Renal Cancer

Contemporary Management

John A. Libertino
Jason R. Gee
Editors

Second Edition

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Dedicated to

Dr. Harris Berman, M.D., Dean of Tufts University School of Medicine

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Contents

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1 Epidemiology, Screening, and Clinical Staging

Sana N. Siddiqui, Christopher R. Haas, and James M. McKiernan

Introduction to Epidemiology

Kidney cancer among adults includes malignant tumors arising from the renal parenchyma and renal pelvis, but the differential of a renal mass should also include benign tumors and inflammatory causes as summarized in Table 1.1. Tumors arising from the renal pelvis are mostly of the urothelial cell type and comprise less than 10% of kidney carcinomas. Renal cell carcinoma (RCC), also known as renal cell adenocarcinoma, accounts for 90% of kidney carcinomas and is much more common than benign tumors or other malignant cancers [1]. Renal cell carcinoma is divided into a variety of histologic subtypes, which may differ in clinical features and prognosis. The most common form of RCC is the clear cell type, comprising 75% of new cases; this is followed by the papillary, chromophobe, medullary, and collecting duct subtypes which make up 10%, 5%, 1%, and 1%, respectively [2].

Kidney cancer is the fourteenth most common cancer worldwide, with over 400,000 new cases in 2018. It is the ninth most commonly occurring cancer in men and the fourteenth most commonly occurring cancer in women [3]. The highest incidence rates can be found in Northern and Eastern Europe, as well as North America [4]. In the United States, kidney cancer ranks as the eighth most commonly diagnosed cancer, where approximately 1.7% of men and women will be diagnosed with kidney or renal pelvis cancer at some point in their lifetime [5]. According to the Surveillance, Epidemiology, and End Results (SEER) program, the prevalence of kidney and renal pelvis cancer in 2015 was estimated to be 505,380 in the United States. The National Cancer Institute (NCI) reports that within the United States, there will be an estimated 65,340 new cases in 2018 with a male-to-female predominance of about 2:1 and almost 15,000 deaths due to kidney and renal pelvis cancers. As a result, kidney cancers account for 3.8% of all new cancer cases and 2.5% of all cancer deaths, and remain the twelfth leading cause of cancer death. Among all new diagnoses of kidney cancer in the United States, 5-year survival is 76% [5].

Incidence and Mortality Rates over Time

From 1992 to 2015, the incidence of kidney cancer in United States increased at 2.4%/year; however, this increase has slowed to a near plateau from 2008 to 2015 [6]. This increase in RCC incidence was most notable in localized and regional disease rather than metastatic RCC in which the overall incidence has been stable. Incidence-based mortality rates increased from

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Table 1.1 Differential diagnosis of a renal mass

Malignant	Benign	Inflammatory
Renal cell carcinoma	Simple cyst	Abscess
Clear cell	Angiomyolipoma	Focal pyelonephritis
Papillary	Oncocytoma	Xanthogranulomatous pyelonephritis
Chromophobe	Renal adenoma	Infected renal cyst
Collecting duct carcinoma	Metanephric adenoma	Tuberculosis
Urothelium derived	Cystic nephroma	Rheumatic granuloma
Urothelial cell carcinoma	Mixed epithelial/stromal tumor	
Squamous cell carcinoma	Reninoma	
Adenocarcinoma	Leiomyoma	
Sarcoma	Fibroma	
Leiomyosarcoma	Hemangioma	
Liposarcoma	Vascular malformation	
Angiosarcoma	Pseudotumor	
Hemangiopericytoma		
Malignant fibroid histiocytoma		
Synovial sarcoma		
Osteogenic sarcoma		
Clear cell sarcoma		
Rhabdomyosarcoma		
Wilms tumor		
Primitive neuroectodermal tumor		
Carcinoid		
Lymphoma		
Metastasis		
Invasion by adjacent neoplasm		

1992 and peaked in 2001, but then started to decline with the sharpest decline in recent years of 32% from 2013 to 2015 [6].

In the last decade, 18 countries experienced increased incidence rates for both men and women, with sharper increases occurring in Latin America, Brazil, Thailand, and Bulgaria [4]. Reporting bias, advancement in health record systems, and accessibility to healthcare providers should also be considered in comparing rates accurately between regions. Increasing incidence and a decreasing mortality-to-incidence ratio have been found to be correlated with increasing human development index levels and gross domestic product per capita [7]. One explanation for the rising incidence in developed nations is the higher prevalence of risk factors for RCC (such as smoking, obesity, physical inactivity, and hypertension) present in developed countries. Increased access to care and availability of advanced therapeutics have been postulated to account for the decreased mortality-to-incidence ratio [6].

Another likely explanation for the higher incidence of kidney cancer observed in developed countries is the greater availability and more liberal use of abdominal computed tomography imaging techniques resulting in more incidental findings of renal masses [8]. Within the United States Medicare population, 43% of patients receive a CT of the chest or abdomen over a 5-year period [9]. Tandem with the detection of more incidental renal masses is the increased diagnosis of small renal masses <4 cm, which now account for 48–66% of new RCC diagnoses [7]. Tumor size has extensively been shown to be correlated with risk of metastasis with a 25% increased odds of metastasis with each cm increase in tumor diameter [10]. In patients with tumor diameter <3 cm, the risk of metastasis is remote with several active surveillance cohorts reporting 0–1.1% metastatic events occurring in tumors <3 cm [11]. In addition to improvements made in local and systemic therapies for RCC, the decreasing mortality rates from RCC can also

partly be attributed to the lead-time bias from earlier diagnosis and treatment of small renal masses [6]. In states and developed nations that have aimed to curtail advanced radiologic testing, there has been recent data to suggest that the incidence of renal cancer has plateaued [12].

Demographic Factors in Renal Cell Carcinoma

Renal cancer is twice as common in males as females, and the rate of incidence has continued to rise twice as rapidly in males compared to females. A 2008 study looking at retrospective data of 39,434 patients from 1988 to 2004 in the California Cancer Registry determined that overall, females showed a higher percent of localized cancer than males which may be responsible for a higher relative survival rate in females. Potential explanations for differences in survival rates also include biological differences in the tumor, more extensive use of healthcare system by females, and a higher prevalence of hypertension in males [13].

With a median age at RCC diagnosis of 64 years old, RCC is primarily a malignancy of the elderly. In fact, 53.9% of patients are diagnosed between the ages of 55 and 74, while less than 10% are diagnosed at less than 45 years of age [5]. As mortality rates continue to decrease in the United States and overall RCC incidence rises, the incidence of RCC in the elderly will also likely continue to rise. Of note, adolescents and young adults more commonly present with rare histologic subtypes such as translocation carcinoma or renal medullary carcinoma. Though RCC in younger patients is rare, translocation carcinomas account for up to 50% of all RCC in patients under the age of 40. [14]

Along with sex and age, race is an important factor in the epidemiology of RCC. Within the United States, SEER data shows that black and Hispanic patients have a higher incidence rate than all other ethnicities, while Asian and Pacific Islander patients have the lowest incidence rates. Caucasians had an incidence of 22.2 per 100,000 person-years between 2011 and 2015 in comparison to 25.3 per 100,000 person-years in the black population [5]. Despite being diagnosed at a younger age with more localized disease, black RCC patients also had a significantly lower survival rate than all other ethnicities [13]. The disparity in survival rates between black patients and other ethnicities is unknown, but can be partially explained by stressors associated with socioeconomic status, comorbidities such as hypertension, and lower likelihood of undergoing nephrectomy or receiving systemic therapies for metastatic disease [15, 16].

RCC tumor subtype also varies among racial groups. Looking at 18 US population-based registries of the SEER program in 2011, a study found that among 84,255 RCC patients, clear cell RCC is more common in white populations than black populations (50% vs. 31%), and the papillary subtype presents more often in people of African or Caribbean descent than Caucasian descent (23% vs. 9%). These authors also found that compared to whites, blacks were four times more likely to have papillary RCC than clear cell RCC, while Asian or Pacific Islanders were less likely to have papillary or chromophobe RCC than white patients [17]. Other rare and aggressive subtypes of RCC such as collecting duct carcinoma and renal medullary carcinoma have been linked to African American heritage, with renal medullary carcinoma seen almost exclusively with sickle cell trait [18, 19].

Risk Factors in the Development of RCC

Risk factors for renal cell carcinoma include male gender, age, smoking, diet, obesity, hypertension, renal disease, family history, certain medication use, and occupational exposures. While some components such as gender and age have been discussed under demographics, current literature regarding the remaining factors is described below.

Smoking

According to the International Agency for Research on Cancer (IARC) and the US Surgeon

General, smoking is a well-established causal risk factor for RCC. Male smokers are shown to have a 50% increased relative risk (RR) and female smokers are shown to have a 20% increased RR for developing these tumors. A 2005 meta-analysis of 24 studies shows that the overall combined RR for developing RCC in someone who has ever smoked a cigarette was 1.38 (95% CI = 1.27–1.5). Furthermore, this data reported a dose-response relationship of increasing RR with more exposure to cigarette smoke. A promising finding from the study indicated that a greater length of abstinence from smoking actually reduced the RR, but this finding requires further investigation [20].

Compared to non-smokers, current smokers with RCC were shown to be at an increased risk for death with an HR of 1.7 (95% CI = 1.2–2.5) [21]. Smokers were seen to have a higher likelihood of increased stage or even metastases at diagnosis. Similarly to chronic obstructive pulmonary disease (COPD), the pathogenesis of cigarette smoking in RCC is linked to carbon monoxide exposure and chronic tissue hypoxia. Smokers with RCC were also shown to have increased DNA damage and mutations within peripheral blood lymphocytes due to N-nitrosamine and benzo[α]pyrene diol exposure compared to a control group [22, 23].

Diet

Many different foods and substances have been researched to look for increased risk of RCC. Most notably, consumption of fruits and vegetables is shown to be inversely related to the development of RCC in a meta-analysis reviewing 13 prospective studies [24]. The role of high fat and protein consumption is more controversial because while it has been considered a risk factor in the past, a large multicenter European cohort study revealed that there is no significant association between the development of RCC and these nutrients [20].

Like fruits and vegetables, alcohol has also been inversely associated with renal cancer risk; this includes beer, wine, and liquor. A dose-dependent risk reduction was discovered in a pooled analysis of 12 prospective studies, showing a 28% lower risk in those who drank more than 15 grams per day. Interestingly, no association was found between total fluid intakes from other beverages, such as water, juice, milk, tea, coffee, or soda, implying that alcohol itself is a modifying factor [25].

Obesity

Obesity was first shown to be associated with RCC as early as 1984 when McLaughlin et al. conducted a case-control analyses that suggested body mass index (BMI) and RCC in women were related [26]. Since then, much more literature has been published regarding the relationship between waist-to-hip ratios, weight gain during adulthood, and mechanisms of its influence on kidney cancer [27]. The World Cancer Research Fund reports that since the 1980s, obesity has continued to increase in both resource-rich countries as well as low- and middle-income countries [28]. Between genders, there is an estimated 24% increased risk in men and 34% increased risk in women for every 5 kg/m increase in BMI [29]. Proposed mechanisms for the development of RCC include insulin resistance, sex hormone dysregulation, inflammatory responses, and oxidative stress [30]. In light of the significant association between obesity and development of RCC, further research is needed to elucidate causal mechanisms and preventative strategies.

Hypertension

According to the Centers for Disease Control and Prevention, about 75 million American adults had high blood pressure in 2011. This translates into 1 in 3 adults having a chronic condition that increases risk for several diseases, such as heart disease, renal failure, and stroke [31]. While chronic hypertension is a leading cause for development of chronic kidney disease, several studies

have shown that hypertension is an independent risk factor for developing RCC. In a meta-analysis of 13 case-control studies from 1966 to 2000, hypertensive patients were found to have a pooled odds ratio of 1.75 for having RCC [32]. Independent dose-dependent and time-dependent effects of hypertension were further elucidated in a 2011 study that showed increasing odds ratios of RCC with worsening control of blood pressure and longer duration of hypertensive diagnosis [33]. Lastly, a Swedish cohort study found an association with decreased RCC risk after a reduction in blood pressure, suggesting that effective hypertension control may lower risk [27]. Like the association with obesity and RCC, the findings relating blood pressure to increased cancer risk also present an opportunity to enact preventative measures.

Chronic Renal Disease

Patients with end-stage renal disease (ESRD) who undergo renal transplantation after long-term hemodialysis or with acquired cystic disease have all been shown to have an increased risk for multiple forms of malignancy, ranging from immune deficiency-related malignancy to urinary tract tumors [31]. Post-transplant kidney cancer is particularly seen in native kidneys of transplanted patients with acquired cystic kidney disease (ACKD). ACKD is present in 40% of graft recipients at time of transplant and appears in another 16% of patients after transplant [34]. A retrospective study looking at the outcomes of RCC in native kidneys of transplant patients determined that the median interval between transplantation and RCC occurrence was 5.6 years and that ACKD was present in 83% of these transplanted patients [35]. The 2018 European Association of Urology guidelines reinforce the risk of RCC in patients with ESRD, stating that the risk is at least ten times higher than in the general population [36]. Furthermore, RCC in patients with ESRD is notably less aggressive, found in younger patients, and often multicentric and bilateral [37].

Family History

While there are several inheritable conditions that portend an increased risk of RCC, the vast majority of RCC occurs sporadically. The question of whether there is an association between family history and sporadic RCC was explored by a study at the University of Texas MD Anderson Cancer Center. Using several analytic strategies, the authors were able to establish significant association between family history of kidney cancer and sporadic RCC. Furthermore, higher risk of developing RCC was found in patients who had an affected sibling rather than a parent or child with an RR of 3.52 (95% CI = 1.70–3.04) found on meta-analysis [38]. These findings stress that while dominant familial RCC syndromes such as VHL, hereditary papillary renal cancer, and Birt-Hogg-Dubé disease exist, there is a role for recessive effects in the inheritance of sporadic RCC.

Medications

Researchers have studied a variety of antihypertensive medications, including diuretics, calcium channel blockers, and beta-blockers, to explore an association with RCC independent of hypertension. Results have remained inconsistent with some showing doubled risk for RCC with long-term diuretic use while others have presented data that was not statistically significant [39]. A 2017 study published by Colt et al. found that while there was no relationship between any antihypertensive drug class and overall RCC, there was some significant data regarding specific histologic subtypes. The authors found that long-term use of diuretics (OR = 3.1, 95% CI = 1.4–6.7) and having ever used calcium channel blockers (OR = 2.8, 95% CI = 1.1–7.4) were associated with papillary RCC, but associations with clear cell RCC were weak or not significant [40]. Possible mechanisms for the carcinogenic effects of antihypertensive medications include conversion of diuretics to nitroso derivatives in the stomach, chemical effects on renal tubular epithelium

over long periods of time, and calcium channel blockers inhibiting apoptosis to facilitate division of malignant cells [41, 42].

Similarly to studies on antihypertensive medications, individual studies examining analgesic's association with RCC have largely been inconsistent. Among the most commonly used analgesics, acetaminophen has been implicated with RCC risk. A large case-control analysis of the US Kidney Cancer Study showed a positive trend for developing RCC with increasing duration of over-the-counter use of acetaminophen, with a twofold risk observed for those who took acetaminophen ≥10 years [43]. However, the effect size was diluted to an odds ratio of 1.5 when prescription use of acetaminophen was included. A meta-analysis of four cohort and nine case-control studies supported this finding with a summarized odds ratio of 1.25 (95% CI = 1.1–1.4) [44]. A potential biological explanation for acetaminophen's effects is the depletion of glutathione at higher doses and the subsequent rise in N-acetyl-p-benzoquinone imine (NAPQI). NAPQI is able to disrupt homeostasis in both kidney and liver cells by binding covalently to DNA [44].

Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been examined for potentially increasing RCC risk. A large meta-analysis identifying 20 studies found increased risk of RCC with non-aspirin NSAID use (RR = 1.25, 95% CI = 1.06–1.46), but no relationship between aspirin use and RCC [45]. Other meta-analytic reviews have not shown a positive association between RCC and NSAID use, including the US Kidney Cancer Study which looked at NSAID use and aspirin use in heart regimens [44]. Theories for NSAID-mediated RCC carcinogenesis reference the inhibition of prostaglandin synthesis leading to chronic subacute renal injuries; these in turn could cause DNA damage and uncontrolled cell proliferation.

Occupational Exposure

Exposure to agents classically considered carcinogenic, including cadmium, uranium, arsenic, nitrate, and radon, has not been established as a risk factor for RCC but is being explored [1]. The most extensively examined substance is trichloroethylene (TCE), a degreaser used for metal cleaning that is also present in adhesives, paint removers, typewriter correction fluids, and spot removers [46]. The US Environmental Protection Agency 2001 draft TCE health risk assessment concluded that epidemiologic studies do show an increased risk of kidney cancer in association with TCE [47]. TCE is considered a Group 2A "probably" human carcinogen by the International Agency for Research on Cancer (IARC).

Screening for RCC

Although 30% of patients present with metastatic disease, the remainder are diagnosed with localized RCC and may be candidates for definitive treatment [48]. Screening programs for earlier detection and treatment have the potential to improve survival outcomes if the ideal screening regimen is identified. The Wilson and Jungner criteria for suitable screening include the following: the condition should be a significant health problem, there should be a recognizable latent or early symptomatic stage, and there should be an accepted treatment for patients with recognized disease [49]. In regard to RCC, well-established treatments with minimal risk are available for localized tumors. There is currently no recommendation for screening for RCC, but several techniques and regimens have been explored.

Cost-effective techniques that have been explored for early detection of RCC include urine dipstick and biomarkers. Identifying hematuria on dipstick has not been reliable for RCC due to a stronger association with bladder cancer, low diagnostic yield, as well as poor sensitivity and specificity. When comparing incidence of all hematuria in patients with RCC to hematuria in patients with urothelial carcinoma, the rates are 35% versus 94%, respectively [50]. A Korean study that performed 56,632 dipsticks as part of a checkup on individuals over the age of 20 found hematuria in 3517 patients, but only three cases of RCC were detected among these patients [51].

This is most likely because microscopic hematuria is a common finding and less likely to indicate cancer in a younger, low-risk population. On the other hand, biomarkers such as aquaporin 1 (AQP1) and perilipin 2 (PLIN2) are soluble urinary proteins with the potential for high specificity and sensitivity, but they still require larger prospective trials [52]. These biomarkers are specific to clear cell and papillary histologic subtypes, implying that they would produce false-negative results in patients with variant histology [53].

Computed tomography (CT) scanning is currently used to screen for a wide variety of malignancies in middle-aged Americans. These screening practices include but are not limited to abdominal CTs for detection of aortic aneurysms, CT colonography, CT angiography, and chest CTs for lung cancer. In an era where many patients are receiving CT imaging, researchers have attempted to detect solid abdominal organ malignancies simultaneously. One study screened 4543 healthy patients over 40 years old who had received an abdominal CT, but solid organ malignancy prevalence was only found to be 0.1%, and therefore, the method was deemed ineffective [54]. The US Preventive Services Task Force recognizes that despite the not infrequent detection of extracolonic incidental lesions on CT, only 3% require definitive treatment [55]. As a result of the overall low incidence of malignant renal masses detected on screening CT with increased costs and burdens to the patient and healthcare system, CT has not been found to be a cost-effective screening strategy for RCC.

Compared to CT, ultrasound has the benefit of using benign sound waves instead of ionizing radiation while also being less expensive. A 2018 cost-benefit analysis for sonographic screening shows that at $36 US dollars per ultrasound, the opportunity to prevent metastatic RCC is worth considering [56]. However, ultrasound is less accurate in detecting renal masses than CT, especially with less sensitivity in detecting lesions under 3 cm in size [57]. There also is a lack of randomized trials to support the use of ultrasound screening for RCC. Rossi et al. identified ten observational studies that were completed, nine of which were published before 2004 [53]. Of these trials, a 1999 Japanese study screened 219,640 patients (ages 29–70 years) over 13 years and detected 193 cases of RCC. These patients were followed to show a 97.4% cumulative survival rate after 5 years and 94.6% at 10 years [58]. A large-scale randomized controlled screening trial would help determine whether these results indicate a lead-time bias or truly represent improved survival outcome.

Other screening considerations include the psychological impact on patients and overdiagnosis of small renal masses that may never become clinically significant. A false-positive screening result may result in a similar degree of patient harm as a false-negative result. Studies have shown that 15–30% of small renal masses are found to be benign after surgical excision [59]. As a result, clinicians must contemplate the psychological and emotional impact of delivering an incorrect diagnosis and potential harm from more unnecessary testing or invasive procedures.

Screening of Targeted Populations

With the establishment of known risk factors and understanding of inheritable conditions, high-risk populations do exist and screening has been evaluated for these patients. In 2005, the European Association of Urology guidelines had recommended annual ultrasounds of native kidneys in patients who have received transplants due to their higher risk for developing RCC [60]. Examining other risk factors, Starke et al. identified 925 patients as high-risk individuals for bladder cancer based on age ≥50, smoking with ≥10 pack-year history, and occupational carcinogen exposure of ≥15 years. After following these patients for 6.5 years, ten of the patients were diagnosed with RCC, indicating a prevalence of RCC in these patients that is roughly ten times higher than the general population [61]. Since then, algorithms for early screening and management have been proposed for asymptomatic high-risk patients [56]. These targeted

screening methods may be endorsed in the future, even if screening of the general population is not.

Incidence of von Hippel-Lindau disease is 1 in 36,000 live births with a penetrance of over 90% by the age of 65, making it the most common hereditary renal cancer syndrome [62]. The von Hippel-Lindau gene, VHL, is a tumor suppressor gene on the short arm of chromosome 3 (3p25.3). The gene encodes a protein that is part of the VCB-CUL2 ubiquitin ligase complex, which is responsible for degradation of hypoxia-inducible factor 1 (HIF-1) and insulin-like growth factor 1 (ILGF-1). Loss of VHL activity leads to cell growth and angiogenesis due to downstream enhanced expression of factors such as VEGF, PDGFB, EPO, and TGF-α. CNS hemangioblastomas, clear cell renal carcinomas, pheochromocytomas, and pancreatic tumors have all been described as part of the phenotypical classifications of VHL. As patients with VHL have a 70% lifetime risk of developing RCC with a mean age of clinical diagnosis at age 40, screening with annual abdominal MRIs from the age of 16 is recommended [63]. MRI is preferred over CT to avoid the substantial cumulative radiation exposure annual CT scans would incur. Pathologic examination of nephrectomy specimens from patients with VHL has revealed that nearly all complex cysts contain RCC [64]. Even normal-appearing parenchyma on CT may harbor large numbers of microscopic tumor foci, explaining the high risk of multiple and bilateral RCC in VHL [65].

