it offers a unique setting where the traditional definitions of curative and palliative setting is blurred with the advances in therapies. The increased challenge of having "cure" as a possibility in patients with metastatic disease increases the challenge for primary team in the shared decision making and patient centered care. A study in RCC that establishes specific tasks that are ideally performed by the specific team (primary oncology team or subspecialty palliative care team) or performed by a team with specific skill set (see Table 18.1) may help develop better interventions for RCC and other cancers.

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