Other autosomal dominant disorders that increase a patient's risk for RCC include hereditary papillary renal carcinoma, Birt-Hogg-Dubé (BHD) syndrome, and hereditary leiomyomatosis and renal cell carcinoma (HLRCC). The American Urological Association states that genetic counseling should be strongly recommended for patients suspected of having familial RCC [66]. These conditions generally require screening in the form of germline mutation testing rather than biomarkers. In BHD families or patients who present with cutaneous fibrofolliculomas, familial pneumothorax, or oncocytic RCC pathology, germline *FLCN* testing should begin at age 21. HLRCC involves a germline mutation of *fumarate hydratase* (*FH*), which is a gene that encodes an enzyme in the TCA cycle. HLRCC-associated kidney cancer has the potential to be lethal, and therefore, testing in suspected patients begins as early as 8 years old. Patients who are affected with HLRCC should subsequently have annual abdominal MRIs to screen for kidney tumors [67].

Clinical Staging

Clinical staging systems are developed to classify malignant diseases in a uniform manner with prognostic capability. They are used to guide treatment and planning decisions and manage expected outcomes by stratifying the risk of cancer progression. Ultimately, uniform staging systems allow for the comparison of patient outcomes worldwide [68]. Flocks and Kadesky proposed one of the earliest kidney cancer staging systems in 1958, including organ-confined, locally invasive, locally metastatic, and distant metastatic disease [69]. The predominant TNM staging system used currently (tumor, nodes, metastases) was developed in 1974 by the American Joint Committee on Cancer (AJCC) and the *Union Internationale Contre le Cancer*, renamed the Union for International Cancer Control (UICC) [70]. This TNM staging system has had several major revisions to improve prognostic accuracy with the most recent update published in 2017 after a structured review process with input from several professional groups (Tables 1.2 and 1.3) [71].

In 1987, T1 and T2 renal lesions were divided at 2.5 cm in largest dimension by imaging, which did not differentiate well between survivals for these groups [72]. In 1997, T2 disease started at 7 cm for greater differentiation from T1 [73]. The 2002 AJCC update further subdivided T1 disease, T1a ≤4 cm and T1b 4–7 cm [74]. Work done by the Cleveland Clinic contributed to this development [75]. They described 485 patients who underwent partial nephrectomy prior to 1997, finding that 5-year cancer-specific survival was better with tumor diameter ≤4 cm compared to 4–7 cm and >7 cm (Fig. 1.1).

Table 1.2 AJCC TNM classification for RCC

Classification	Definition
Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤7 cm in greatest dimension, limited to the kidney
T1a	Tumor ≤4 cm in greatest dimension, limited to the kidney
T1b	Tumor >4 cm but ≤7 cm in greatest dimension, limited to the kidney
T2	Tumor >7 cm in greatest dimension, limited to the kidney
T2a	Tumor >7 cm but ≤10 cm in greatest dimension, limited to the kidney
T2b	Tumor >10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor extends into the renal vein or its segmental branches, or invades the pelvicalyceal system, or invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)
Node (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Table 1.3 Stages of RCC

Stage	TNM classifications
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T1 or T2, N1, M0 T3, N0 or N1, M0
Stage IV	T4, any N, M0 Any T, any N, M1

This was confirmed in a multi-institutional study of more than 2200 patients, showing a difference in disease-free survival (DFS) at 5 and 10 years between T1a (95.3% and 91.4%), T1b (91.4% and 83.4%), and T2 (81.6% and 75.2%) tumors [76]. This outcome difference has been further substantiated irrespective of the form of surgery performed. Oncologic outcomes among tumors with diameter greater than 4 cm were worse than tumors less than 4 cm regardless if radical or partial nephrectomy was performed [77].

Several groups have attempted to further reclassify T1 and T2 disease. Investigators at the Mayo Clinic proposed a cutoff of 5 cm for better postoperative DFS prediction [78]. In a similar study, a group at UCLA suggested that disease-specific patient survival was more accurate if T2 started at 4.5 cm [79]. Ficarra and colleagues reported that a cut point of 5.5 cm improved cancer-related outcome stratification [80]. These same groups examined T2 patients with tumors >7 cm to gain better prognostic ability. This was supported by work from an international collaboration finding that for T2 disease, tumors larger than 11 cm have worse DFS [81]. Frank and colleagues studied an additional 544 T2 patients and proposed a 10-cm cut-off point to sub-classify patients [82]. This was eventually codified in the seventh edition TNM staging update with subdivision of the T2 category into 7–10 cm and >10 cm (Fig. 1.2) [83]. The collective evidence from the multitude of these retrospective studies indicates that primary tumor size plays an important role in predicting survival.

The T3 category was changed significantly in the 2009 seventh edition TNM staging update. T3 had previously included invasion of perinephric fat, adrenal gland, renal vein, or different levels of the IVC [74]. Direct adrenal gland invasion is now classified as T4 and will be discussed subsequently. Invasion of perinephric fat has been shown to have minimal impact on prognosis. Murphy and colleagues reported on their series of 717 patients at Columbia University Medical Center and found that the absolute size of T2 tumors was more predictive of DFS than the presence of renal capsular invasion, implying that some T3 tumors may not fare as poorly as larger

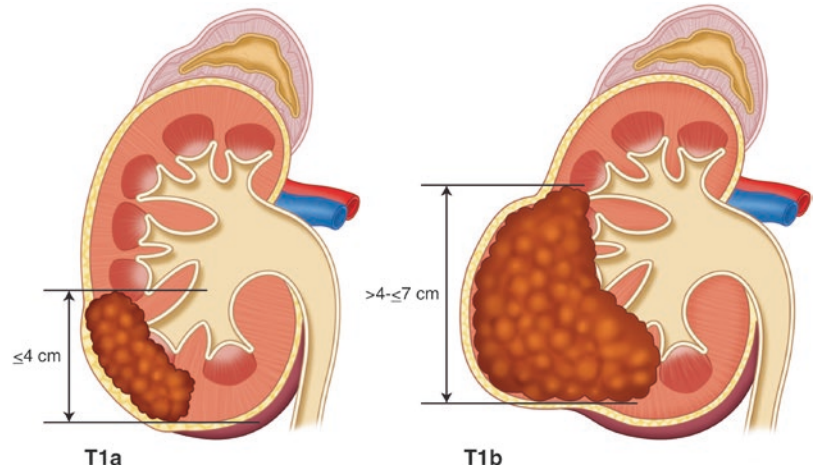

Fig. 1.1 Stage T1a – limited to kidney and ≤4 cm; T1b tumors (4–7 cm)

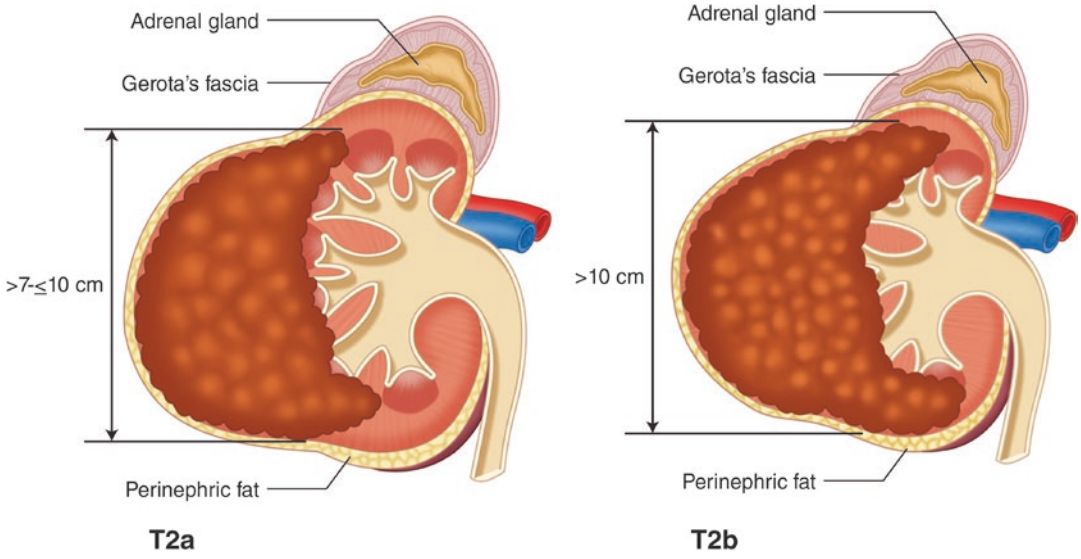

Fig. 1.2 Stage T2a – limited to kidney and 7–10 cm; T2b tumors (>10 cm)

T2 tumors [84]. Similarly, Lam et al. describe dividing patients with fat invasion only (2002 TNM T3a disease) into greater than 7 cm or ≤7 cm and found that smaller tumors behaved more like T2 tumors and that larger tumors were similar to those with renal vein involvement (2002 TNM T3b) [85]. Seimer et al. reviewed nearly 1800 cases and found that perinephric fat invasion did not play an independent prognostic role though tumor size did [86].

Other studies have found that the location or type of fat invasion does play a prognostic role. Renal sinus fat invasion has been shown to have worse 5-year cancer-specific survival compared to perinephric fat invasion (71% vs. 45%) [87, 88]. The Mayo Clinic group also describes a group of patients with 2002 TNM classification T3 or T4 disease that were reclassified based on the presence of perinephric fat invasion and level of tumor thrombus. Patients with perinephric fat invasion alone were more likely to die of disease than patients with renal vein thrombus alone [89]. In a slightly less complex system, the group from MD Anderson reported on a cohort of patients with pT3N0/NxM0 disease and found that the presence but not extent of venous throm-

bus correlated with survival. Unlike the Mayo Clinic findings, they reported that patients with extra-renal extension into fat, regardless of location, had similar DFS as those with any amount of venous thrombus alone. Subjects with both were at greater risk of death from RCC [90]. This was confirmed by da Costa and colleagues in Brazil which also found equivalent disease-specific survival for fat invasion or renal vein thrombus alone [91].

In the most recent eighth edition TNM staging update published in 2017, changes in kidney cancer staging were minimal and focused on clarifying T3a disease classification (Fig. 1.3). In the seventh edition, the term "grossly" was used to describe renal vein and segmental branch invasion. Because it is common to have tumor involvement that is missed within the vasculature, this term was removed from the new edition. A 2007 study examined the venous systems

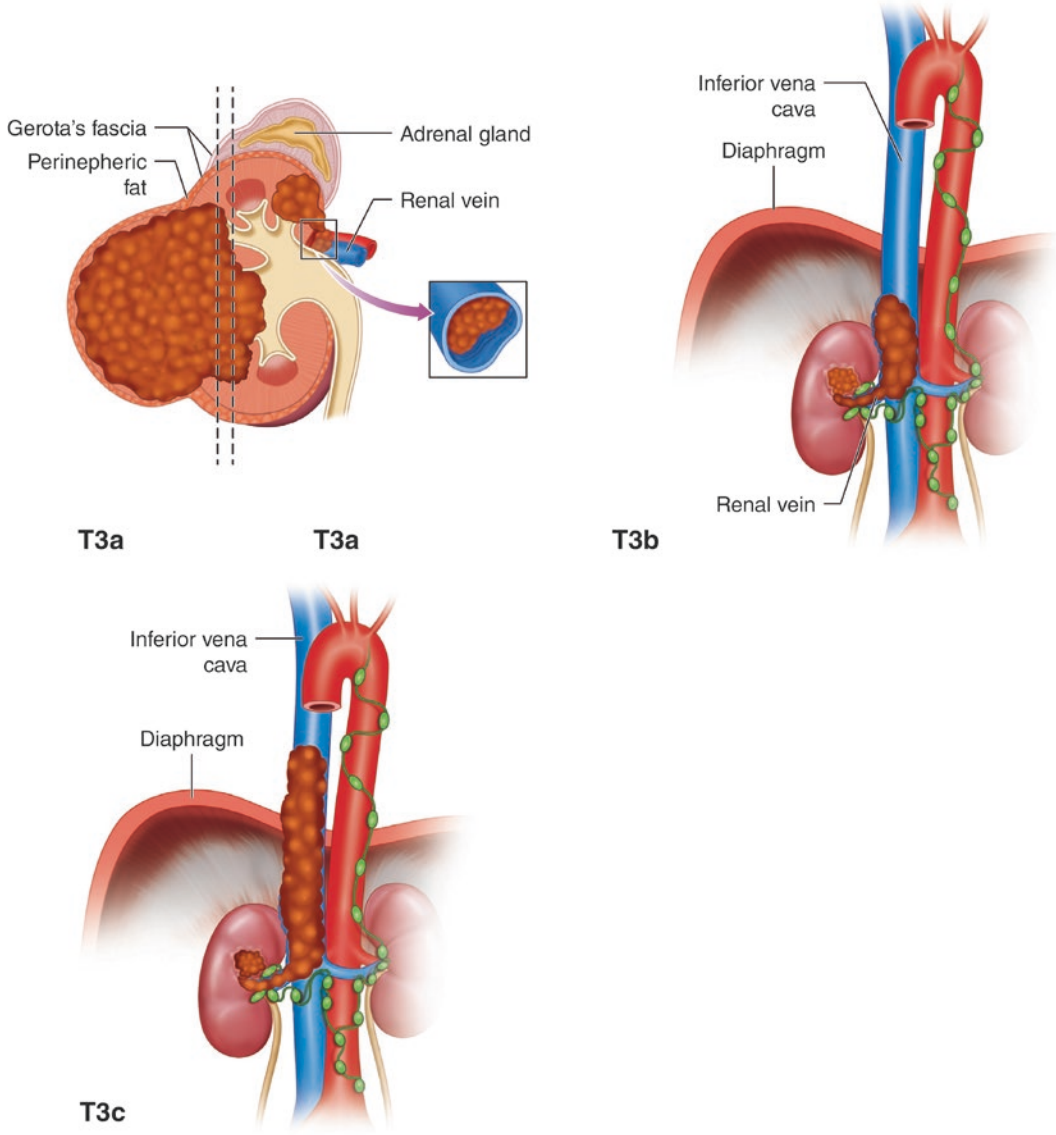

Fig. 1.3 Stage T3a – tumor thrombus extends into renal vein or invades perirenal and/or renal sinus fat. Stage T3b – extends into IVC below the diaphragm. Stage T3c – extends into IVC above the diaphragm or invades wall of IVC

of fifty-four pT3b clear cell tumors and compared them with ten normal renal kidneys. The investigators found that intravenous tumor extension is the first step in extra-renal spread with renal sinus fat invasion usually occurring secondarily and that tumor within the sinus fat usually represents venous involvement when confirmed histologically [92]. Therefore, it is evident that grossly examining a tumor for venous invasion would not be a reliable method of staging. Furthermore, the update has clarified invasion of the pelvicalyceal system as T3a because this part of the collecting system is contained within the hilum [93].

Renal Vein and IVC Involvement

The extent of tumor thrombus in the inferior vena cava (IVC) has long been used in the TNM system and occurs in 5–10% of patients with RCC [94]. It is well established that IVC tumor thrombus (T3b–c) carries a worse prognosis than renal vein thrombus (T3a). Moinzadeh and Libertino compared long-term outcomes of patients with renal vein involvement versus thrombus extending only as far as the subhepatic IVC and found a significant difference in 10-year cancer-specific survival rate (66% vs. 29%, $p = 0.0001$) [95]. A multi-institutional European cohort of 1192 patients clearly demonstrated that disease-free survival is significantly different between renal vein invasion versus IVC invasion. Dividing the cohort into T3a, T3b, and T3c, median survival times were 52.0, 25.8, and 18 months, respectively. The survival difference between T3a and T3b/T3c was significant ($p < 0.001$), whereas the difference between infradiaphragmatic and supradiaphragmatic IVC thrombi did not reach significance ($p = 0.613$ (120)) [96].

There has been a long-standing controversy with regard to the prognostic value of the extent of tumor thrombus in the IVC. Examining the SEER database from 2000 to 2007, Whitson et al. demonstrated that tumor thrombus extension above the diaphragm did not correlate with survival [94]. Similarly, neither renal vein nor IVC extension was found to be an independent predictor of worse prognosis when considering other factors such as tumor size, histology, and nodal status in a cohort of 1082 patients from Memorial Sloan Kettering Cancer Center [97]. A large population-based analysis of the SEER database showed that tumor size, adverse histology, positive lymph nodes, and/or metastasis held more prognostic value than the extent of IVC thrombus extension [94]. In contrast to the aforementioned studies, several studies have shown survival differences dependent on the degree of IVC tumor thrombus extension. In a series of 222 nephrectomy and tumor thrombectomy patients, Kim et al. reported that patients with a thrombus in the renal vein or infradiaphragmatic IVC fared better than those with supradiaphragmatic IVC thrombi (3-year disease specific survival of 35% vs. 12%) [98]. A German group also confirmed this in their series of 111 patients with median survival of 25.1 months versus 13.2 months ($p = 0.032$) [99]. A recent large multinational study of 636 non-metastatic RCC patients with tumor thrombus found thrombus level above the hepatic veins to be an independent predictor of recurrence in a nomogram model including six patient and tumor characteristics [100]. As many studies demonstrate survival differences between infra- and supradiaphragmatic IVC extension, this criterion continues to play a role in stratification of risk in the current TNM system.

T4

Previous versions of the TNM system treated ipsilateral adrenal gland involvement similarly to other T3a features. However, direct adrenal gland invasion is rare, occurring only in about 2.5% of cases [101]. When compared to perinephric or renal sinus fat invasion, direct adrenal gland invasion has a worse 5-year cancer-specific survival (36% vs. 0%) [101]. Siemer et al. analyzed the prognostic significance of direct adrenal gland invasion controlling for tumor size and found worse cancer-specific survival in this group, leading them to propose reclassifying direct adrenal gland invasion as T4 (Fig. 1.4) [86]. Similarly, Thompson et al. found that T3a

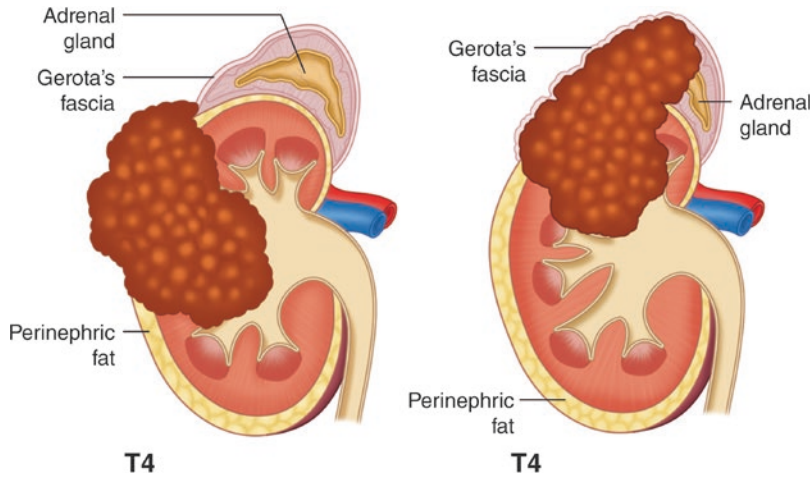

Fig. 1.4 Stage T4 tumor extends beyond Gerota's fascia or contiguously into the ipsilateral adrenal gland. (Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer-Verlag New York, www.springer.com)

or T3b tumors with direct adrenal extension had similar 5-year cancer-specific survival to patients with extension beyond Gerota's fascia at 20% and 14%, respectively. These patients were significantly more likely to die from RCC (HR 2.11, $p = 0.004$) [102].

Nodal Status

Prior versions of the TNM system included both size and number of lymph nodes involved to stratify lymph node disease in patients with renal cell carcinoma. The seventh and eighth editions simplify nodal involvement into a binary system, disease absence or presence in any regional lymph nodes. Terrone et al. from Torino, Italy, reviewed 618 cases that had regional lymphadenectomy at the time of nephrectomy and found a node-positive rate of 14%. Patients were stratified by the 2002 TNM node criteria (number of nodes involved), and no difference was found between 1 positive node and more than 1 positive node [103]. In a similar study, 2000 patients with RCC were reviewed, and survival for the 69 with nodal involvement was similar regardless of the number of lymph nodes involved [104]. These authors also suggest that poorer survival was associated with extra-nodal extension of disease. The prognosis for patients with lymph node involvement may be similar to those with metastatic disease, though their effect may be additive as having both nodal and distant metastases confers worse survival [105].

Metastatic Disease

Patients with metastatic disease have uniformly worse survival than localized RCC [106]. Memorial Sloan Kettering developed a widely used risk stratification criteria for metastatic RCC patients (the Motzer criteria), with each of the following parameters receiving 1 point: Karnofsky performance status (<80%), high lactate dehydrogenase (>1.5 times upper limit of normal), low serum Hb, high corrected serum calcium (>10 mg/dL), and time from diagnosis to systemic treatment <1 year. Favorable-risk patients have no risk factors, intermediate-risk one or two risk factors, and poor-risk three or more risk factors. Median survival for favorable-, intermediate-, and poor-risk groups are 20, 10, and 4 months, respectively [107]. As management of metastatic RCC has been rapidly evolving with improved targeted therapies and now

immunotherapy, the median survival of patients with metastatic RCC is expected to improve across all risk groups.

Improving the TNM Staging System

Staging systems like the TNM system should be continuously reviewed and updated as necessary. Though the AJCC seventh and eighth editions improve upon the 2002 edition, there may already be areas for improvement. In a large collaboration from Italy, authors found continued support for using primary tumor size to stratify 5339 renal tumors. Some groups, such as T2b and T3a or T3c and T4, had similar disease-specific outcomes. Analyzing only the 4848 N0/NxM0 patients, there were no differences in survival between T1a and T1b, T2b and T3a, and T3c and T4 [106]. Furthermore, a group of investigators from Korea compared the prognostic ability of the sixth and seventh TNM editions in 1691 patients. They found a similar concordance index in both schemas (0.906 and 0.904 for version 6 and 7, respectively). A concordance index this high suggests that both do an excellent job separating patients with different outcomes, though the seventh edition of the AJCC TNM system does not offer improvement over the sixth edition [108].

In an effort to further enhance staging, several academic centers also advocate for adding more patient-related features to the TNM system. Using symptoms at presentation of none, local, or systemic symptoms, Patard et al. found that symptom grading correlated with TNM stage and that when included in a model with TNM, age, ECOG performance status, and other features, symptom grade was independently related to cancer-specific survival [109]. An integrated system was also proposed at UCLA. This system includes TNM, grade, and ECOG performance status and was superior to the 1997 TNM system alone and has been externally validated [110]. The stage, size, grade, and necrosis model have also been suggested and may offer improved prognostic ability of the UCLA model [111]. Though it may be augmented, TNM staging system remains the basis for most prognostic systems. It will continue to undergo periodic updates and refinements, so that it can best serve the needs of patients and physicians.

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2 Molecular Biology and Genetics of Renal Cell Carcinoma

Sanaz Ghafouri, David C. Johnson, Kristen Kelly, Allan Pantuck, and Alexandra Drakaki

Introduction

Renal cell carcinomas (RCCs) are a diverse family of epithelial tumors originating from the renal cortex. More specifically, these cancers arise from different cells in the kidney, have different underlying genetic and molecular alterations, appear different histologically, and behave different clinically. That being said, these cancers all share one commonality in that they tend to be chemotherapy and radiation resistant [1].

Linehan et al. evaluated inherited RCC extensively and concluded that it is a metabolic disease, with unique gene mutations regulating cellular metabolism via alterations in oxygen, iron, nutrient, and energy sensing pathways, creating an oncologic-metabolic shift, known as the "Warburg effect," which ultimately leads to malignancy [2]. Understanding the genes involved in RCC has enabled the development of targeted approaches to therapy for each cancer type [2]. Much has been learned about the genetics of kidney cancer since the discovery of the von Hippel-Lindau (VHL) gene in the 1990s. Most recently the Cancer Genome Atlas (TCGA) has provided the most extensive catalogue of genetic mutations responsible for cancers, including RCCs, by using genome sequencing and bioinformatics.

Clear Cell Renal Cell Carcinoma

Clear cell renal cell carcinoma (ccRCC), the most common type of RCC, is caused by genes that control oxygen sensing like VHL and genes that maintain chromatin states like PBRM1. ccRCC is closely associated with VHL gene mutations, in both hereditary and sporadic cases. VHL tumor suppressor gene normally stabilizes hypoxia-inducible transcription factors (HIF-1a and HIF-2a) resulting in ubiquitin-mediated proteolysis through hydroxylation. When the VHL tumor suppressor gene is mutated, there is an increase in HIF, which leads to the up-regulation of VEGF, EGF, and TGF-a, in turn promoting angiogenesis and tumorigenesis. Germline mutations of the VHL disease gene lead to ccRCC through the one-hit hypothesis. However, VHL gene is mutated in 60–80% of sporadic forms of the disease, and it is this sporadic mutation,

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along with contralateral allele loss or loss of heterozygosity, that leads to the two-hit hypothesis [3, 4].

PBRM1, a subunit of PBAF WI/SNF chromatin-remodeling complex, histone deubiquitinase *BAP1*, and histone methyltransferase *SETD2* were mutated in 41%, 15%, and 12% of ccRCCs, respectively [5–7].Thus, oncogenic metabolism and epigenetics are central features of ccRCC.

Somatic Alterations

The Cancer Genome Atlas consortium compared the patterns of somatic copy number alterations of 417 clear cell renal cell carcinoma (ccRCC) nephrectomy specimens to normal genomic material and found that ccRCC had 19 somatic copy number alterations (SCNAs), which are fewer than in other cancers, such as colon and breast. However, the SCNAs that were observed usually involved the entire chromosomes or chromosome arms, rather than focal sites as in other cancers. The loss of the short arm of chromosome 3 was the most common SCNA, observed in 91% of the studied samples. Importantly, this SCNA contains four of the most commonly mutated genes: VHL, PBRM1, BAP1, and SETD2 [8].

There were also arm-level losses on chromosome 14q in 45% of the samples, which is associated with the loss of HIF-1a, a protein marker associated with more aggressive disease [9]. Sixty-seven percent of the samples had gains of chromosome 5q, which upon focal amplification showed that there are 60 genes in the 5q35 region which may be associated [8]. Focally amplified regions involved protein kinase C member PRKCP and MDS1 and EVI1 complex locus MECOM at 3p26, the p53 regulator MDM4 at 1q32, MYC at 8q24, and JAK2 at 9p24; meanwhile, focally deleted regions included tumor suppressor genes CDKN2A at 9p21 and PTEN at 10q23, NEGR1 at 1p31, QKI at 6q26, CADM2 at 3p12, PTRPD at 9p23, and NRXN3 at 14q24 [10].

Whole Exome Sequencing

Whole exome sequencing of the 417 tumors identified 36,353 somatic mutations, which include 16,821 missense mutations, 6383 silent mutations, and 2999 small insertions and deletions (indels), with average of 1.1 ± 0.5 non-silent mutations per mega base. Of these, there were 19 significantly mutated genes, with VHL, PBRM1, SETD2, KDM5C, PTEN, BAP1, MTOR, and TP53 being the eight most commonly altered genes. Eleven additional significantly mutated genes were present and considered to be of lower significance but included known cancer genes. Among these significantly mutated genes, only mutation of BAP1 correlated with poor survival [11]. In 20% of the ccRCC tumor specimens, none of the 19 significantly mutated genes were identified [7].

DNA Methylation Profiles

Epigenetic silencing with loss of function of VHL was found in 7% of ccRCC tumor specimens, mutually exclusive with a VHL mutation. Two hundred eighty-nine more genes had epigenetic silencing in 5% of tumors. The tumor suppressor gene UQCRH was hypermethylated in 36% of tumors, and though this is not known to be linked to ccRCC, the promoter hypermethylation frequency seemed to correlate proportionally with higher stage and grade [10, 12]. They also found that mutations in SETD2, a nonredundant H3K36 methyltransferase, were associated with increased loss in DNA methylation in non-promoter regions of the genes, which means that H3K36 trimethylation is possibly involved in maintaining a heterochromatic state [13].

RNA Expression

There are four stable subsets in both mRNA (m1–m4) and miRNA (mi1–mi4) expression datasets, which have similarities to ccA and ccB expression subtypes. The ccA and ccB subtypes

are previously studied clusters of gene expression data of ccRCC tumors, which exclude biologic or clinical information, and can help to distinguish genes playing an integral role in ccRCC using reverse transcription technology, which has prognostic significance. Cluster m1 corresponds to ccA, clusters m2 and m3 correlate to ccB, and cluster m4 accounts for the 15% of tumors unclassified in the ccA and ccB subtypes [14]. There is good prognosis associated with the m1 or ccA subtypes [7]. The m1 subtype comes from genes associated with chromatin-remodeling processes and a greater proportion of *PBRM1* mutations (39% in m1 vs 27% in others, $p = 0.027$). The m3 subtypes are associated with deletion of *CDKN2A* (53% vs 26%; $p < 0.0001$) and mutations in *PTEN* (11% vs 1%; $p < 0.0001$). The m4 subtype had higher frequencies of *BAP1* mutations (17% vs 7%; $p = 0.002$) and *mTOR* mutations (12% vs 4%; $p = 0.01$) [7].

Survival differences in the miRNA subtypes correlated with mRNA data. For example, miR-21 correlates strongly with worse outcome, and DNA promoter methylation levels inversely correlated with expression of miR-21, miR-10b, and miR-30a. miRNA interactions are important to epigenetic regulation in ccRCC [7].

Integrative Data Analysis

There are 25 subnetworks of genes within a genome-scale protein-protein interaction network, and VHL is the largest and most frequently mutated network. The second most frequently mutated subnetwork is *PBRM1*, *ARID1A*, and *SMARCA4*, which are key genes in the PBAF *SWI/SNF* chromatin-remodeling complex [7].

The mutations in the chromatin regulators *PBRM1*, *BAP1*, and *SETD2* were associated with altered expression patterns of large numbers of genes when compared to samples bearing a background of *VHL* mutation. Each chromatin regulator had a distinct set of downstream effects, reflecting diverse roles for chromatin remodeling in the transcriptome [7].

Additionally, 28% of tumors had alterations in multiple components of the PI3K/Akt/mTOR pathway. This included two genes from the broad amplicon on 5q35.3, *GNB2L1/RACK1* and *SQSTM1/p62*, both of which had been associated with activation of PI3K signaling [15, 16]. Furthermore, mRNA expression levels of these two genes were correlated with both DNA copy number level increases and alteration status of the PI3K pathway. The mutual exclusivity module also includes frequent overexpression of EGFR, which correlates with increased phosphorylation of the receptor and which has been previously associated with lapatinib response in ccRCC [17].

Prognostic Significance

Worse survival has been noted to be associated with reduced AMP-activated kinase (AMPK) and increased acetyl-CoA carboxylase (ACC), as these lead to a metabolic shift toward increased fatty acid synthesis [18]. Poor prognosis correlated with down-regulation of AMPK complex and the Krebs cycle genes and with up-regulation of genes involved in the pentose phosphate pathway (*G6PD*, *PGLS*, *TALDO*, *TKT*) and fatty acid synthesis (*FASN*, *ACC*).

When examining epigenetic drivers of glycolytic shift, it was discovered that decreased promoter methylation of genes *miR-21* and *GRB10*, which translates to increased expression of these genes, was associated with worse and better outcome, respectively. Both miR-21 and GRB10 regulate the PI3K pathway. *miR-21* is inducible by high glucose levels and down-regulates PTEN, while GRB10, a tumor suppressor gene, negatively regulates PI3K and insulin signaling [19]. Promoter methylation of *miR-21* and *GRB10* is based on their mRNA expression, as well as the mRNA expression of other genes and protein expression in the metabolic pathways.

Loss of Chromosome 3/VHL Gene Mutations

The inactivation of the VHL gene, located on chromosome 3p25-26, has long been the defining

genetic characteristic of ccRCC [20].The vast majority of ccRCC tumors (>90%) demonstrate a loss of heterozygosity in the VHL gene; however, inactivation can alternatively occur through genetic mutations (50–66%) or promoter hypermethylation (10–20%) [21–23]. Studies conflict on the prognostic implications of VHL gene mutations. Several published reports suggest that somatic mutations in the VHL gene are associated with less advanced tumor stage and improved PFS, CSS, and OS [24–27], while others demonstrate worse PFS, CSS, and OS with loss-of-function (primarily frameshift and nonsense) mutations [24, 28]. However, in a recent validation cohort using 350 Cancer Genome Atlas specimens, VHL mutations were not associated with CSS [29].

Carbonic Anhydrase IX (CAIX)

CAIX is a transmembrane glycoprotein that regulates tumor growth by helping maintain cellular pH balance in hypoxic conditions. Hypoxia inhibits binding between the VHL protein and HIF-1α, resulting in the accumulation of HIF-1α, subsequent formation of the active HIF-1α-HIF-1β dimer, and downstream transcription of hypoxia-inducible genes, including CAIX [30]. The hypoxic environment of many solid tumor types induces CAIX expression through this mechanism. Accordingly, high CAIX expression in these cancers portends poor survival outcomes [31].

However, in RCC, the characteristic inactivating mutations in the VHL protein impair proteasomal degradation of HIF in normoxic conditions, making CAIX expression in RCC hypoxia-independent [22]. As a result, high CAIX expression is nearly universal in ccRCC (>95%), while oncocytoma, chromophobe, and PRCC tumor cells express considerably lower levels and CAIX expression is absent in normal kidney tissue [32, 33]. This unique mechanism for CAIX overexpression helps explain its distinct prognostic characteristics in ccRCC.

A study by Bui and colleagues in 2003 found that low CAIX expression (below a cutoff of ≤85% CAIX staining) was associated with poor DSS in both metastatic and non-metastatic ccRCC patients [34]. Several subsequent studies yield conflicting results; however, a 2014 meta-analysis of 15 studies concluded that low CAIX expression was associated with worse DSS, OS, and PFS. Furthermore, low CAIX was associated with more advanced clinicopathologic disease, including tumor grade, depth of invasion, lymph node metastasis, and distant metastasis [35]. Two studies evaluated the prognostic ability of CAIX specifically in non-metastatic ccRCC, again with somewhat conflicting results. While Zareti and colleagues found no association with CAIX expression and OS or adverse pathologic features in 95 patients, Chamie et al. demonstrated an association between low CAIX and poor DFS and OS in 831 patients with high-risk, non-metastatic ccRCC [36, 37].

More research is needed to determine whether CAIX is a useful prognostic biomarker for treatment response. Initial reports suggested that high CAIX expression was associated with better response and clinical outcomes after treatment with interleukin-2 immunotherapy [38–40]. However, a more recent prospective, non-randomized trial did not support this conclusion [41]. Among patients receiving targeted therapy, CAIX expression was not associated with treatment response with sorafenib or temsirolimus [42, 43]; however, it was suggested to have prognostic utility in terms of objective response rate and OS for patients receiving sunitinib [44]. Further investigation into whether CAIX predicts response to newer immunotherapy agents is ongoing.

Chromatin-Remodeling Tumor Suppressor Genes

New sequencing technologies have recently implicated multiple novel driver genes with potential prognostic significance for patients with ccRCC and PRCC. Three of these genes, polybromo 1 (PBRM1), the SET domain-containing protein 2 (SETD2) gene, and the BRCA1-associated protein-1 (BAP1) gene, are two-hit

tumor suppressor genes involved in chromatin remodeling that are frequently inactivated due to their close proximity (3p21) to the VHL gene (3p25) [45].

Approximately 41% of ccRCC tumors harbor PBRM1 gene mutations, including in 13/14 without VHL mutations, making it the second most commonly mutated gene in ccRCC [46]. PBRM1 and BAP1 are largely mutually exclusive – the presence of a PBRM1 mutation reduces the odds of a mutated BAP1 by 70% [47]. In patients with ccRCC, PBRM1 mutation was associated with improved OS in one study [48]; however, multiple reports demonstrate no association with CSS [29, 49]. Interestingly, when evaluating PBRM1, BAP1, SETD2, and KDMC5, PBRM1 was the only one of these mutations associated with advanced stage at presentation [49]. In the unlikely event that PBRM1 and BAP1 mutations coexist, patients experience significantly lower CSS from ccRCC [48]. In a somewhat conflicting report on the prognostic implications of PBRM1 protein expression using immunohistochemistry and mRNA expression analysis, da Costa and colleagues found a significant association between PBRM1-negative ccRCC and worse DSS and higher recurrence rates [50].

Considered a driver of tumor aggressiveness, BAP1 mutations occur in 5–15% of ccRCC cases and are associated with decreased CSS and OS [7, 23]. Compared to missense mutations, truncating mutations appear to confer significantly worse CSS [49]. Researchers evaluated immunohistochemical BAP1 protein expression in ccRCC and found that the 10.5% of BAP-1 negative patients had significantly worse DSS. BAP1-negative status remained an independent marker of poor prognosis after adjusting for the UCLA integrated staging system and was associated with a threefold increase in disease-specific death in patients with low-risk ccRCC (Mayo Clinic stage, size, grade, and necrosis score of ≤ 3) [51].

The prognostic implications of SETD2 for patients with ccRCC are less well defined. Gulati and authors failed to confirm the findings of Hakimi et al. that SETD2 mutations are associated with decreased CSS in a Cancer Genome Atlas cohort. The same study by Hakimi reported no effect on CSS in a smaller single institution cohort [29].Two contemporaneous studies demonstrated decreased RFS in patients with SETD2 mutations [23, 49].

Tumor Suppressor Gene p53 (Chromosome 17)

The tumor suppressor gene p53 is the most frequently mutated gene identified in the Cancer Genome Atlas – present in 42% of tumor samples across a range of cancer types [52]. This gene encodes tumor protein 53 (TP53), a transcription factor that is overexpressed in times of cellular or genetic stress to promote cell cycle arrest and DNA repair or to initiate apoptosis if the normal cellular conditions are not restored [47]. While the accumulation of inactivated TP53 is found in approximately 50% of all human cancers, this mutation is quite rare in ccRCC (2.2%) [45, 48]. Nonetheless, it appears that alternative mechanisms to gene alterations may account for the suppressed function of the TP53 pathway in ccRCC, and possible interactions between TP53 and histone acetyltransferase E1A-binding protein (EP300), among others, may confer poor clinical outcomes [53].

A systematic review of studies prior to 2009 concluded that while increased TP53 expression was associated with worse PFS and OS from RCC, the p53 gene mutation itself was not [54]. While one validation cohort using the Cancer Genome Atlas specimen supports the suggestion that p53 gene mutation is not a poor prognostic indicator for CSS [29], multiple other analyses arrive at conflicting conclusions. In another analysis of the Cancer Genome Atlas, p53 mutations were associated with decreased CSS for ccRCC [52]. Furthermore, a 2018 analysis of all subtypes of RCC revealed that p53 mutations confer a worse prognosis for ccRCC and PRCC, but not across all types of RCC in the Cancer Genome Atlas cohort [55]. The assertion that increased expression of TP53 predicts worse outcomes in ccRCC is refuted by Kankaya et al. and Godlewski et al., who report no association between TP53 expression and CSS or OS, respectively [56, 57].

Somatic Copy Number Variations

Genetic mutations that alter chromosomal copy number occur frequently in ccRCC. In a large, prospective analysis of 282 patients undergoing extirpative surgery for sporadic ccRCC, the most common mutations include loss of 3p (60%), loss of Y in males (55%), gains of 5q (33%), monosomy 14 or partial loss of 14q (28%), trisomy 7 (26%), loss of 8p (20%), loss of 6q (17%), loss of 9p (16%), and loss of 4p (13%). Several of these cytogenetic abnormalities may be associated with pathologic factors and disease-specific survival [26].

Loss of 9p

9p-deleted non-papillary tumors are associated with larger size, higher grade and tumor classification stage, and spread to lymph nodes and distant sites on presentation [58–60].Additionally, loss of 9p is an independent predictor of poor disease-specific survival [61]. In patients with small, localized ccRCC, loss of 9p, but not tumor size, is associated with metastatic progression and recurrence after nephrectomy, suggesting its utility in identifying a more aggressiveness phenotype [62].

Deletions of 9p are typically characterized by loss of the entire chromosome (85%); however, structural aberrations may also confer prognostic significance [26]. Microsatellite alterations at 9p22-23 were associated with the down-regulation of protein tyrosine phosphatase receptor delta and were an independent predictor of cancer-specific death [63]. Additionally, loss of heterozygosity at 9p21, resulting in inactivation of tumor suppressor gene CDKN2A/B, was also associated with increased risk of cancer-specific death from ccRCC [64]. Furthermore, CDKN2A mutation was the only example of an alteration that decreased survival across all of the major histologic subtypes in the most recent Cancer Genome Atlas analysis [55]. Finally, a recently published report implicates loss of 9p as a potent genetic driver of metastasis and mortality in ccRCC, further stoking enthusiasm as a useful prognostic biomarker [65].

Loss of 14q

Numerous reports conclude that loss of 14q is associated with larger tumors, higher pathologic stage, more aggressive tumor grade, and presence of metastasis at presentation through a deficient HIF-1α tumor suppressor pathway [9, 66–70].

While one study demonstrated no association with recurrence in locally advanced ccRCC [59], Kroeger and colleagues demonstrated that among patients harboring loss of 3p mutations, loss of 14q conferred a threefold risk of recurrence in patients with localized disease and a fivefold recurrence risk in all patients, when including those with lymph node involvement and distant metastasis [27]. Using single-nucleotide polymorphism analysis, Monzon et al. confirmed a higher likelihood of disease recurrence in patients with 14q loss [70].

Data supporting the prognostic significance of 14q loss on DSS is highly suggestive, but less convincing than the importance of 9p loss. Several reports conclude that 14q loss is associated with worse DSS on univariate analysis [26]. However, its prognostic significance is not maintained on multivariate analysis or when systematically evaluated in a recent Cancer Genome Atlas cohort [29]. While the association between 14q loss and DSS trended toward worse DSS in patients without 3p deletions, 14q loss was associated with a significant twofold greater risk of DSS in patients with 3p deletions. Finally, loss of 14q was identified as the other hallmark genomic alteration in metastatic ccRCC; however, unlike 9p loss, it did not reach statistical significance for metastatic progression or survival [65].

Gain of 8q

Gain of chromosome 8q may up-regulate the proto-oncogene c-MYC, resulting in uncontrolled cell proliferation, evasion of immune response, metastatic spread, and angiogenesis through the mitogen-activated protein kinase pathway [71].Accordingly, gain of 8q mutations are poor prognostic indicators in other urologic and non-urologic malignancies [72–75].

Two large cohorts suggest the potential of 8p gain as a prognostic biomarker for both ccRCC and PRCC [76]. Cytogenetic analysis revealed 8p gains in 6–8% of tumors and they were associated with larger, higher-grade tumors and greater likelihood of lymph node and distant metastasis. Cancer-specific mortality was significantly higher in patients with gain of 8p mutations in both cohorts. Additionally, 8p gain was associated with lower OS [77].

Papillary Renal Cell Carcinoma

Papillary renal cell carcinoma accounts for 15–20% of RCCs and has two main subtypes, type 1 and type 2, based on specific genetic alterations. Type 1 is often multifocal, characterized by papillae and tubular structures with small cells that contain basophilic cytoplasm and small, uniform oval nuclei, whereas type 2 is more heterogeneous and has papillae with large cells with eosinophilic cytoplasm and large spherical nuclei with prominent nucleoli. In most patients, papillary RCC is indolent, bilateral, and multifocal, while it can present as solitary lesions with aggressive clinical course [78–80].

Somatic Alterations

The Cancer Genome Atlas consortium compared 161 tumor specimens, 75 type 1, 60 type 2, and 26 uncharacterized, to normal specimens, similarly to the study done for ccRCC. Type 1 tumors were mostly stage I, whereas type 2 tumors were frequently stage III or IV. The single-nucleotide polymorphism (SNP) array-based profiling of somatic copy number alterations exposed distinct patterns across the three subgroups. Type 1 subgroup had gains of chromosomes 7 and 17 and lower frequency of gains of chromosomes 2, 3, 12, 16, and 20. The other two subgroups were mostly type 2 tumors, associated with high degree of aneuploidy with multiple chromosome losses, including chromosome 9p loss, which was associated with poor survival [79].

Type 1 papillary renal cell cancer can be sporadic or rarely hereditary. Hereditary papillary renal cell cancer has an increased risk of type 1 disease, by activating germline mutations of MET gene. Non-hereditary papillary renal cell cancer has somatic MET mutations in 13–15% of cases [81, 82]. There is a hereditary cancer syndrome that includes hereditary leiomyomatosis and RCC (HLRCC), which increases the risk of developing an aggressive form of type 2 papillary renal cell cancer, due to a germline mutation of the tricarboxylic acid (TCA) cycle enzyme gene, fumarate hydratase, to be discussed in more depth later [83–85]. The increased oxidative stress and activation of the NRF2/antioxidant response element (ARE) pathway are responsible for causing this aggressive cancer [86, 87]. Then there are mutations in genes like CUL3 and NFE2L2 (NRF2) that regulate the NRF2/ARE pathway, which cause sporadic papillary renal cell carcinoma [88].

The proto-oncogene mesenchymal-epithelial transition factor (MET) gene and its ligand, the hepatocyte growth factor (HGF), are both located on chromosome 7. About 75% of sporadic papillary RCC cases are associated with trisomy 7. When there is a gain-of-function mutation, HGF binds MET receptor, constitutively activating it causing a dysregulated tumorigenic state through the PI3K pathway [89, 90]. Type 2 papillary renal cell carcinomas were found to be more genetically diverse, and TCGA found that they were associated with multiple chromosome losses, including frequent chromosome 9p loss, which contains the tumor suppressor CDKN2A gene. CDKN2A-altered tumors have increased phosphorylation of retinoblastoma protein and increased expression of cell cycle-related genes. Compared to type 1 papillary RCC and other type 2 RCCs, those associated with chromosome 9p loss were associated with decreased overall survival [79]. Type 2 has also been associated with a loss of chromosome 22, which encodes NF2 from the HIPPO pathway and SMARCB1, a fundamental component of the SWI/SNF complex. Additionally, mutations on chromosome 1 have been associated with fumarate hydrogenase and the HIF pathway. Additionally, CpG island methylator phenotype

(CIMP) is the most aggressive subtype of type 2 papillary renal cell carcinomas and is found to have overall lowest rate of mutations and is associated with early-onset disease, poor survival, and germline or somatic mutation of the fumarate hydratase (FH) gene. TCGA found that it was associated with universal hypermethylation of the CDKN2A promoter. They have decreased expression of fumarate hydrogenase mRNA and increased expression of genes associated with cell cycle progression and response to hypoxia. It is also associated with loss of chromosome 22, like the other subtypes of type 2 mentioned above, as well as loss of chromosome 13q, at a similar rate to chromophobe RCC (60% vs 61.3%), which encodes RB1 and BRCA2.

Whole Exome Sequencing

Whole exome sequencing identified 10,380 somatic mutations in 157 tumors, with 1.45 nonsilent mutations per mega base. There were five frequently mutated genes which included MET, SETD2, NF2, KDM6A, and SMARCB1 that were recurrently mutated in papillary RCC with 24% of cases, which suggests alterations to MET signaling pathway, HIPPO signaling pathway, and chromatin modifier pathways are important to papillary renal cell carcinoma tumorigenesis. There were six other significantly mutated genes FAT1, BAP1, PBRM1, STAG2, NFE2L2, and TP53 with 36% of cases having mutation in at least one of these [79].

RNA Expression

By analyzing copy number alterations, DNA methylation, messenger RNA, microRNA levels, and protein expression, the investigators of TCGA identified four major tumor clusters. C1 is type 1 enriched, C2a and C2b are type 2 enriched, and C2c consists only of CIMP papillary renal cell cancer. C1 was strongly associated with gain of chromosome 7, MET mutation, mRNA cluster 1, and low tumor stage. C2a was mostly type 2 papillary RCC and associated with low tumor stage and DNA methylation cluster 2. C2b is exclusively type 2 and associated with DNA methylation cluster 1, higher tumor stage, and mutation of SETD2. C1 and C2a were associated with best survival, and C2b had poorer survival. C2c was the CIMP tumor subtype associated with worst survival of them all [79].

TCGA also had a pathway analysis comparing mRNA signatures of type 1 and type 2 papillary RCC, which showed that mRNA expression highlighted the NRF2 antioxidant response (ARE) pathway as an important feature of the type 2 papillary RCC [34]. NQO1 is a gene activated by the NRF2-ARE pathway, and its expression is lowest in C1, intermediate in C2a and C2b, and highest in C2c. Increased NqO1 expression is associated with decreased survival. There is increased activation of NRF2-ARE pathway in type 2 tumors and mutations in NRF2-ARE pathway genes like NFE2L2, CUL3, KEAP1, and SIRT1 [88].

Integrative Data Analysis

According to TCGA research network, there was a percentage of smaller tumors that did not have an identifiable driver mutation. 27% of them had driver mutations for known cancer-associated genes, such as *PTEN*, *NRAS*, *KRAS*, *TP53*, *TSC2*, and those in the *MLL* and *ARID* families. 23% of them had low-frequency somatic events in genes associated with cancer, and of these, 70% were type 1 with gain-of-function chromosome 7 which includes MET and other potential driver genes such as epidermal growth factor receptor. This gain of chromosome 7 is seen with tumors like Wilms tumor and papillary thyroid cancer [79].

Prognostic Biomarkers in Papillary Renal Cell Carcinoma

PRCC has a characteristic genetic alteration pattern, typically involving chromosomes 7, 17, 12, 16, and 20 without involvement of chromosome 3, confirming the diagnostic utility of cytogenetic

analysis for the PRCC subtype as a whole. Furthermore, type 1 and type 2 PRCC display different alteration patterns, which may provide insight into their distinct biologic behavior [91]. However, small sample size, retrospective analysis, and short follow-up generally limit studies evaluating the prognostic significance of protein expression and cytogenetic aberrations in PRCC.

In the largest available cytogenetic analysis of PRCC, approximately one third of papillary tumors harbored an abnormal karyotype, with a greater number of chromosomal aberrations found in type 2 PRCC (median 8 vs 6, $p = 0.018$). Several cytogenetic abnormalities were exclusively found in type 2 PRCC (loss of 1p, loss of 3p, gain of 5q), while trisomy 17 was more commonly found in type 1 PRCC. While trisomy 17 was associated with less aggressive tumors at presentation and longer DSS, loss of 1p, loss of 3p, and loss of 9p were associated with worse clinicopathologic tumor features and DSS [92]. Additionally, mutations in tumor suppressor gene p53 are associated with lower DSS for PRCC, and alterations in chromatin-remodeling gene PBRM1 are associated with lower OS in type 1 PRCC [55].Furthermore, gain of 8p may confer worse DSS and OS in patients with PRCC [77].

Further downstream, high PTEN, EpCAM, and gelsolin expression and no endothelial VEGF expression appear to correlate with improved DSS across both subtypes, while low CAIX expression was associated with higher DSS in type 2 PRCC [92].

Chromophobe RCC

The chromophobe subtype of renal cell carcinoma (ChRCC) accounts for 5% of non-clear cell RCC [93].Tumor cells originate from the intercalated cells of the distal tubules of nephrons and are typically slower growing and less likely to be metastatic [94].ChRCC was among the first of rare tumor types to be characterized by the Cancer Genome Atlas (TCGA) [95]. This RCC subtype is a known feature of Birt-Hogg-Dube syndrome (an autosomal dominant disorder associated with folliculin gene mutation on the short arm of chromosome 17) [96], tuberous sclerosis complex (associated with TSC1 and TSC2 mutations), and Cowden syndrome (associated with PTEN mutations) but can also occur sporadically [97].

Somatic Alterations

In 2014 Davis et al. analyzed 66 samples of sporadic chromophobe samples. SNP array analysis revealed that the majority (86%) of samples had a loss of one copy of the majority of chromosomes 1, 2, 6, 10, 13, and 17 with losses of 3, 5, 8, 9, 11, 18, and 21 occurring less frequently (12–58%). Of note, the folliculin gene implicated in Birt-Hogg-Dube syndrome is not known to be implicated in sporadic ChRCC [98]. Analysis of copy number alterations by histologic subtype demonstrated some variability with copy number alterations occurring less frequently among eosinophilic samples [99]. Moreover, use of the GISTIC (Genomic Identification of Significant Targets in Cancer) algorithm, which uses large numbers of cancer samples to identify presumed driver SCNAs by analyzing the frequency and strength of observed events, showed no focal copy number events which would suggest less chromosomal complexity compared to ccRCC [100].

Whole Exome/Genome Sequencing

Whole exome sequencing performed by Davis et al. revealed that ChRCC samples had a lower rate of somatic mutations compared to most other cancers. In particular, the somatic mutation rate was three times less than that found in ccRCC. Ultimately tumor suppressor genes TP53 (32% of cases) and PTEN (9% of cases) were identified as mutations of special significance [99]. Durink et al. also found FAAH2, PDHB, PDXDC1, and ZNF765 to be of significance in their study of 167 primary tumors [81]. While BAP1 is associated with decreased survival among other tumor types, there is no correlation in the case of PRCC or ChRCC. Conversely,

CDKN2A mutations were associated with decreased survival across all tumor types including ChRCC [55].

Whole genome sequencing in the Davis et al. study revealed genomic rearrangement breakpoints of the TERT promoter in 10% of ChRCC samples [99]. This DNA region has a role in the function of the enzyme telomerase, and point mutations in TERT have previously been identified in other human cancers [101]. Davis et al. identified that alterations in TERT in ChRCC were correlated with kataegis phenomenon (the occurrence of many mutations occurring close to each other) thus revealing a new mechanism of TERT up-regulation in malignancy [102]. Changes in TERT expression in ChRCC may represent a cancer-driving event.

Integrative Data Analysis

Genes relevant to many other malignancies that were identified with lower frequency by Davis et al. included mTOR, NRAS, TSC1, and TSC2. Overall, this implies that the mTOR pathway was affected in 23% of cases. Familial forms of ChRCC are known to activate the PTEN pathway though 47% of the sporadic cases studied did not display alternations in the PTEN or the p53 signaling pathways. In 2018 Ricketts et al. revealed that mutations affecting the PI3K/AKT pathway were present in ccRCC (16.2% of cases), PRCC (9.8%), and ChRCC (18.9%). Also, mutations affecting chromatin-remodeling pathways were found to be less of a feature of ChRCC (14.9%) compared to ccRCC (69.3%) and PRCC (53%).

ChRCC samples with alterations in the PI3K/AKT pathway were associated with decreased survival in ChRCC but not other tumor subtypes [55]. Moreover, PTEN mutations were associated with decreased survival in ChRCC.

DNA Methylation Profiles

DNA methylation has previously been analyzed in order to identify a cell of origin for the various RCC subtypes with no hypermethylation observed in ChRCC samples [103]. Ricketts et al. found that ccRCC samples were more likely to have hypermethylation events and were less likely to be hypomethylated than ChRCC. Hypermethylation in this analysis was found to be correlated with poorer survival across all RCC subtypes as well as higher stage of disease. Hypermethylation in ChRCC was also correlated with mutations in TP53. Hypermethylation of either SFRP1 or DKK1, regulators of the WNT pathway, was associated with worse survival in ChRCC as well as ccRCC and PRCC.

Mitochondrial DNA Analysis

Mitochondrial DNA analysis of chromophobe tumor cells has shown increased gene expression for those genes that code for enzymes found in the Krebs cycle and electron transport chain. For example, mitochondrial genome copy numbers were found to be four times higher in ChRCC than in normal kidney tissue [99]. This is in contrast to ccRCC where mitochondrial function appears to be suppressed. In particular, genes for complex I of the electron transport chain were found to be mutated in 18% of cases in the Davis et al. study, most commonly MT-ND5. Nonetheless, mutations in MT-ND5 (which is essential to the function of complex I) were not associated with loss of oxidative phosphorylation. Suppression of aerobic metabolism is a common evasive mechanism of tumor metabolism not supported by mtDNA analysis for ChRCC [104]. It is unclear how the loss of complex I contributes to tumorigenesis or whether it may promote alternate metabolic pathways. More recently, Ricketts et al. have found that mitochondrial DNA mutations were present in 20% of ChRCC samples and that these samples were enriched for high-heteroplasmy truncating mutations compared to other subtypes, meaning that there was a large mutational burden present intermixed with wild-type mitochondrial DNA among the samples [105]. ChRCC samples generally were found to have increased expression of genes responsible for activation of the pyruvate

dehydrogenase complex which in turn facilitates the TCA cycle and process of oxidative phosphorylation. Similarly, 5′-activated protein kinase (AMPK), a positive regulator of mitochondrial production, was enhanced in ChRCC. Other RCC subtypes demonstrated a poor prognosis with high expression of the ribose synthesis pathway and low expression of AMPK pathway genes or genes associated with aerobic metabolism. A small subset of ChRCC samples with these features were noted to have higher stage and poorer survival and were more likely to demonstrate hypermethylation, unusual chromosomal copy number patterns, and sarcomatoid features.

Immune Signature Analysis

The clinical relevance of the immune system in the pathogenesis and treatment of various malignancies is of increasing interest. Identifying gene "signatures" or patterns of enriched genes among immune cells in tumor samples can be important in recognizing biomarkers that can be used to understand tumorigenesis or prognosis or to detect potential treatment targets [106].

Immune signature analysis in the Ricketts et al. study identified increased expression of the T helper 17 cell gene signature in ChRCC. While not statistically significant, expression of this signature was associated with increased survival in this subtype. While present only in outliers of the ChRCC group, the T helper 2 cell signature was associated with poor survival across all tumor types.

RNA Expression

RNA expression analysis performed in the Ricketts et al. study proved useful in distinguishing the various types of RCC. For example, a single enriched cluster for each of messenger RNA (mRNA), microRNA (miRNA), and long non-coding RNA (lncRNA) was characteristic of the ChRCC samples which shared an lncRNA cluster with the CpG island methylator phenotype (CIMP-RCC). Furthermore, assessment of sets of associated genes revealed mRNA signatures that further depicted the RCC subtypes. In ChRCC, the signature identified was an ion transmembrane transport signature [55].

Summary

In conclusion, RCC is not one identifiable cancer but a family of epithelial kidney tumors with distinct genetics, molecular alterations, histology, and behavior that arise from the same tissue of origin. The genetic mutations responsible for the various subtypes of RCC have been catalogued using genomic sequencing on the DNA, RNA, miRNA, and proteomic levels, all of which have shed light to these distinctions and, in turn, aided our ability to prognosticate and manage the various forms of RCC.

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3 Familial and Hereditary Syndromes in Renal Cell Cancer

Mark Wayne Ball and Peter A. Pinto

Introduction

Kidney cancer is a heterogeneous group of diseases that are clinically, genetically, and morphologically distinct. Currently, the World Health Organization recognizes 16 subtypes of renal cell carcinoma (RCC) [1], and up to 12 hereditary conditions have been identified with increased lifetime risk of developing renal tumors [2]. Together, the different forms of RCC will be diagnosed in almost 74,000 persons and lead to 15,000 deaths in the United States in 2019 [3].

Hereditary kidney cancer is thought to represent around 5% of kidney cancer cases [2]; however, the true incidence may be higher due in part to limitations in understanding the role of cancer susceptibility genes in RCC. Upward of 25% of kidney cancer cases have multifocal tumor involvement [4, 5]. Furthermore, a multigenerational study of Icelandic people indicated that 58% of RCC cases thought to be sporadic occur in patients with one or more family members with RCC, supporting the notion that far more cases of seemingly sporadic RCC are actually hereditary in origin [6].

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Clinicians treating patients must recognize the hereditary syndromes as their management strategies can differ from one another as well as differ from sporadic kidney cancer treatment paradigms. Specific management strategies have been developed to provide oncologic control and maximize kidney function in this population. It is not uncommon that patients with a hereditary syndrome are not recognized either due to unfamiliarity, incomplete penetrance, poor family history, or the development of de novo mutations – any of which can mislead clinicians with limited experience with these patients. Recognizing these syndromes and understanding their genetics directly translates in how patients are managed both in terms of local disease management with surgery [7] and advanced disease management with systemic therapy [8].

Clinical Features of Hereditary RCC and Genetic Testing

All physicians involved in the treatment of patients with cancer have the responsibility to consider if a patient may benefit from genetic counseling and initiate the referral process. Some individuals may present with a known family history of a hereditary syndrome, which may simplify the genetic workup. These individuals still benefit from appropriate counseling to ensure they are appropriately diagnosed. A provider cannot assume that a cancer in an affected organ

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means that individual is affected. For these individuals, knowledge of the family mutation can greatly limit the costs of genetic testing. Rather than test multiple genes and do whole exome sequencing, a genetic counselor can perform an analysis of the region of interest.

Many patients may present with a previously undiagnosed hereditary RCC syndrome. While they may represent a de novo mutation, other factors may have limited prior diagnosis in affected first-degree relatives including poor family history, incomplete penetrance, and unrecognized features. Specific features should raise the suspicion of a clinician for a hereditary syndrome (Table 3.1). Bilateral, multifocal tumors that occur at early age of onset are key features of the hereditary RCC syndromes. Dermatologic manifestations are common to several of the cancer syndromes. Evaluation by an experienced dermatologist can often aid genetic testing. Detailed family history on both the maternal and paternal side should note which family members had a history of RCC and denote the age of onset. Prior personal and family past medical history should note the presence of benign and malignant tumors in organs such as the brain, spine, pancreas, small and large bowel, adrenal, uterus, breast, and eyes. A perceptive clinician with knowledge of the various hereditary conditions can be critical to a successful diagnosis. Besides assisting with the case of the individual patient, a family diagnosis can help all members of that lineage.

Description of Hereditary Syndromes

Von Hippel-Lindau

VHL is an autosomal dominant inherited multisystem disorder that affects 1:35000 individuals. Affected patients are predisposed to develop kidney tumors, kidney cysts, pheochromocytomas and paragangliomas, pancreatic neuroendocrine tumors, pancreatic cysts and islet cell tumors, hemangioblastomas of the central nervous system and retina, endolymphatic sac tumors, and cystadenomas of the epididymis and broad ligament (Fig. 3.1) [9]. Linkage analysis of families with VHL identified a novel gene at chromosome 3p25 [10]. *VHL* was identified as a tumor suppressor gene in which both copies of the gene are inactivated to drive tumorigenesis. Nearly all VHL-associated renal tumors demonstrate loss of chromosome 3p or somatic "second hit" *VHL* mutations [11, 12]. VHL patients inherit one mutant copy of the gene, and then the second, functional copy is damaged or lost, leading to tumorigenesis. As a result of improved mutation detection methods enabling a nearly 100% detection rate, germline *VHL* mutations have been identified in over 900 families worldwide who present with >200 different mutations [9, 13, 14].

Approximately 25–60% of patients with VHL develop bilateral, multifocal renal lesions consisting of cysts and clear cell RCC [15]. While cysts are considered benign in sporadically occurring patients, they are often lined with malignant tissue in patients with VHL and should be removed at the time of surgery [16]. Prior to the current management recommendations, a third of patients died of metastatic RCC [15, 17]. With proper screening, recommended with ultrasounds beginning in childhood, renal lesions are identified early and treatment can prevent the development of metastatic disease [15]. The historic management of those with multifocal RCC included bilateral radical nephrectomy with hemodialysis. The past two decades has seen the emergence of patients having been managed with repeat partial nephrectomy.

Management of VHL-associated renal tumors is focused on preventing metastasis while preserving the renal function. To that end, our institutional practice has been to perform active surveillance when tumors are less than 3 cm in diameter and resecting all ipsilateral tumors with a nephron-sparing approach once the largest tumor has reached 3 cm [18]. Considering the multiple small tumors and the need to preserve normal renal parenchyma, enucleation of the tumors is used and has been demonstrated to be a safe surgical technique [19]. In general, the overarching goal of the surgeon is to "reset the clock" meaning to remove as many lesions as possible in one surgery in an attempt to prolong the interval

Table 3.1 Hereditary kidney cancer syndromes

Name	Gene	RCC histology	Non-renal manifestations	Preferred surgical approach	Surveillance
Von Hippel-Lindau (VHL)	*VHL* (3p25)	Clear cell RCC, cystic RCC,	CNS hemangioblastomas, retinal angiomas, pancreatic neuroendocrine tumors and cysts, epididymal/broad ligament cyst adenomas, pheochromocytoma	Enucleation	Until largest tumor reaches 3 cm
Hereditary papillary renal carcinoma (HPRC)	*MET* (7q34)	Type 1 papillary RCC	None	Enucleation	Until largest tumor reaches 3 cm
Birt-Hogg-Dube (BHD)	*FLCN* (17p11.2)	Chromophobe RCC, oncocytoma, hybrid oncocytic tumors	Cutaneous fibrofolliculomas, lung cysts, spontaneous pneumothorax	Enucleation	Until largest tumor reaches 3 cm
Hereditary leiomyomatosis and renal cell carcinoma	*FH* (1q42)	Type 2 papillary RCC	Cutaneous leiomyomas Uterine leiomyomas	Partial nephrectomy with wide excision; consider lymphadenectomy	No surveillance
Succinate dehydrogenase-deficient RCC	*SDHB (1p36)*, *SDHC (1q21)*, *SDHD (11q23)*	SDHB: Oncocytic RCC SDHC/D: Clear cell RCC	Pheochromocytomas, paragangliomas, gastrointestinal stromal tumors	Partial nephrectomy with wide excision; consider lymphadenectomy	No surveillance
BAP1-associated RCC	*BAP1* (3p21)	Clear cell RCC	Benign melanocytic tumors, malignant uveal and cutaneous melanoma, and malignant mesothelioma	Partial nephrectomy with wide excision	No surveillance
MITF family translocation RCC	*TFE3 (Xp11)*, *TFEB (6p21)*, *MITF (3p13)*	Various RCC histologies	MITF: Melanoma	Partial nephrectomy with wide excision.	No surveillance
Tuberous sclerosis complex (TSC)	*TSC1* (9q34) *TSC2* (16p13)	Angiomyolipomas, RCC, renal cysts	Facial angiofibromas, ungual/periungual fibroma, shagreen patch, retinal hamartomas, subependymal nodule, cortical hamartoma	Enucleation	RCC: Until largest tumor reaches 3 cm. AML: Surveillance until 4 cm or symptomatic
Familial translocation RCC	Chromosome 3 translocation	Clear cell RCC	None	Enucleation	Until largest tumor reaches 3 cm

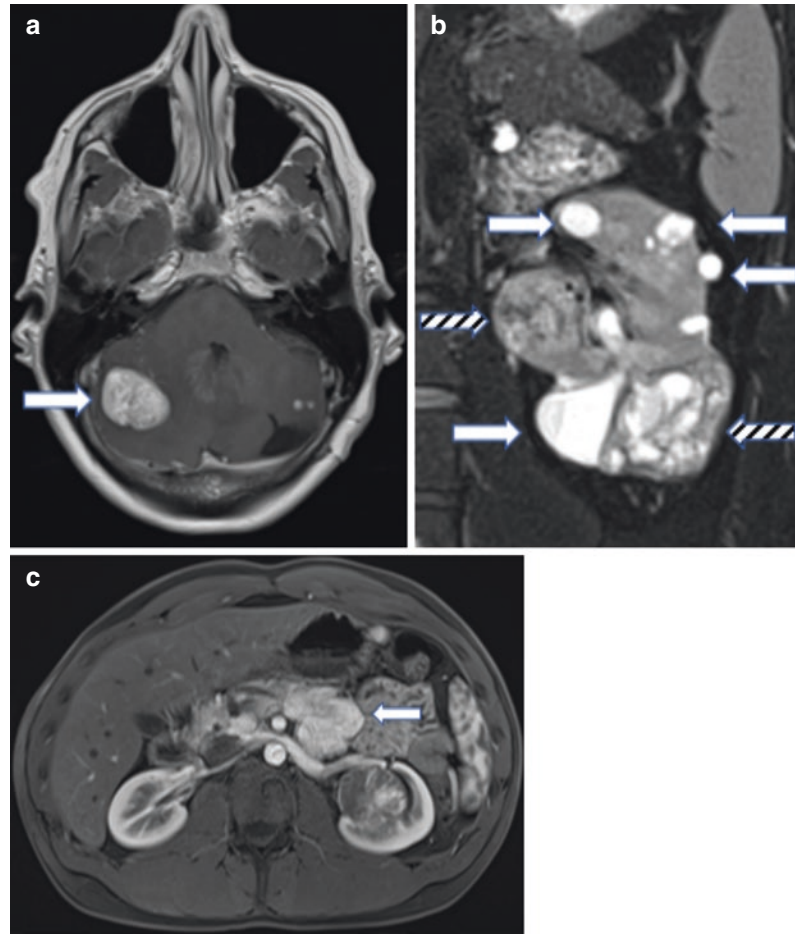

Fig. 3.1 VHL-associated lesions: (**a**) cerebellar hemangioblastoma, (**b**) multifocal kidney tumors (striped arrows) and cysts (white arrows), (**c**) pancreatic neuroendocrine tumor

between ipsilateral renal surgeries. Toward that end, all solid and complex lesions are removed with frequent intraoperative ultrasound being utilized to localize and ensure complete removal of all tumors.

Hereditary Papillary Renal Cell

Hereditary papillary renal carcinoma (HPRC) is a rare, autosomal dominant inherited disorder in which affected individuals are at risk to develop bilateral, multifocal type 1 papillary renal carcinoma [20]. Germline mutations in the *MET* proto-oncogene located at 7q31 were identified in the germline of individuals affected with HPRC by linkage analysis [21–23].

HPRC-associated renal tumors are characterized by "incipient lesions" in the apparently "normal" surrounding kidney parenchyma, with an estimation of >3000 of these microscopic papillary tumors in a single kidney that suggest multiple, independent, early events [24, 25]. HPRC patients are at risk to develop renal tumors during the fifth and sixth decades of life [22, 26]; however, early-onset HPRC families have also been reported [27]. Age-dependent penetrance has been estimated at 67% by the age of 60 years with complete penetrance by 80 years of age [22]. Fewer than 40 families with HPRC have been reported to date, underscoring the rarity of this inherited renal cancer syndrome.

HPRC lesions are often hypoechoic to renal parenchyma and may be poorly enhancing.

Hypoenhancing CT lesions can be confused with hyper-dense cysts. MRI may be more useful than CT scan for detecting and monitoring HPRC renal lesions. Similar to the approach with patients affected with VHL, active surveillance until the largest renal tumor reaches the 3-cm threshold is recommended for management of patients affected with HPRC. Nephron-sparing surgical approaches are recommended for HPRC-associated renal tumors as HPRC renal tumors tend to be bilateral and multifocal and numerous surgical procedures may be required to treat recurrent tumors.

Birt-Hogg-Dubé

Birt-Hogg-Dubé (BHD) is an autosomal dominant inherited cancer syndrome in which patients are at risk for developing benign hair follicle hamartomas (fibrofolliculomas), multiple and bilateral pulmonary cysts, spontaneous pneumothoraces, and renal tumors (Fig. 3.2) [28, 29]. The most common manifestations of BHD, fibrofolliculomas, and lung cysts occur in >83% of affected individuals and tend to develop after puberty [29–31]. Approximately 24–38% of BHD-affected individuals will experience at least one spontaneous pneumothorax event during their lifetime with a median age of occurrence of 38 years [29–31]. BHD-affected individuals have a 6.9-fold greater risk for developing renal tumors compared to unaffected family members [29]. Bilateral, multifocal renal tumors have been reported to develop in 29–34% of BHD-affected patients [30, 31], but this rate may reflect ascertainment bias since frequency of renal tumors was considerably lower in other BHD cohorts [32]. The median age of renal tumor diagnosis is 48–51 years [29, 30]. BHD-associated renal tumors may present with variable histologies including hybrid oncocytic tumors (50%) that contain features of chromophobe renal cancer and oncocytoma, chromophobe renal carcinoma (34%), clear cell renal carcinoma (9%), and oncocytoma (5%) [33]. Renal tumors with different histologies can arise even in a single kidney of a BHD patient. Microscopic oncocytic lesions ("oncocytosis") can be seen scattered throughout the "normal" renal parenchyma of most patients and may represent precursors of BHD-associated renal tumors [33].

Patients with BHD often have imaging of their kidneys starting from the age of 20–25 years [34]. Abdominal imaging every 3 years is recommended for affected individuals with no renal masses. In recommending the frequency of imaging for individuals with renal masses, the urologic oncologic surgeon takes into consideration the tumor size, location, and growth rate. Renal ultrasound is not recommended as the sole modality for screening. As with VHL and HPRC, it is recommended that BHD-associated tumors be monitored until the largest tumor reaches the

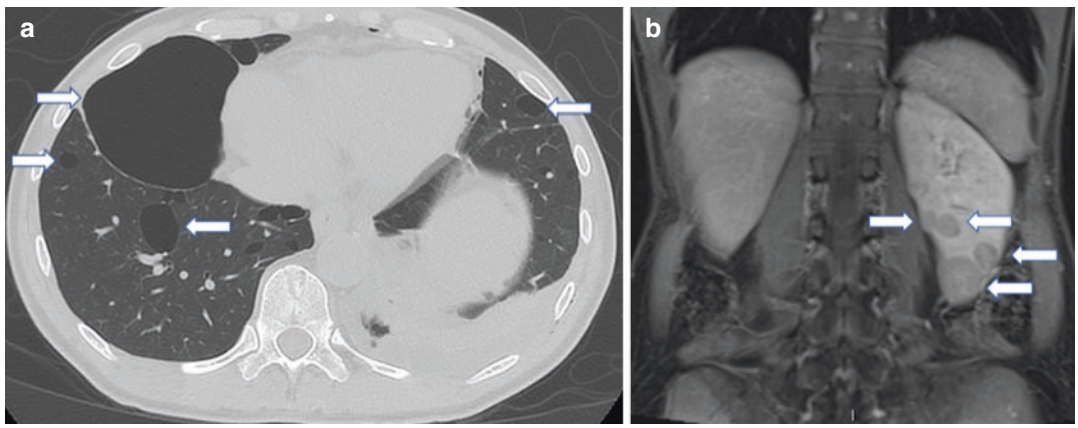

Fig. 3.2 BHD-associated lesions: (**a**) lung cysts, (**b**) multifocal renal masses

3-cm threshold, at which time surgical intervention is recommended [7, 34]. As BHD patients are at risk for the development of bilateral, multifocal tumors, partial nephrectomy is recommended whenever possible.

Hereditary Leiomyomatosis and Renal Cell

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is a familial cancer syndrome associated with cutaneous leiomyomas, uterine leiomyomas, macronodular adrenal hyperplasia, and type II papillary kidney cancer [35–38] (Fig. 3.3). Cutaneous leiomyoma is a common clinical feature that can occur on the arms or trunk. Kidney cancer, which presents in approximately 10–15% of HLRCC patients, may be solitary, multifocal, and/or bilateral. These tumors have the potential to spread, even when tumors are small (0.5–2 cm) [36, 39, 40]. These type 2 papillary tumors demonstrate a distinct histologic staining pattern that is characterized by cells with abundant eosinophilic cytoplasm and a large nucleus containing prominent inclusion-like eosinopholic nucleoli surrounded by peri-nucleolar halos [36].

HLRCC is characterized by an autosomal dominant inheritance pattern and is associated with germline mutation of the *FH* gene at chromosome 1p42.1 gene which encodes the Krebs cycle enzyme, fumarate hydratase [39–41]. Somatic loss of the remaining functional "wild-type" copy of *FH* is observed within HLRCC renal tumors resulting in biallelic loss of fumarate hydratase activity. Inactivation of this enzyme leads to a metabolic shift to aerobic glycolysis with decreased oxidative phosphorylation.

The initial experience with these tumors was much different than the other hereditary RCC syndromes with patients having an extremely aggressive disease. Over half of the patients in the initial series demonstrated regional or distant disease even when associated with small renal primaries [37]. Peripheral renal cysts or lesions too small to characterize are common in these patients. When not observed closely, we have observed individuals develop disseminated disease when not closely monitored.

It is recommended that HLRCC patients undergo annual abdominal screening by contrast-enhanced CT or MRI. Our practice is to recommend lifelong annual imaging beginning at age 8. Because patients affected with HLRCC are at risk for the development of bilateral renal tumors over their lifetime, nephron-sparing approaches are recommended when possible. HLRCC-associated renal tumors have an invasive growth pattern and an open surgical procedure with intraoperative ultrasound and a wide surgical margin and ipsilateral hilar lymphadenectomy is recommended. In contradistinction to the recommended management approach for many VHL-, HPRC- and BHD-associated renal tumors, active surveillance is not recommended for HLRCC-associated renal tumors [34, 42].

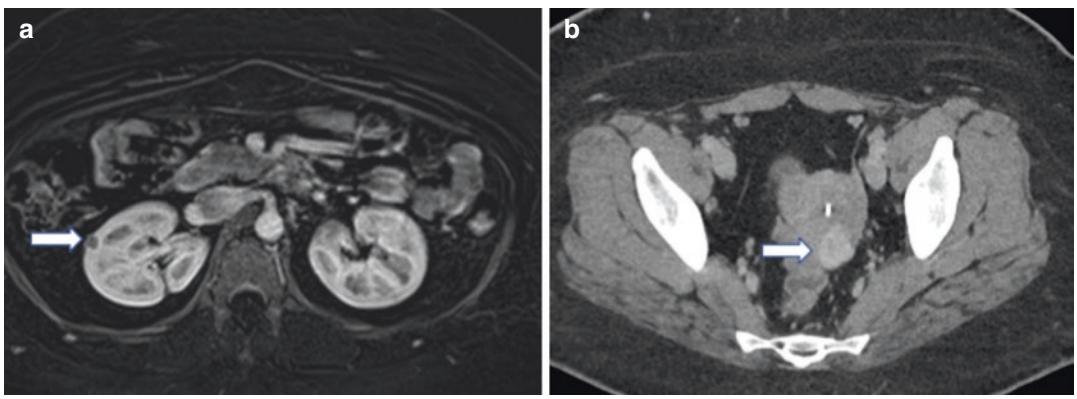

Fig. 3.3 HLRCC-associated lesions: (**a**) small papillary type 2 tumor, (**b**) uterine leiomyoma

Succinate Dehydrogenase-Deficient Kidney Cancer

Succinate dehydrogenase-deficient kidney cancer is associated with and seen as a part of familial paraganglioma/pheochromocytoma. It is an inherited cancer syndrome associated with an increased risk for pheochromocytoma, paraganglioma, gastrointestinal stromal tumor, and renal cell carcinoma. This syndrome demonstrates an autosomal dominant inheritance pattern and is associated with germline mutations within one of the four succinate dehydrogenase complex subunit genes: *SDHA*, *SDHB*, *SDHC*, and *SDHD* or a succinate dehydrogenase complex assembly factor, *SDHAF2* [43]. Germline mutation in all five genes has been associated with the development of bilateral or multifocal pheochromocytomas or paragangliomas, while succinate dehydrogenase-deficient renal cell carcinoma (SDH-RCC) has been associated with germline mutation of SDHB, SDHC, and SDHD. SDH-RCC can be aggressive and patients have demonstrated locally advanced or disseminated disease when tumors are still relatively small (1–2 cm) [43]. These tumors demonstrate a variety of histologic staining patterns including clear cell and oncocytic neoplastic patterns [43, 44].

The current clinical practice at the National Cancer Institute involves annual imaging with enhanced CT or MRI. These patients are monitored and managed in a similar fashion as the HLRCC patients since even small renal SDH-RCC masses have been known to metastasize [43]. As these tumors are considered aggressive, active surveillance is not recommended. Nephron-sparing approaches, with wide surgical margin, are recommended when possible [7, 34].

BAP1-Associated RCC

BAP1-associated RCC is seen as a part of *BRCA1-associated protein-1 (BAP1)*-associated tumor predisposition syndrome. It is an autosomal dominant inherited disorder in which patients are at risk for the development of benign melanocytic tumors, malignant uveal and cutaneous melanoma, malignant mesothelioma, and RCC. RCC can develop in ~10% of *BAP1* mutation carriers and is associated with an aggressive clear cell RCC [45]. Several families with *BAP1* germline mutations have been reported in which renal cell carcinoma is the only manifestation [46, 47].

The potentially aggressive nature of BAP1-associated tumors requires individualized management. It is recommended that patients with germline BAP1 alteration have annual abdominal imaging to evaluate for the presence of renal tumors. Because of the potential aggressive nature of these tumors and the lack of long-term outcomes in these patients, active surveillance is not currently recommended. Nephron-sparing surgery, depending on the tumor size and location, is recommended when possible. Patients affected by germline mutation of the *BAP1* gene are at risk for the development of bilateral, multifocal, and recurrent renal tumors, and preservation of renal function is recommended whenever possible [7, 34, 48].

MITF Family Translocation RCC

The microphthalmia-associated transcription factor (MiTF) family of genes includes TFE3, TFEB, and MITF. Members of this transcription factor family share similar protein structures and drive the transcription of similar genes. TFE3 and TFEB RCCs are caused by somatic chromosomal translocations, while MITF RCC is caused by a germline mutation, and together RCC that develops as a result of these alterations is referred to as MITF family translocation RCC. Translocation RCCs are defined as a histologically variable subtype of sporadic RCCs and make up approximately 1–5% of RCC tumors [49].

TFE3 is on the X chromosome at Xp11, and TFE3 RCC is said to account for 20–45% of renal tumors in children and young adults [50]. Xp11 translocation tumors can show a wide spectrum of morphology. Histologically, tumors frequently display a papillary architecture formed by clear cells with granular eosinophilic cytoplasm. TFE3 RCC can spread when the tumors

are small (2 cm) and, like HLRCC- and SDH-associated RCC, active surveillance is not recommended for TFE3 or TFEB translocation RCC. TFE3-fusion RCCs have been seen with late-onset metastasis which makes a long clinical follow-up necessary [50].

TFEB-translocation RCC is less common than TFE3 RCC and involves chromosome 6p21. Histologically, TFEB-fusion RCCs typically present with a biphasic microscopic architecture, characterized by large, epithelioid cells with clear and eosinophilic cytoplasm (mimicking ccRCC) and small, eosinophilic cells with hyperchromatic nuclei forming rosette-like structures [50].

MITF RCC is associated with a germline missense mutation of MITF (p.E318K). Affected patients have a >fivefold increased risk to develop RCC and co-occurrence of RCC and melanoma [51]. The p.E318K mutant MITF protein is affected by impaired sumoylation, differentially regulates DNA binding, and drives enhanced transcriptional activity of genes involved in cell growth, proliferation, and inflammation. This may explain the oncogenic role of the MITF p.E318K mutation [51].

Because TFE3 and TFEB alterations are not hereditary, associated RCCs are often not recognized until the time of surgery. Partial nephrectomy is acceptable in this population [52], although the safety of enucleation for these tumors is unknown. Management of germline MITF-altered RCC is currently unknown, but we do not currently advocate active surveillance in this population.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a multisystem, autosomal dominant inherited hamartomatous disorder affecting both adults and children. Affected individuals are predisposed to develop a variety of skin lesions including facial angiofibromas, hypopigmented macules, shagreen patches, and ungual fibromas that are detected in more than 90% of affected individuals. Pulmonary lymphangioleiomyomatosis characterized by proliferation of abnormal smooth muscle cells and cystic changes in the lung affects adolescent girls and women with TSC. Cerebral cortex tubers develop in >80% of TSC patients and can lead to a number of neurologic manifestations including epilepsy, cognitive disability, and neuro-behavioral abnormalities. Bilateral, multifocal renal angiomyolipomas, which are benign tumors of the kidney consisting of abnormal vessels, immature smooth muscle cells, and fat cells, develop in an estimated 55–75% of TSC patients occurring as early as 10 years of age [53]. Additionally, renal cell carcinomas with a variety of histologies may develop in TSC-affected individuals. Although the lifetime risk is similar to the general population (2–3%), the age of onset of renal tumor in TSC patients is younger, an average age of 36 years in one study [53, 54]. In addition to AMLs, patients with TSC are also at an increased risk to develop RCC.

Renal management of TSC is aimed at renal function preservation. AMLs greater than 4 cm may be at risk for spontaneous bleeding, although some studies suggest a bleeding risk for 3-cm lesions [55]. Historically embolization has been used; however, recent advances in microwave ablation have also shown successful treatment of AMLs with this method [56]. Renal AMLs may be seen in up to 75% of patients with TSC and can develop in patients as young as 10 years old. The main differential for solid lesions in this population includes fat-poor AML and RCC.

Intense effort is underway to develop a systemic therapeutic approach for patients with TSC-associated renal masses. In 2008, a clinical trial of sirolimus in patients with TSC-associated AML showed encouraging results, and this area remains very promising for future research [57].

Chromosome 3 Translocation Kidney Cancer

The identification of a family with recurrent multifocal clear cell kidney cancer without VHL identified a different genetic alteration involving chromosome 3: a balanced germline translocation t(3;8)(p14;q24) [58]. Subsequently, germline chromosome 3 translocations have been

identified involving chromosomes 1, 2, 4, 6, and 8 [59, 60]. Histologically, familial translocation tumors are similar to VHL-associated RCC tumors, and patients are at risk for the development of bilateral and multifocal RCC. The average age of onset is later than in VHL, in the fourth–fifth decade of life. Some clear cell kidney tumors in patients affected with chromosome 3 translocations have been shown to have loss of the 3p derivative chromosome and mutation in the *VHL* gene. These findings led to the proposition of a "three-hit" hypothesis for the carcinogenesis of these tumors where the first hit is inheritance of the germline chromosome 3 translocation, the second hit is loss of the derivative chromosome, and the third hit is somatic mutation of the remaining allele of a chromosome 3p (i.e., *VHL* or others) [61].

The diagnosis of a chromosome 3 translocation is made on germline karyotype. Patients should undergo regular cross-sectional imaging to identify kidney tumors that require surgical resection. Management is similar to VHL, with active surveillance until tumors reach 3 cm followed by nephron-sparing surgery.

Management of Hereditary Cancer Syndromes

Active Surveillance

Patients with hereditary kidney cancer syndromes such as HPRC and VHL may never be completely disease-free as their kidneys can contain hundreds if not thousands of incipient lesions. Patients treated with radical nephrectomy may cure the individual of cancer, but this places patients at risk to the complications of renal insufficiency. Partial nephrectomy in patients with hereditary cancer syndromes was first advocated in patients with VHL [62]. While over half of patients frequently had disease recurrence, almost all patients demonstrated excellent cancer-specific survival [62]. As patients are predisposed to tumors throughout their life, it is not feasible to remove all lesions at the first sign of emergence. Such an approach would lead to cumulative renal damage from frequent surgery. Our institution was the first to assess a strict cut point for renal intervention in patients with VHL and HPRC. Prior to tumors reaching 3 cm, all patients were closely observed. With this approach, no patients developed metastatic disease and all patients were able to avoid end-stage renal disease [63]. When tumors approached this size threshold, patients would undergo partial nephrectomy and removal of all solid lesions when feasible. Besides VHL and HPRC, other hereditary cancer syndromes such as BHD and FRC have been managed successfully with close surveillance of small renal masses and intervention with a 3-cm rule [64].

Surveillance is not recommended for individuals with HLRCC as small lesions have shown the propensity for locoregional and distant spread [37]. As SDH and HLRCC share similar biology, we also do not recommend surveillance for this patient population. Other syndromes such as TSC can also be associated with aggressive malignancy and observation should be cautioned in these individuals [65, 66]. More clinical experience is needed to evaluate the aggressiveness of kidney cancer associated with BAP1 or MITF prior to recommending a surveillance strategy.

Surgical Management

Multifocality occurs in both hereditary and sporadic cases. Multifocality refers to having more than one tumor in a single kidney, while bilaterality refers to at least 1 tumor in each kidney. Multifocality and bilaterality are commonly encountered together with nearly 9 of 10 patients with multifocal RCC also having bilateral tumors [67]. Over half of patients with bilateral tumors will also have multifocal disease [68]. Bilateral, multifocal (BMF) patients, whether hereditary or sporadic, pose challenges to the treating surgeon, as these patients are often at increased risk of requiring multiple interventions over a lifetime in order to definitively treat their condition. The traditional management of bilateral, multifocal RCC was bilateral nephrectomy and initiation of dialysis. Those individuals who did not demonstrate

disease recurrence could be candidates for future renal transplantation [69–71]. Due to the significant cardiovascular morbidity associated with dialysis, partial nephrectomy in these patients has been considered imperative rather than elective. Various studies have demonstrated the safety of partial nephrectomy even in the setting of over a dozen renal tumors [72, 73]. This may involve simultaneous or staged bilateral renal interventions or may require repeat ipsilateral renal intervention. For example, in some syndromes, there is a high rate of ipsilateral tumor recurrence over time due to the presence of incipient microscopic tumors throughout the renal parenchyma and subsequent development of de novo tumors [19, 74]. Even in predominantly sporadic RCC series, multifocality by itself increases the likelihood of ipsilateral tumor [75]. Repeat renal surgeries pose the risk of increased complications and perioperative morbidity and blood loss [76–81].

The resection of multiple lesions requires specific surgical considerations over ischemia and margin status. Removing multiple lesions can lead to prolonged ischemia, placing the remaining normal parenchyma at risk. Therefore, when feasible, tumor removal without ischemia should be considered. While this leads to increased blood loss, tumor removal is performed in a coordinated, stepwise fashion, from easiest to most challenging tumor. This approach maximizes the number of lesions removed and allows the anesthesiologist to maintain hemodynamic stability. After each resection, hemostatic agents and pressure to the defect can control much of the venous bleeding. After several minutes arterial and persistent venous bleeding can be oversewn.

Enucleation

Tumor enucleation is routinely performed in patients with VHL, HPRC, and BHD.[91] Performing a wide margin on multiple lesions would lead to significant loss of adjacent parenchyma. When enucleation is employed in appropriate cases, most lesions can be enucleated without renal hilar clamping. First, the renal capsule is incised circumferentially around the tumor, and the renal parenchyma is gently separated bluntly. Once identified, the tumor capsule is followed typically with blunt dissection. The closed scissors in combination with gentle fenestrated bipolar are used to bluntly peel the tumor from the surrounding parenchyma. The assistant is critical during this portion to ensure visualization of the junction between the tumor capsule and the normal renal parenchyma. Placement of the suction catheter against the normal parenchyma with intermittent suction, with gentle retraction away from the tumor, while the surgeon gently retracts against the tumor creates an operating space in which the surgeon can identify the plane of dissection. While blunt dissection is usually sufficient to separate the tumor from the surrounding compressed renal parenchyma, perforating vessels are sometimes encountered. These can be controlled with bipolar cautery, point monopolar cautery, and small clips or can be cut sharply and later oversewn.

If the true enucleation plane is identified, then the surrounding parenchyma that is peeled away tends to have been compressed by the tumor growth. As such, it does not bleed as briskly as cutting into normal, non-compressed renal parenchyma. Once the tumor is completely removed from its defect, the base is inspected. If the true enucleation plane is followed throughout the dissection, the likelihood of entry into the collecting system and significant renal vasculature is minimal. Consequently, complex renorrhaphy involving collecting system and major vasculature repair are often unnecessary. Generally, defects with arterial bleeding can be controlled using a running suture along the base. The defect is then filled with hemostatic agent and Surgicel. Given the numerous tumors throughout the kidney, defects are not closed immediately because closed renal defects are difficult to image with ultrasound after the capsule is re-approximated. In addition, the ultrasound probe can be placed into the defect once hemostasis is achieved which may allow for better imaging of and access to deeper lesions adjacent to the renal sinus fat and collecting system. Periodic intraoperative ultrasound is performed

throughout the partial nephrectomy to ensure maximum removal of all clinically significant tumors. Repeated use of the ultrasound is critical because multi-tumor partial nephrectomy results in substantial distortion of the kidney which may make finding target tumors more difficult. Serial use of the ultrasound allows the surgeon to keep real-time spatial relationships among tumors and intra-renal landmarks thereby facilitating complete excision of all targeted and clinically relevant lesions.

Wide Excision

For HLRCC and SDH renal tumors, our approach has been a wide surgical excision as we have observed an infiltrating pattern outside the pseudocapsule. Our institutional practice is to avoid robotic surgery in known HLRCC cases, as tumor spillage due to lack of haptic feedback can occur. Because normal parenchyma is transected, bleeding is more substantial than in enucleation, and it may be better suited to an approach that incorporates clamping the renal artery.

The role of enucleative surgery in the remaining hereditary cancer syndromes is unclear; however, as this approach has been proven safe with sporadic tumors, it likely is safe in these syndromes [82].

Conclusions

Patients with bilateral, multifocal, and early-onset kidney cancer frequently have a hereditary kidney cancer syndrome. Genetic testing in those suspected of these syndromes is recommended. If a known syndrome is identified, family members should be tested in order to begin appropriate screening protocols. The management of several of the kidney cancer syndromes has been refined over the past few decades to prevent cancer dissemination, maximize kidney function, and minimize surgical morbidity. The molecular characterization of these syndromes may lead to exploitation of these aberrant pathways with a systemic therapy approach.

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Pathology of Renal Cell Carcinoma

4

Franto Francis and Ming Zhou

Introduction

Many histological parameters obtained from routine pathological examination of renal tumors provide invaluable prognostic value. In the current WHO classification, the major histologic variants, namely, clear cell, papillary, chromophobe, and oncocytomas, account for 90–95% of renal cell neoplasms [1]. The classification also includes some less commonly encountered types, several of which such as MiT family translocation, tubulocystic, and succinate dehydrogenase-deficient RCCs were newly introduced into the 2016 edition of the WHO classification and the "unclassified type." These tumor types represent the most common RCC subtypes encountered clinically. However, many other less common subtypes of RCC have been described with distinct clinical, pathological, and genetic features, and it is likely that additional ones will be identified in the future. As the molecular mechanisms of renal tumors have been increasingly elucidated, molecular classification may eventually replace morphological classification. The clinical, pathological, and genetic features in combination will eventually enable urologists and oncologists to predict individual tumor behavior and stratify patients into more sophisticated risk groups, ultimately rendering individualized and precision management and treatment options.

There are estimated 65,690 new cases and 14,970 deaths from kidney cancer in the USA in 2018, and it is the sixth and tenth most common cancer type in males and females, respectively [2]. Arising from the renal tubular epithelial cells, renal cell carcinoma (RCC) accounts for more than 90% of primary kidney tumors in adults. It encompasses a group of heterogeneous tumors with diverse clinical, pathological, and molecular characteristics as well as varied prognostic implications and distinct therapeutic options and responses. It is therefore of paramount importance to accurately classify renal tumors. In this chapter, we review the pathological and molecular characteristics of major histological subtypes of RCC that are recognized in the current WHO 2016 classification of renal tumors [1]. We also discuss several newly described subtypes of RCC and RCC associated with inherited cancer syndromes. The prognostic significance of various histological parameters will also be highlighted.

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Pathological Classification of RCC

In addition to rendering an accurate diagnosis, pathological examination of RCC also provides relevant prognostic information and guidance to therapy.

The current 2016 WHO classification of RCC [1] follows on earlier Heidelberg [3] and Rochester classifications [4] that in turn represent expansions of the Mainz classification [5]. The current classification emphasizes the heterogeneity of RCC and defines distinct types of RCC based on unique morphologic and genetic characteristics. The WHO classifications represent a major change from the earlier classifications where tumors were considered as a single relatively uniform group, and incorporate genetic characteristics into the classification.

In the current WHO classification, the major histologic RCC subtypes, namely, clear cell, papillary, and chromophobe RCC, account for 90–95% of renal carcinoma (Table 4.1). This classification also includes some less commonly encountered types, including multilocular cystic renal neoplasm of low malignant potential, hereditary leiomyomatosis and renal cell carcinoma associated RCC, collecting duct carcinoma, renal medullary carcinoma, MiT family translocation carcinoma, succinate dehydrogenase-deficient RCC, mucinous tubular and spindle cell carcinoma, tubulocystic RCC, acquired cystic disease-associated RCC, and clear cell papillary RCC. An important category retained in this classification is the "unclassified type" which is assigned when a tumor does not readily fit into any of the recognized subtypes. This unclassified group is useful to define a group of renal cancer whose clinicopathological and molecular characteristics are not well-defined yet if clearly different from other histological subtypes. These 14 tumors represent the most common RCC subtypes encountered clinically. However, other renal cancers have been recently described with clinical, pathological, and genetic features distinct from these 14 tumors, and it is likely that additional ones will be recognized in the future. As the molecular mechanisms of renal tumors are increasingly elucidated, molecular classification will supplement and may eventually supplant the morphological classification.

Table 4.1 2016 World Health Organization Classification of Renal Cell Carcinoma [1]

Renal cell carcinoma
Clear cell renal cell carcinoma
Multilocular cystic renal neoplasm of low malignant potential
Papillary renal cell carcinoma
Hereditary leiomyomatosis renal cell carcinoma (HLRCC)-associated renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
MiT family translocation carcinomas
Succinate dehydrogenase (SDH)-deficient renal carcinoma
Mucinous tubular and spindle cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Clear cell papillary renal cell carcinoma
Renal cell carcinoma, unclassified

Pathologic and Molecular Characteristics of Subtypes of RCC

Renal Cell Carcinoma, Clear Cell Type (CCRCC)

Clinical Features

CCRCC is the most common histological subtype and accounts for 60–70% of all RCCs. Although it may occur in all age groups, it most commonly affects patients in their sixth to seventh decades of life with a male to female ratio of approximately 2: 1 [1]. Most CCRCC arises sporadically; however, 2–4% of cases present as part of an inherited cancer syndrome, which include von Hippel-Lindau syndrome, Birt-Hogg-Dube syndrome, and constitutional chromosomal 3 translocation syndrome [6–8]. As a general rule, familial CCRCC presents at a younger age and is much more likely to be multifocal and bilateral.

Pathology

Grossly, CCRCC usually presents as a unilateral and unicentric, round and well-demarcated mass with a fibrous capsule. The mean diameter is 6.2 cm; however, smaller lesions are increasingly

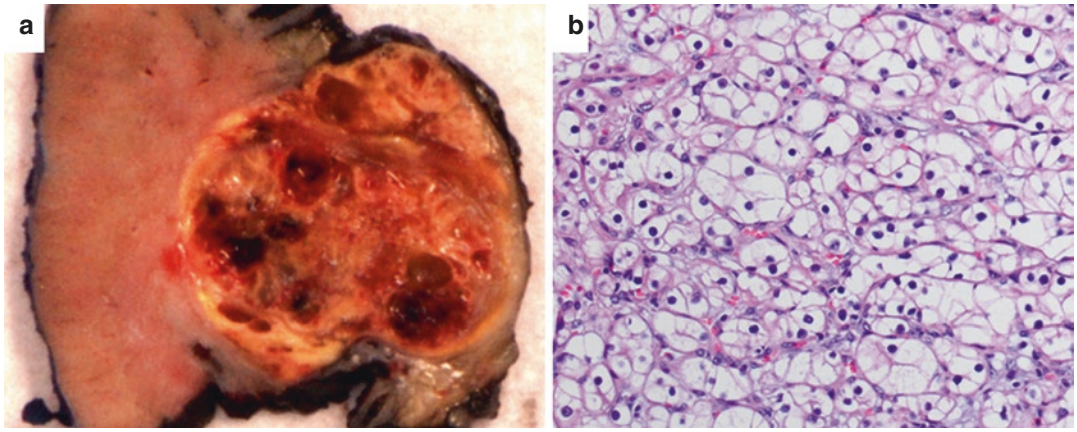


Fig. 4.1 Clear cell renal cell carcinoma. (**a**) Grossly the tumor is a well-circumscribed solid mass with characteristic bright golden yellow color. (**b**) Clear cell RCC is composed of compact nests of tumor cells with clear cytoplasm separated by delicate arborizing vasculature

detected due to the wide use of radiologic imaging techniques. The cut surface often has a characteristic golden yellow color with a variable degree of hemorrhage, necrosis, cystic degeneration, and calcification (Fig. 4.1a). Bilaterality and/or multicentricity occur in <5% of sporadic CCRCC cases but are more common in inherited cancer syndromes.

Microscopically, the tumor cells are arranged in compact nests, sheets, or alveolar or acinar structures separated by thin-walled blood vessels. Tumor cells have clear cytoplasm (Fig. 4.1b) due to rich cytoplasmic lipid and glycogen content that is lost during tissue processing and slide preparation imparting an empty or clear appearance. In high-grade and poorly differentiated tumors, cells no longer show cytoplasmic clearing but instead acquire a granular eosinophilic cytoplasm. In high-grade areas, loss of typical alveolar or acinar growth pattern is quite common, and solid and sometimes rhabdoid, papillary, or sarcomatoid histology may be found. Sarcomatoid differentiation occurs in about 5% of cases and is regarded as high-grade tumor with ominous prognosis.

Molecular Genetics

Nearly 90% of sporadic CCRCCs harbor chromosome 3p alterations that comprise deletion, mutation, or promoter methylation of several important genes, including *von Hippel-Lindau* (*VHL*) gene on chromosome 3p25–26. Genomic analyses have recently revealed that the 3p location also contains other important tumor suppressor genes that are lost or mutated in 15–40% of sporadic CCRCCs [9]. These genes are mostly involved in the chromatin remodeling complex, and include *PBRM1*, *SETD2*, and *BAP1* genes [10]. BAP1-mutated CCRCC tend to be high grade with an aggressive clinical course and poor outcomes [11]. Other cytogenetic alterations in CCRCC associated with poorer outcomes include losses of chromosomes 14q, 4p, and 9p [12].

Somatic mutations in *VHL* gene have been found in 18% to 82% of sporadic CCRCC cases. Loss of heterozygosity at the *VHL* locus has been reported in up to 98% of cases [13–15]. Hypermethylation of the *VHL* gene promoter resulting in gene inactivation has been detected in 5–20% of patients without gene alteration. The vast majority of CCRCC showing somatic *VHL* mutations also exhibit allelic loss or loss of heterozygosity (LOH) at the second *VHL* locus, consistent with Knudson's two-hit model of tumorigenesis.

VHL protein plays a critical role in the cellular response to hypoxia [16]. Hypoxia inducible factor (HIF) is a transcriptional factor whose cellular level is regulated by VHL. Under normoxic condition, HIF is hydroxylated, and the wild-type VHL protein binds to and targets this form of HIF for ubiquitin-mediated degradation in proteasomes. Consequently, HIF levels are kept low within normal cells under normoxic conditions. Under hypoxic condition, however, HIF is not hydroxylated and cannot be recognized by VHL and therefore accumulates. This in turn activates

many downstream hypoxia-driven genes, including genes that promote angiogenesis (vascular endothelial growth factor [*VEGF*] and platelet-derived growth factor β [*PDGF-β*]), cell growth or survival (transforming growth factor α [*TGF-α*]), anaerobic metabolism (*Glut-1*), acid base balance (*CA IX*), and red cell production (*erythropoietin*). Along the way, numerous intracellular signal transduction pathways are activated, including PI3 kinase-Akt-mTOR pathway and Ras/Raf/ERK/MEK pathway, which are involved in various cellular processes, including cell proliferation, survival, and differentiation [16, 17]. These signal transduction pathways serve a beneficial role by stimulating angiogenesis and compensatory metabolic changes in normal cells coping with hypoxia. When *VHL* gene is inactivated by mutation or promoter hypermethylation, no functional VHL is produced. The end result is activation of the aforementioned cellular processes that are no longer controlled by normal physiological mechanisms and therefore contribute to tumorigenesis and many of the clinical manifestations of CCRCC. The elucidation of these mechanisms has allowed development of targeted therapies that specifically act within these pathways. These agents that target the critical components of these pathways have been investigated in clinical trials and approved for patients with advanced stage CCRCC, and they also target VEGF using neutralizing antibody bevacizumab [18]; VEGFR and PDGFR using small molecule inhibitors of tyrosine kinase, such as sorafenib and sunitinib; EGFR using erlotinib; and mTOR using temsirolimus [19, 20]. More recently, immune checkpoint inhibitors such as nivolumab that target programmed cell death 1 receptor have been approved as second-line therapy in advanced CCRCC [21].

Prognosis

In CCRCC, about 50% are stage I and II, 45% are stage III, and less than 5% are stage IV. Prognosis of patients with CCRCC is most accurately determined by stage. Within stages, grade (nuclear grade) has strong predictive power. Sarcomatoid transformation, which was once considered a histologic type, is now recognized as a reflection of high-grade evolution and, when present, has a significant adverse impact on survival with few patients surviving to 5 years.

Renal Cell Carcinoma, Papillary Type (Papillary RCC, PRCC)

Clinical Features

PRCC is the second most common type of RCC and accounts for ~15% of RCCs. While the gender and age distribution are similar to those of CCRCC, the morphologic appearance and prognosis are quite different. Papillary RCC has a better prognosis with a 5-year survival approaching 90% [22]. The vast majority of tumors occur sporadically, but some develop in members of families with hereditary papillary renal carcinoma (HPRCC) [6, 7].

Pathology

Grossly, PRCC typically presents as a well-circumscribed mass enclosed within a pseudocapsule. Some tumors appear entirely necrotic and friable (Fig. 4.2a). PRCC is more likely to be bilateral and multifocal than other types of RCC.

Microscopically, PRCC is composed of varying proportions of papillae, tubulopapillae, and tubules (Fig. 4.2b). Occasionally, it has tightly packed tubules or papillae and imparts a solid appearance. The papillae characteristically contain delicate fibrovascular cores infiltrated by foamy histiocytes. Necrosis, hemorrhage, acute and chronic inflammation, hemosiderin deposition, and psammoma bodies are common.

PRCC is further subclassified into 2 morphological variants based on the histology [23]. Accounting for about 2/3 of PRCC, type 1 tumor contains papillae that are delicate and short, lined with single layer of tumor cells with scant cytoplasm and low-grade nuclei (Fig. 4.2b). In contrast, papillae in type 2 PRCC are large and lined with cells having abundant eosinophilic cytoplasm and large pseudostratified nuclei with prominent nucleoli (Fig. 4.2c). However, recent studies have found that type 2 PRCC is a heterogeneous group. Some renal tumors with specific genetic changes, such as HLRCC-associated RCC, MiT family

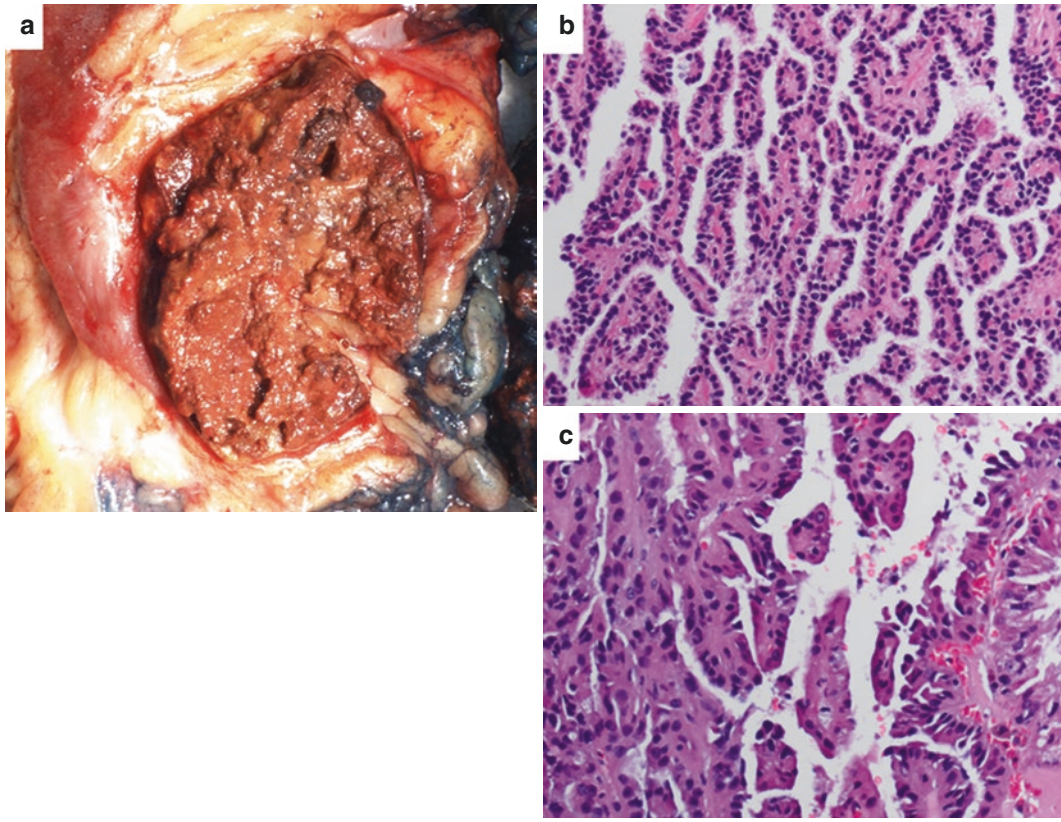


Fig. 4.2 Papillary renal cell carcinoma. (**a**) Grossly the tumor has a thick fibrous capsule and is extensively necrotic. (**b**) Type 1 PRCC is composed of papillae covered by a single layer of tumor cells with scant cytoplasm and low grade nuclei. (**c**) Type 2 tumor cells have abundant eosinophilic cytoplasm and large pseudostratified nuclei with prominent nucleoli

translocation RCC, TSC-mutated RCC, and fumarate hydratase-deficient RCC, may have some type 2 features and should be considered and excluded before a diagnosis of type 2 PRCC is rendered.

Molecular Genetics

Trisomy or tetrasomy 7, trisomy 17, and loss of Y chromosome (in men) are the most common cytogenetic changes in PRCC [24]. Additional gain of chromosomes 3, 12, 16, 20, and other chromosomes are often associated with tumor progression. Type 1 and 2 PRCC have distinct genetic features. A recent TCGA study [25] confirmed that type 1 PRCC is characterized by alterations in cell signaling involving the *MET* gene. *MET* gene mutations or other alterations that affect its activity were identified in 81% of type 1 PRCCs examined. This finding suggests that it may be possible to treat type 1 PRCCs with specific inhibitors of the MET cell signaling pathway, including the MET/VEGFR inhibitor foretinib, which is currently being tested in phase II clinical trials in PRCC and other cancer types [26, 27]. Type 2 PRCC was found to be more genetically heterogeneous characterized by *CDKN2A* silencing, *SETD2* mutation, and increased expression of the NRF2-antioxidant response element pathway. A CpG island methylation phenotype (CIMP) was found in a distinct subgroup of type 2 PRCC that was associated with the least favorable outcome. Across all type 2 PRCCs examined, 25% demonstrated decreased expression of *CDKN2A*, a tumor suppressor gene that regulates the cell cycle. Loss of CDKN2A expression was also associated with a less favorable outcome.

Prognosis

Papillary RCC has an overall low risk of tumor recurrence and cancer death after nephrectomy. Patients with type 1 PRCC have a better prognosis than those with type 2 tumor. However, predictors of outcome appear to relate to stage and nuclear grade, whereas morphological subdivision of papillary RCC itself does not appear to provide significant predictive potential. Nevertheless, recognition of the diversity, especially the genetic differences, within RCC with papillary architecture [28] may allow a better understanding of this subtype and lead to a better classification system.

Renal Cell Carcinoma, Chromophobe Type (Chromophobe RCC, ChRCC)

Clinical Features

ChRCC accounts for approximately 5% of RCCs and is believed to arise from the intercalated cells of the collecting ducts [29]. ChRCC can occur in patients of wide age range. Males and females are affected almost equally. The prognosis is significantly better than that of CCRCC, with disease recurrence in <5% of patients [22]. Most cases arise sporadically, while some familial cases are associated with Birt-Hogg-Dube syndrome [6–8, 30].

Pathology

ChRCC is typically a solitary, well-circumscribed and non-encapsulated mass with homogenous light brown solid cut surface. Hemorrhage and/or necrosis are uncommon. A central stellate scar can be seen in large tumors (Fig. 4.3a).

Microscopically, the tumor cells are usually arranged in solid sheets with tubulocystic architecture in some cases. The classic ChRCC tumor consists of large and polygonal cells with finely reticulated cytoplasm due to numerous cytoplasmic microvesicles and prominent "plant cell-like" cell membrane. The nuclei are typically irregular, hyperchromatic, and wrinkled with perinuclear haloes (Fig. 4.3b). Not infrequently, the tumor consists predominantly of cells with intensely eosinophilic cytoplasm, termed eosinophilic variant [31]. However, there is no substantial difference in the clinical characteristics between the two variants.

Molecular Genetics

ChRCC harbors extensive chromosomal loss, most commonly involving chromosomes Y, 1, 2, 6, 10, 13, 17, and 21 [32]. Occasionally, ChRCC occurs in Birt-Hogg-Dube syndrome, characterized by mutations in *Birt-Hogg-Dube* (*BHD)* gene on 17p11.2, which encodes the protein folliculin [33]. However, *BHD* mutations are rarely

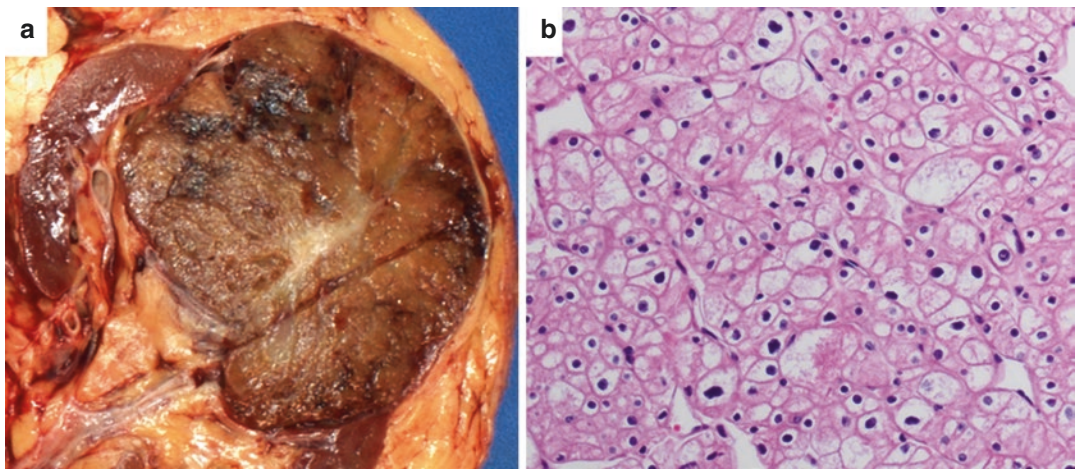


Fig. 4.3 Chromophobe renal cell carcinoma. (**a**) Grossly, it is a circumscribed, non-encapsulated mass with a homogenous light brown cut surface. (**b**) Large and polygonal tumor cells have finely reticulated cytoplasm, prominent cell border, and irregular nuclei with perinuclear clearing

found in sporadic ChRCC. It has been suggested that ChRCC may evolve from oncocytoma after acquiring additional cytogenetic abnormality [34]. Recent comprehensive molecular analyses by TCGA identified multiple somatic mutations involving mitochondrial DNA and in *P53* and *PTEN* genes, and rearrangements of the *TERT* promoter region in a significant subset of cases [35].

Prognosis

The prognosis of these tumors is generally accepted as favorable except in a small subset that can show aggressive behavior with local recurrence, metastasis, and/or death due to disease. The subset with an adverse outcome varies in series (in part related to case selection) with death of disease ranging from none to 15%. On multivariate analysis, sarcomatoid transformation, microscopic tumor necrosis, and higher pT stage were identified as independent predictors of aggressive biological behavior [36].

Other Uncommon Subtypes of Renal Cell Carcinoma

Other subtypes of RCC are uncommon and collectively account for <5% of RCC cases in the kidney. However, they have clinical, pathological, and genetic characteristics distinct from the more common types discussed previously. The clinical, pathological, and genetic features of these uncommon RCC subtypes are summarized in Table 4.2. There are several other entities that have been identified only recently and/or have limited data and therefore not included in the 2016 WHO classification. Several of these entities are reviewed in the Table 4.3.

Renal Cell Carcinoma, Unclassified Type

RCC, unclassified type, is a term for the designation of RCC that does not fit into any of the accepted RCC categories in WHO classification. It is important to understand that this is a diagnostic category rather than a true biological entity. These tumors represent a heterogeneous group with poorly defined clinical, morphological, or genetic features and therefore cannot be classified using the current criteria. Most but not all unclassified tumors are poorly differentiated and are associated with a poor prognosis. As our understanding of RCC improves, this category is destined to diminish and perhaps eventually disappear.

Renal Cell Carcinomas in Inherited Cancer Syndromes

Less than 5% of RCC occur in the setting of inherited cancer syndromes, including von Hippel-Lindau disease (VHLD), hereditary papillary renal cell carcinoma (HPRCC), hereditary leiomyomatosis and renal cell carcinoma (HLRCC), Birt-Hogg-Dube (BHD) syndrome, and others such as familial pheochromocytoma paraganglioma syndrome and tuberous sclerosis complex [6–8]. Each inherited cancer syndrome predisposes patients to distinct subtypes of RCC which often occur at a younger age and have a higher incidence of bilaterality and multifocality than sporadic cases [37].

von Hippel-Lindau Disease (VHLD)

VHLD is an autosomal-dominant hereditary condition with stigmata including CCRCCs, central nervous system hemangioblastomas, pheochromocytomas, pancreatic cysts, and endolymphatic sac tumors of the inner ear [38]. It is caused by germline mutations in *VHL* gene. VHLD patients are born with a germline defect in one of the alleles, and the second allele is inactivated by somatic mutations. Renal lesions in VHLD are always CCRCC and tend to be bilateral and multifocal. Dozens or even hundreds of microscopic tumor foci can be identified in resected kidney specimens. VHLD-related RCC develops early with a mean age of onset of 37 years as compared with 61 years for sporadic CCRCC. Although metastasis typically only occurs when tumors are

Table 4.2 Clinical, pathological, and genetic features of uncommon RCC subtypes included in the 2016 WHO classification [1]

RCC subtype	Clinical Features	Pathology		Genetics	Prognosis	Reference
		Grossly	Microscopically			
Multilocular cystic neoplasm of low malignant potential	<1% of renal tumors; related and morphologically similar to CCRCC; mean age 51 years (range 20–76); Male/female = 1.2–2:1	Solitary, well-circumscribed, entirely cystic mass; no grossly visible nodules or necrosis	Variably sized cysts lined with one or several layers of flat or plump clear cells; no expansile cellular nodules; low-grade nuclei (grade 1 or 2)	3p deletion as observed in CCRCC	Excellent; No local or distant metastasis after complete surgical removal	[97]
Carcinoma of the collecting ducts of Bellini (Fig. 4.4a)	<1% of all renal tumors; arising in the collecting ducts of Bellini; Often seen in fourth to seventh decade with mean age 55 years; male/female = 2:1	Poorly circumscribed; usually centrally located; cut surface gray, white, and firm	High-grade infiltrative tumor cells form complex tubulocystic structures; prominent desmoplastic stroma	Variable results; Allelic loss on chromosomes 1q, 6p, 8p,9p, 13q, 19q32, and 21q; 1q32.1–32.2 deletion; *c-erB2* amplification	Poor; 1/3 presenting with metastasis; 2/3 patients dead of disease within 2 years of diagnosis	[1, 98]
Medullary carcinoma	Exceedingly rare; almost exclusively in patients with sickle cell hemoglobinopathies or traits; majority are African-Americans; Mean age 19 years (5–69); Male/female = 2:1.	More common in right kidney; poorly circumscribed, centrally located; tan to gray, with varying degrees of hemorrhage and necrosis	High-grade infiltrative tumor cells with reticular, microcystic, or solid patterns; Desmoplastic stroma; may have abundant neutrophils	Increased *HIF1α* gene expression; LOH or loss of *SMARCB1* gene and chromosome 22; amplification of *ABL* gene	Highly aggressive; 95% presenting with metastasis; often dead of disease within 6 months of diagnosis	[1, 99]
Mucinous tubular spindle cell carcinoma (Fig. 4.4b)	Mean age 53 years (range 13–82); Male/female = 1:4; Incidental finding in most cases	Sharply circumscribed; gray-white with myxoid appearance; many have minimal hemorrhage and/or necrosis	Elongated compressed tubules and bland spindle cells with low-grade nuclei embedded in a myxoid stroma	Multiple chromosomal losses, most frequently involving chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22; 3p alterations and gain of chromosome 7, 17 not present; *VSTM2A* overexpression	Favorable; majority of patients remain disease-free after surgical resection; rare reports of metastasis and death of tumor	[1, 100–102]

MiT family translocation carcinoma (Fig. 4.4c)	Wide age range but more common in younger patients; most common RCC in children and young adults and accounts for 40% of RCCs in this age group; male/female = 1:1; occurs post-chemotherapy in some cases; affects adult patients with female predominance	Usually circumscribed but unencapsulated; not distinct from other RCCs	Xp11 tumors show papillary structures lined with clear cells, psammomatous calcification, and hyalinized fibrovascular cores; t(6:11) tumors show biphasic pattern with larger epithelioid nests of clear to granular cells and smaller eosinophilic cells	Chromosomal translocation involving TFE3 gene on Xp11.2 with several different translocation partners resulting in overexpression of the TFE3 protein; less common tumors with t(6:11) translocation showing MALAT1-TFEB gene fusion	Similar to CCRCC; among Xp11 tumors, ASPSCR1-TFE3 RCCs usually present more frequently with regional metastases (75% in studies) than PRCC-TFE3 RCCs (36%); t(6:11) RCCs generally show a more indolent course	[1, 100, 103, 104]
Tubulocystic carcinoma (Fig. 4.4d)	Occurs in fifth and sixth decade (range 30–94 years); male/female = 7:1	Usually solitary; circumscribed and unencapsulated; spongy cut surface resembling "bubble wrap"	Circumscribed collection of tubules and cysts with varied sizes; separated by fibrous stroma; no desmoplastic reaction; lining cells usually exhibit high-grade nuclei and eosinophilic cytoplasm; some cases with poorly differentiated foci and prominent nucleoli represents HLRCC	Gain in chromosome 7 and 17 and loss of Y in some cases; rarely harbors mutations in fumarate hydratase gene	Not fully established; majority cases have indolent clinical course; recurrence or metastasis in a few cases	[1, 100, 103, 104]
Clear cell papillary carcinoma (Fig. 4.5e)	Mean age 60 years; male/female =1:1	Small tumor with mean size of 2.4 cm; cystic mass having prominent fibrous capsule or stroma	Branching tubules, acini, and/or clear cell ribbons with low-grade nuclei; positive for CK7 and CAIX, and negative for CD10	Do not exhibit the genetic changes characteristic of CCRCC or PRCC	Low grade and stage; mostly biologically benign or indolent tumors	[1, 100, 105]
Acquired cystic kidney disease (ACD)-associated RCC (Fig. 4.5f)	More than one-third of RCCs in patients with ESRD / ACD, usually on long-term hemodialysis (clear cell papillary RCC and PRCC are other common variants); 2–7% RCC incidence in ACD patients	Frequently multicentric and bilateral; generally well circumscribed	Various architectures including papillary and solid; prominent intra- or intercytoplasmic lumina imparting sieve-like, cribriform appearance; frequent intratumoral calcium oxalate crystals	Gains in chromosomes 3, 7, 16, 17, and Y	Mostly indolent behavior with rare metastasis usually in cases with dedifferentiated pathology	[97, 100, 106, 107]

Table 4.3 Emerging and provisional renal cell carcinoma (2016 WHO classification) [1]

RCC subtype	Clinical features	Pathology		Genetics	Prognosis	Reference
		Grossly	Microscopically			
Thyroid-like follicular carcinoma	Very rare; mean age 45 years	Wide size range; tan to brown; well-circumscribed	Prominent pseudocapsule; micro- and macro-follicles lined with low-grade cells; colloid-like material present in >50% of follicles; thyroid IHC markers negative	Limited data; no distinctive IHC or molecular marker	Mostly indolent, with rare cases reporting distant metastases	[44, 100, 108, 109]
ALK-rearrangement-associated RCC	Rare and diverse tumor; wide age range, children to >50 years; M:F = 1.4:1	3.0–7.0 cm; often medullary location; white to whitish-grey, solid or solid-cystic	Morphologic similarity to renal medullary carcinoma but low KI-67 and SMARCB1 (INI1) expression retained; large polygonal/spindle cells with eosinophilic cytoplasm and intracytoplasmic lumina; abundant mucin	ALK rearrangement with vinculin (ALK-VCL) or other fusion partners	Diverse clinical behavior, not fully established with limited follow-up; potentially treated with ALK inhibitors	[110, 111]
RCC with (angio) leiomyomatous stroma	Variable	Variable	Clear tumor cells; low grade; arranged in tubulopapillary pattern; prominent smooth muscle and vascular stroma	Negative for 3p deletions and trisomy 7, 17; association with *TCEB1* gene mutations described	Mostly favorable prognosis	[44, 109]

greater than 3 cm, RCC is nevertheless the leading cause of death in this syndrome. However, VHLD patients with renal involvement fare better in 10-year survival than their sporadic counterparts [39].

Hereditary Papillary Renal Cell Carcinoma (HPRCC)

HPRCC is an inherited renal cancer characterized by a predisposition to multiple bilateral papillary renal tumors of type 1 histology. To date, kidney is the only organ to be affected in these patients [40]. HPRCC is associated with a germline mutation in the tyrosine kinase domain of the *c-met* proto-oncogene on chromosome 7q31. *c-met* gene encodes a cell surface receptor protein for hepatocyte growth factor (HGF) and has tyrosine kinase activity [6–8]. Gain-of-function mutations result in activated cellular processes that contribute to carcinogenesis, including angiogenesis, cell motility, proliferation, and morphogenic differentiation. The tyrosine kinase domain of MET is a promising therapeutic target [26, 27] (Fig. 4.4).

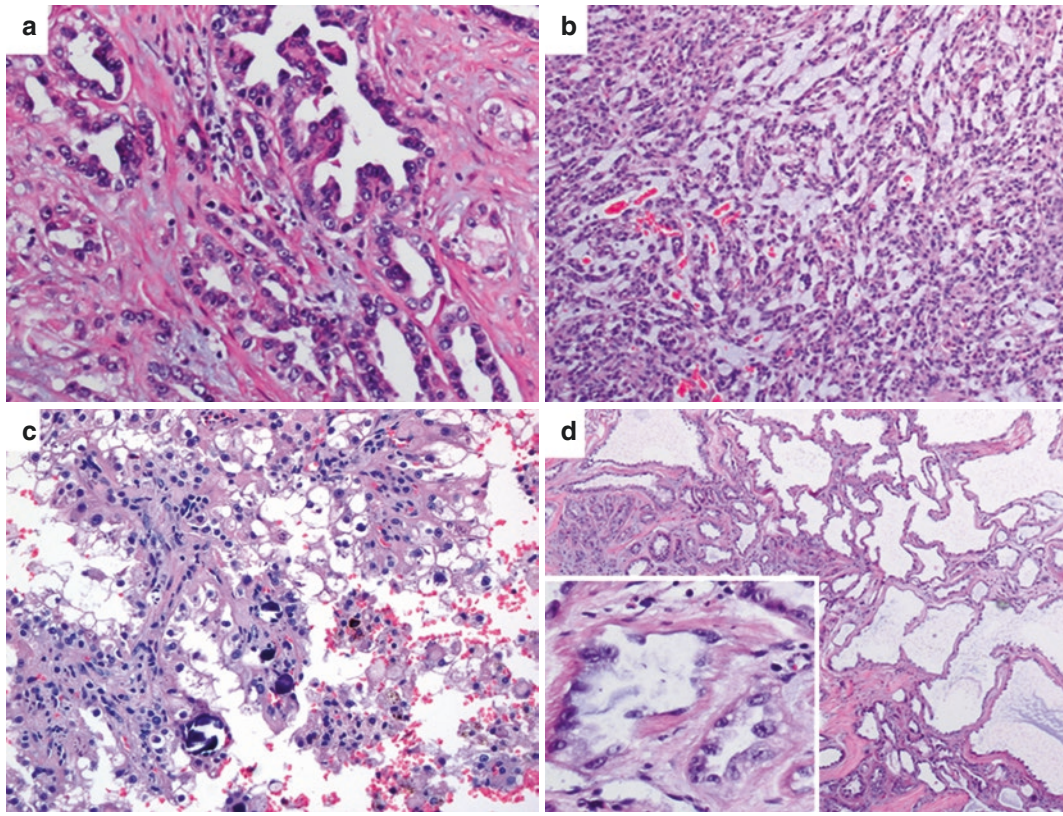
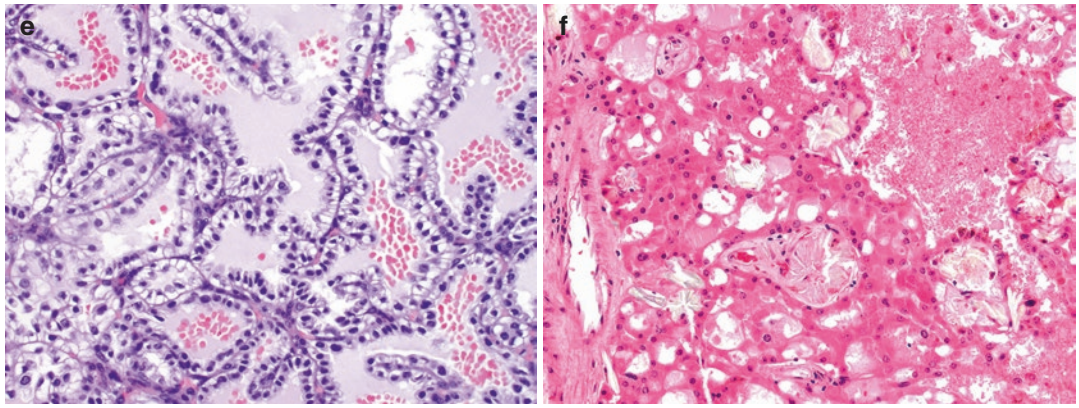


Fig. 4.4 Several uncommon renal cell carcinoma subtypes. (**a**) Collecting duct carcinoma consists of high-grade tumor cells forming complex tubules or tubulopapillary structures embedded in a remarkably desmoplastic stroma. (**b**) Mucinous tubular and spindle cell carcinoma is composed of elongated cords and collapsed tubules with slit-like spaces embedded in a lightly basophilic myxoid background. The tumor cells have low-grade nuclear features. (**c**) Xp11.2/TFE3 translocation renal cell carcinoma with characteristic papillary structure lined with tumor cells with abundant partly clear, partly eosinophilic cytoplasm and high grade nuclei. Psammomatous calcification is also present. (**d**) Tubulocystic renal cell carcinoma is composed of closely packed tubules and cysts separated by thin, fibrous septae. The lining tumor cells have a hobnail appearance and prominent nucleoli (Insert, high magnification). (**e**) Clear cell papillary renal cell carcinoma comprises tubules and stubby papillae lined with cells with clear cytoplasm and low grade nuclei, the latter characteristically aligned towards luminal surface. (**f**) Acquired cystic disease-associated renal cell carcinoma is composed of cribriform nests of cells with abundant eosinophilic cytoplasm. Calcium oxalate crystals with "sun-burst" appearance are often found in the tumor



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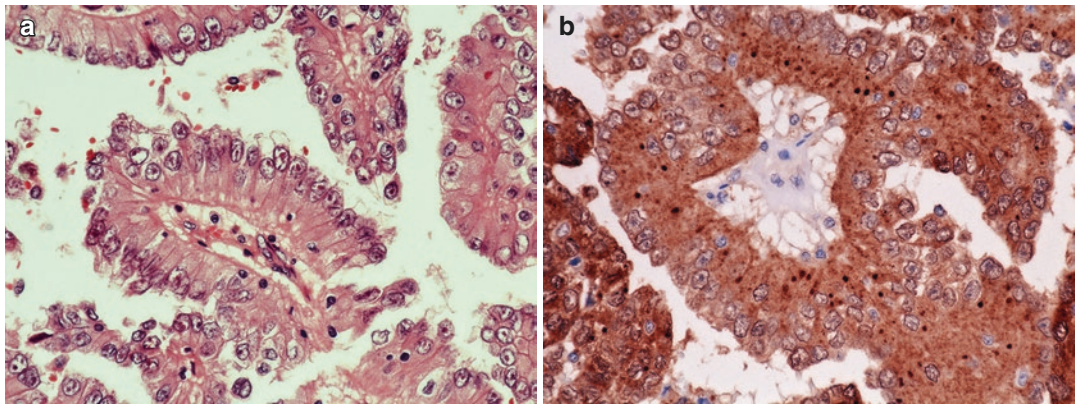

Fig. 4.5 Renal cell carcinoma in hereditary leiomyomatosis/renal cell carcinoma syndrome. (**a**) Tumor cells have large nuclei with prominent eosinophilic nucleoli surrounded by clear halos. (**b**) Immunohistochemically, tumor cells show diffuse and strong nuclear and cytoplasmic S-(2-succino)-cysteine (2SC) protein

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)

HLRCC is an autosomal dominant inherited cancer syndrome characterized by cutaneous leiomyomas and early onset uterine leiomyomas, occasional uterine leiomyosarcoma, and RCCs [41]. The renal tumors in these patients are aggressive and can present with early metastases, even when the tumors are small. Radical nephrectomy including adrenal gland resection and regional lymphadenectomy is the choice of therapy. The tumor usually behaves in an aggressive fashion with frequent metastasis to regional lymph nodes, adrenal gland, liver, or lung [41–43]. Grossly, the renal tumor is usually solitary and unilateral and forms a solid mass with frequent minor cystic component. Histologically, the tumor characteristically shows mixed architectural patterns with papillary, tubular, tubulopapillary, solid, and cystic configurations [41, 42]. Sometimes, collecting duct carcinoma-like or tubulocystic carcinoma-like patterns can also be observed [42]. The most characteristic feature foci of large nuclei with prominent eosinophilic nucleoli are surrounded by clear halos (cytomegaloviral inclusion-like) (Fig. 4.5a) [41–43]. These nuclear features may also be observed in uterine leiomyomas. Immunohistochemically, HLRCC tumors show diffuse and strong nuclear and cytoplasmic S-(2-succino)-cysteine (2SC) protein (Fig. 4.5b), and this staining pattern is absent in

other high-grade RCCs and is considered diagnostic of HLRCC [42]. However, this antibody is not commercially available. Genetically, somatic mutation of fumarate hydratase (FH) gene or loss of heterozygosity is observed in addition to FH germline mutation on chromosome 1 (1q42.3–43) in most cases [41–43]. FH is required to convert fumarate to malate in Krebs cycle and inactivation of *FH* impairs it, thereby activating anaerobic metabolism and upregulation of HIF and hypoxia inducible genes. The term "FH-deficient" RCC has been proposed recently for those tumors that show the typical histomorphology and immunohistochemical profile described above but lack or have uncertain information regarding clinical or family history and genetic status [44]. Suspected cases should be confirmed by FH gene sequencing.

Renal Cell Carcinomas in Hereditary Pheochromocytoma Paraganglioma Syndrome

Hereditary pheochromocytoma paraganglioma syndrome is an autosomal dominant syndrome with incomplete penetrance, caused by germline mutations in one of the four subunits of succinate dehydrogenase (SDH) that form the mitochondrial complex 2 on the inner membrane of mitochondria [45]. The SDH complex plays a critical role in Krebs cycle. Mutation in any of the four subunits, SDHA, B, C, or D, causes hereditary paraganglioma/pheochromocytoma syndrome which predisposes patients to pheochromocytoma, paraganglioma, or gastrointestinal stromal tumor and RCC. SDHB is mutated in the vast majority of cases. This tumor tends to affect young adults. The tumor is grossly well-circumscribed, and the cut surface demonstrates tan to brown color. Cystic change may be seen. Histologically, the tumor is composed of cuboidal to oval cells with eosinophilic cytoplasm and "bubbly" appearance due to the presence of intracytoplasmic vacuoles (Fig. 4.6a) which ultrastructural studies have shown to be giant mitochondria. The morphology can be reminiscent of a renal oncocytoma, but the nuclear atypia is typically greater than an oncocytoma and lacks the homogenous cytoplasmic granularity. Nuclei are generally of low grade, but high-grade including sarcomatoid change may occur. Immunohistochemically, tumor cells are positive for PAX8 and AMACR, but negative for SDHB staining. Because mutations in any of the SDH subunits destabilize the mitochondrial complex 2 and lead to loss of SDHB proteins, SDHB IHC has been shown to be a very effective way to screen for SDH mutation (Fig. 4.6b). Surgical resection is the choice of treatment. Tumors without high-grade component or coagulative necrosis

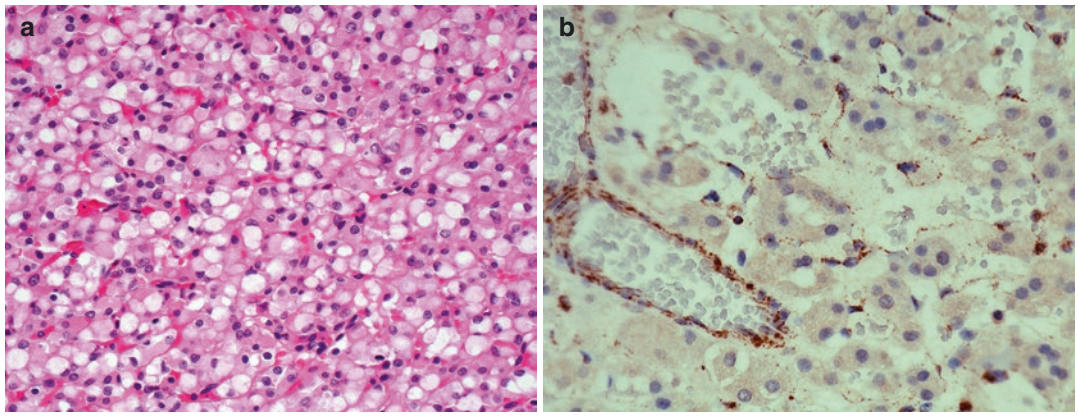

Fig. 4.6 Succinate dehydrogenase-deficient renal cell carcinoma. (**a**) Tumor is composed of cuboidal to oval cells with eosinophilic cytoplasm and "bubbly" appearance due to presence of intracytoplasmic vacuoles. (**b**) Tumor cells are negative for SDHB staining immunohistochemically. Note the vascular endothelial cells are positive for SDHB with brown chunky granular staining

behave in an indolent fashion, but those with dedifferentiation or in young adults are likely to behave aggressively [46–48].

Renal Tumors in Tuberous Sclerosis Complex (TSC)

Tuberous sclerosis complex (TSC), an autosomal dominant syndrome with inactivating mutations in tumor suppressor genes *TSC1* and *TSC2*, affects the central nervous system and other organs [49, 50]. In the kidney, TSC is most commonly associated with the development of angiomyolipomas (in ~80% of cases). RCC occurs in 2–4% of patients [51–53] and presents at a young age with a female predominance and multiple lesions in half of the patients. These patients present with a wide array of tumors, including clear cell RCC, papillary RCC, chromophobe RCC, unclassified RCC, and renal oncocytoma, as well as newly described entities like renal angiomyoadenomatous tumor (or RCC with smooth muscle stroma), chromophobe RCC-like, eosinophilic-solid cystic morphology, and hybrid oncocytic/chromophobe tumor (HOCT). Concurrent renal angiomyolipoma is frequent (also see discussion in "angiomyolipoma" below). Immunohistochemically, tumor cells show positive stain for PAX8, cytokeratin 7, CD10, vimentin, and carbonic anhydrase IX, but the negativity for HMB45, SDHB, TFE3, and AMACR stains [51, 52]. By FISH analysis, gain of chromosomes 7 and 17 was observed in a few cases. For treatment, surgical resection has been performed for the majority of patients. These tumors generally pursue an indolent clinical course, but nodal metastases have been reported. Recently, sporadic renal tumors with morphological features similar to RCCs in TSC have been reported to harbor somatic mutations in TSC1, TSC2 and mTORC1 genes and are considered the sporadic counterpart of RCCs in TSC.

Birt-Hogg-Dube Syndrome (BHD)

RCC is also part of the Birt-Hogg-Dube syndrome, an autosomal dominant disorder characterized by benign skin tumors (fibrofolliculomas, trichodiscomas of hair follicles, and skin tag), renal epithelial neoplasms, lung cysts, and spontaneous pneumothorax [54]. Renal neoplasms are often multifocal and bilateral, the most common being hybrid oncocytic tumors (50%) with features of both ChRCC and oncocytoma but diagnostic of neither [55]. Renal tumors can also include ChRCC (33%), oncocytomas (5%), and occasionally CCRCC or PRCC. *BHD*, the gene implicated in the syndrome, on 17p11.2, is a potential tumor suppressor gene and encodes the protein folliculin. The oncocytic tumors (hybrid oncocytic tumors, ChRCC, and oncocytoma) generally have favorable prognosis.

Common Benign Renal Tumors

Papillary Adenoma

By 2016 WHO definition, papillary adenomas are unencapsulated epithelial neoplasms up to 15 mm (1.5 cm) in size with papillary and/or tubular architecture, comprised of tumor cells with low-grade nuclei [1]. The maximum size was increased from 5 mm in the previous definition to 15 mm in the most recent WHO definition because the tumors up to 15 mm almost never metastasize.

Clinical Features

Papillary adenoma is the most common renal cell neoplasm, frequently seen as incidental findings in nephrectomy specimens or at autopsy. In one autopsy study, papillary adenomas were found in up to 40% of patients older than 70 years of age. Its incidence increases with age and also in patients who are on long-term dialysis.

Pathology

Papillary adenomas appear as small (<15 mm), well-circumscribed, yellow or white nodules in the renal cortex. They have papillary, tubular, or tubulopapillary architecture similar to papillary RCC but are usually unencapsulated. The tumor cells have uniform small nuclei and inconspicuous nucleoli equivalent to WHO/ISUP grade 1 or 2 nuclei.

Molecular Genetics

Papillary adenomas share many genetic alterations with PRCC. Both have combined gains of chromosomes 7 and 17 and loss of the Y chromosome in men. PRCCs acquire additional genetic alterations, including trisomy 12, 16, or 20. The cytogenetic findings support the hypothesis that papillary adenoma is a precursor of PRCC [56].

Renal Oncocytoma

Clinical Features

Renal oncocytoma accounts for 5% of surgically resected non-urothelial renal neoplasms. Patients vary greatly in age with a peak incidence in the seventh decade of life. The male to female ratio is 2: 1. Most cases are sporadic, although familial cases have been reported in association with Birt-Hogg-Dube syndrome and familial renal oncocytoma syndrome.

Pathology

Oncocytoma is typically solitary and well-circumscribed and has varying degrees of encapsulation. The cut surface exhibits a characteristic homogeneous mahogany-brown color (Fig. 4.7a). A central stellate scar can be seen in 1/3 of the cases, more commonly in larger tumors. More than 10% of cases are multifocal or bilateral.

Microscopically, oncocytoma is characterized by bright eosinophilic cells, termed oncocytes, arranged in nested, acinar, or microcystic pattern associated with a loose hypocellular and hyalinized stroma (Fig. 4.7b). Extension of oncocytoma into the perinephric fat, or rarely into vascular space, can be found sometimes and does not adversely affect the benign prognosis of the lesion.

Molecular Genetics

Most oncocytomas are composed of a mixed population of cells with normal and abnormal karyotypes [57]. Combined loss of chromosomes 1 and X/Y is the most frequent chromosome abnormality. Translocations involving chromosome 11, with a breakpoint at 11q12–13, have also been reported. Other rare chromosome rearrangements have been reported, such as t(1;12)(p36;q13), loss of chromosome 14, and gain of chromosome 12 [58]. Oncocytoma can be a manifestation of Birt-Hogg-Dube syndrome.

Whether oncocytoma and ChRCC are related is still controversial. They not only have overlapping morphological features but also share some cytogenetic changes, such as the loss of heterozygosity at chromosome 1 [59]. However, monosomy of chromosomes 2, 10, 13, 17, and 21 occurred exclusively in ChRCC [60].

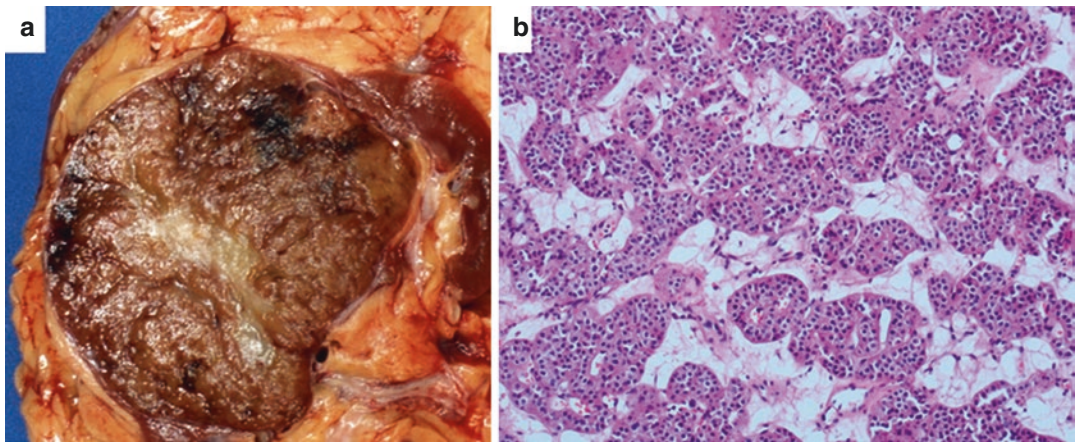

Fig. 4.7 Renal oncocytoma. (**a**) Grossly, it is a solitary, well-circumscribed, non-encapsulated mass with homogeneous dark-brown cut surface. (**b**) It consists of bright eosinophilic cells nested in a loose stroma. The tumor cells are uniform, round to polygonal with granular eosinophilic cytoplasm, and regular round nuclei

Angiomyolipoma

Clinical Features

Angiomyolipoma (AML) is a renal mesenchymal tumor comprising variable proportions of adipose tissue, smooth muscle bundles, and blood vessels. The prevalence in autopsies is 0.3% and 0.1% in ultrasound-screened patients. It accounts for 0.3–3% of all renal tumors in surgically resected renal neoplasms. AMLs are strongly associated with tuberous sclerosis (TS), in which most individuals will have multiple angiomyolipomas affecting both kidneys. Patients with TS develop AML earlier (mean age at diagnosis at 25–35 years with TS versus 40–45 years without TS). The male to female ratio in surgical series is 4: 1. AMLs, particularly those associated with TS, are usually asymptomatic and detected by imaging studies. Intra-abdominal bleeding owing to rupture may be an uncommon presentation initially or during follow-up.

Pathology

AML is typically well-circumscribed, non-capsulated mass with or without lobulation and sometimes with subtle infiltrative edges. The cut surface depends on the relative amount of three tissue components.

As its name implies, AML consists of thick-walled blood vessels, spindle cells with smooth muscle features, and mature adipose tissue in variable proportions (Fig. 4.8). Blood vessels typically have an eccentrically thickened wall with spindle cells spun off the wall. Spindle cells range from mature-appearing smooth muscle cells to immature spindle cells, epithelioid cells, and even bizarre cells with atypical nuclear features. Mature adipose tissue may have cytologic atypia. Classical AMLs are benign; however, ¼ to 1/3 of epithelioid AML are malignant with local and distant metastasis. Pathological features that correlate with adverse outcomes include large size, tumor necrosis, atypical mitosis, and diffuse atypical nuclei. Melanocytic markers, including Melan-A and HBM-45, are positive in AMLs and are often used to confirm the diagnosis.

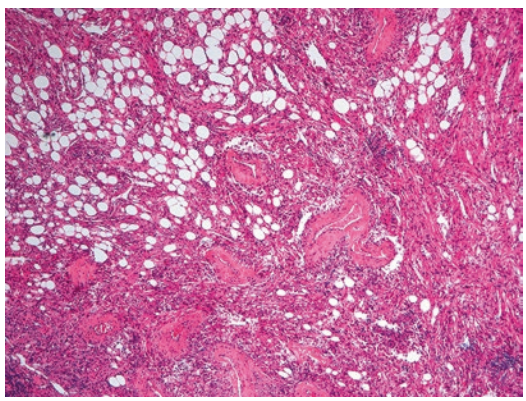

Fig. 4.8 Renal angiomyolipoma consists of thick-walled blood vessels, spindle cells with smooth muscle features, and mature adipose tissue in variable proportions

Molecular Genetics

The origin and genetic basis of AMLs is uncertain. AMLs in TSC show evidence of bi-allelic inactivation of the *TSC1* or *TSC2* gene, corresponding to the germline mutation present in such individuals. With loss of heterozygosity for the *TSC2* region, *TSC2* inactivation by mutation is likely a necessary genetic event in the pathogenesis of most sporadic AMLs [61–63].

Pathological Prognosis Parameters for Renal Cell Carcinoma

Stage

The role of staging as defined in the AJCC/UICC tumor-lymph node and metastasis (TNM) classification has been well validated and is widely accepted as a key prognostic parameter in RCC. With higher stage, lymph node invasion, and metastasis to other organs, there is a progressively worse prognosis and shorter survival. A key to the TNM classification is the tumor size. Several studies have found that risk of malignancy increases with the size of mass lesions. In an analysis of over 2700 patients undergoing nephrectomy for renal tumors, Frank *et al*. found that, whereas nearly half of all tumors <1 cm were benign, only 6% of those >7 cm were benign. For each 1 cm increase in size, the likelihood of malignancy in renal tumors increased by 17% [64]. In another study, size was shown to

correspond with higher grade such that each 1 cm increase in size increased the likelihood of having a tumor of high grade by 25%. This translated into a 0% incidence of high-grade features in tumors <1 cm to 59% in tumors >7 cm [65].

The current 2017 AJCC TNM staging system remains largely same as the 2010 staging system with only minor changes (Table 4.4) [66]. The word "grossly" was eliminated from the description of renal vein involvement, and "muscle containing" was changed to "segmental veins." In addition, invasion of the pelvicalyceal system was added as T3a disease. While organ confined renal tumors that are >7 cm in size are staged as pT2, these are uncommon in routine practice. Studies have shown large kidney tumors very frequently show extrarenal invasion, usually in the renal sinus, when subjected to careful gross sampling [67, 68]. Invasion into perinephric fat and renal sinus fat is both staged as pT3a. Recent studies, however, suggest that invasion of renal sinus is more ominous prognostically [69, 70].

Table 4.4 Pathology stage of primary renal cell carcinoma (AJCC 2017) [66]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest admission, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2 b	Tumor more than 10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor extends into the renal vein or its segmental branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor extends into the vena cava below the diaphragm
T3c	Tumor extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia including contiguous extension into the ipsilateral adrenal gland
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M1	Distant metastases

WHO/ISUP Nucleolar Grading

The nuclear grading of renal tumors underwent a major change in 2012 when the three-decade old Fuhrman system was replaced by the International Society of Urologic Pathologists (ISUP) grading system [71]. This new grading system selects the most prognostically relevant criterion, nucleolar prominence, out of the three nuclear features used by Fuhrman grading to define grades 1, 2, and 3 (see Table 4.5). Grade 4 tumors still require severe nuclear pleomorphism and/ or sarcomatoid /rhabdoid change to be graded as such in the new ISUP system, similar to in the Fuhrman grading system. This simplified approach also has the advantage of reducing inter-observer variability seen with the Fuhrman system. This new grading system was adopted by the 2016 WHO RCC classification and is often referred to as the WHO/ISUP grading system. Large studies since the initial proposal have validated this grading as superior to Fuhrman grading system for both clear cell [72] and papillary renal cell carcinoma [73]. Previous studies have shown that nuclear grading is not predictive of chromophobe RCC behavior [74]. The WHO/ISUP grading system

Table 4.5 WHO/ISUP nuclear grading system [71]

Grade	Nucleolar features
1	Nucleoli absent or inconspicuous and basophilic at 400× magnification
2	Nucleoli conspicuous and eosinophilic at 400× magnification, visible but not prominent at 100× magnification
3	Nucleoli conspicuous and eosinophilic at 100× magnification
4	Marked nuclear pleomorphism and/or multinucleate giant cells and/or rhabdoid and/ or sarcomatoid differentiation

has yet to be validated for other newly described variants, and there is some suggestion that it may not be as useful in some [75]. In some tumors such as tubulocystic RCC which often have prominent nucleoli, a grading system based on nucleolar prominence may not be applicable.

Sarcomatoid and Rhabdoid Differentiation

Sarcomatoid differentiation is present in about 5% of RCCs and can be observed in any RCC subtype [76]. Therefore, sarcomatoid RCC is not considered a distinct subtype of RCC; rather, it is thought to represent a high-grade and poorly differentiated component.

RCC with sarcomatoid differentiation typically has other adverse pathological features, including large tumor size, extension into perinephric fat and vessels, and presence of hemorrhage and necrosis. It is also significantly associated with an increased likelihood of distant metastasis and cancer-specific death. It is an adverse independent prognostic indicator in both univariate and multivariate analysis [77, 78]. Any RCC with sarcomatoid differentiation is assigned a WHO/ISUP grade 4. A recent large study showed the extent of sarcomatoid differentiation to be an independent prognostic variable on multivariate analysis. Patients with ≥30% of sarcomatoid differentiation in their RCCs were 52% more likely to die from the disease than those with <30% sarcomatoid differentiation [79].

Sarcomatoid components usually appear as bulging, lobulated areas with white to gray, firm and fibrous cut surface within a tumor. Histologically, the sarcomatoid component ranges from malignant spindle cells to occasionally those resembling leiomyosarcoma, fibrosarcoma, angiosarcoma, rhabdomyosarcoma, and other sarcomas. The co-existing RCC component, including clear cell, papillary, chromophobe RCC, and sometimes collecting duct RCC, can often be identified and is used to subtype the RCC with sarcomatoid differentiation. Rarely, such subtyping may not be possible when the sarcomatoid component overruns RCC epithelial components.

Rhabdoid differentiation can be identified in approximately 5% of RCCs with tumor cells having large eccentric nuclei, macronucleoli, and prominent acidophilic globular cytoplasm. The presence of rhabdoid component is also associated with high grade and high stage with frequent extrarenal extension. The rhabdoid foci may account for 5% to 90% of the tumor area. It is a marker of high risk for metastasis and poor prognosis even when the rhabdoid component is limited [61]. A recent study confirmed that rhabdoid differentiation was an adverse prognostic variable independent of tumor grade, stage, and presence of necrosis or metastasis and conferred an increased risk of death (with a hazard ratio of 5.25) [80].

Tumor Necrosis

For CCRCC, tumor necrosis, identified either macroscopically or microscopically, is an adverse pathological factor and is associated with worse clinical outcomes in both uni- and multivariate analysis. Studies from Mayo Clinic clearly showed that histological necrosis is associated with twice the cancer-specific death rate compared to those without necrosis [22]. The presence and extent of histological necrosis in CCRCC are independent predictors of survival in localized but not metastatic cases, although one recent study showed limited prognostic value [81]. Both two outcome prediction models, SSIGN (stage, size, grade, and necrosis) from Mayo Clinic and the postoperative outcome nomogram from Memorial Sloan Kettering Cancer Center, incorporate tumor necrosis in their models [82, 83]. A few studies also report that the proportional extent of necrosis correlates with a worse outcome and cancer-specific death in clear cell RCC [84, 85]. ISUP thus recommends recording the presence and extent of microscopic tumor necrosis [86], and this has been incorporated into the current pathology reporting template. Some recent studies have shown that modifying the WHO/ISUP grading system by incorporating presence and extent of tumor necrosis provides additional prognostic

information compared with grade alone [86, 87]. The data on the prognostic role of tumor necrosis in non-clear cell RCC is limited.

Microvascular Invasion

Microvascular invasion (MVI), defined as neoplastic cells invading the vessel wall or neoplastic emboli in the intratumoral vessel detected microscopically, is present in 13.6–44.6% of RCC. It is more common in RCC of high stage and grade and large size. An important prognostic factor in other malignancies includes liver, testis, bladder, and upper tract urothelial carcinoma the prognostic role of MVI in RCC is however controversial. Unlike macrovascular invasion, presence of MVI does not change the pathologic stage of RCCs. Further studies are needed to better define its prognostic significance. Several studies have demonstrated that MVI may have an independent predictive role for either disease recurrence or cancer-specific mortality after adjusting for other clinical and pathologic covariates [88–90], whereas other studies have not found such prognostic values [91].

Histologic Subtyping in Localized and Metastatic RCC

The issue on prognostic utility of histologic subtypes remains debated with some convinced of the independent prognostic acceptance of subtype, while others are not. However, over the last decades, based on series and cumulative reports on RCC subtypes, the prognostic value of histologic typing of RCC has been widely accepted. In general, chromophobe RCC is considered an indolent, low-stage tumor with low risk of recurrence. Papillary RCC is presented as having a slightly higher risk of recurrence but less than in clear cell type. Additionally, collecting duct renal cell carcinoma is recognized as a highly aggressive tumor with an expectation for a more adverse outcome than CCRCC. It should be mentioned that, while distinct biological differences between histologic types are accepted, proof of prognostic importance is required from evaluation of large cohort studies where other associated clinical data are concurrently examined [92]. Among the newly identified RCC subtypes, some tumors such as HLRCC-associated RCC appear to have aggressive behavior and poor outcomes; the follow-up data is limited.

The biological and genetic differences in RCC types suggest that histologic subtyping has prognostic and therapeutic potential in metastatic RCC. In most studies, metastatic papillary and chromophobe RCC appear to have a worse prognosis as compared to clear cell RCC. In a series of metastatic RCC [93], 64 patients (less than 10%) were non-clear cell type. These were found to be resistant to systemic cytokine and conventional therapy (particularly immunotherapy) and poor survival (overall survival of 9.4 months with 29 months for those with chromophobe, 11 months for those with collecting duct, 5.5 months for those with papillary RCC). In a study on IL-2 evaluating the influence of histologic types on response to treatment, non-clear cell type showed a poor response to therapy [94]. As the treatment of metastatic RCC moves from cytokines to targeted agents that inhibit angiogenic growth factors, the evaluation of histologic type is expected to play an increasingly important role in determination of therapy. Earlier trials restricted treatment with targeted agents to clear cell type; however, subsequent studies have shown response of metastatic papillary or chromophobe RCC to sorafenib or sunitinib [95]. A recent systematic review and meta-analysis of the literature on targeted therapy approved for CCRCC in non-clear cell RCC showed significantly lower response rates and poorer progression-free survival and overall survival than in CCRCC [96]. Further studies are awaited to determine most appropriate therapeutic strategy related to histologic types. Prospective controlled studies may enable data for predictive models to incorporate histologic type in nomograms for treatment of metastatic disease.

Each histologic type of RCC shows differences in pathologic and clinical parameters including prognostic relevance; however, the extent of type in outcome prediction remains

controversial. Most studies show relevance for outcome of each histologic type when correlated with survival by univariate analysis; however, only few studies are able to show differences in outcome once other key prognostic attributes such as stage and grade are taken into account (using multivariate analysis). These studies with disparate results highlight the challenges to prove outcome relevance, such as the requirement for large cohort size to allow sufficient statistical strength and the importance of standardized pathology review, often missing in pooled multi-institution datasets. Evidence of this is seen in single institution large cohort series which have shown independent value of subtypes, while pooled studies have not. As greater knowledge is gleaned on RCC, newer entities are emerging which may shift distribution of cases, such as from papillary RCC and unclassified RCC to other subtypes, potentially strengthening the prognostic value in separation of entities. Despite the contested independent value of subtype for outcome prediction, separation of RCC into subtypes is well accepted and substantiated on clinical, biological, and molecular differences [92].

Summary

Renal cell carcinoma encompasses a group of heterogeneous tumors with diverse clinical, pathological, and molecular characteristics as well as distinct prognosis and therapeutic responses. The current 2016 WHO classification is based primarily on morphology, but genetic features of renal tumors have been increasingly incorporated into the classification scheme**.** Many histological parameters obtained from routine pathological examination of renal tumor provide invaluable prognostic values. The clinical, pathological, and genetic features in combination will eventually enable urologists to predict individual tumor behavior and stratify patients into more sophisticated risk groups, ultimately rendering individualized management and treatment options.

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Imaging of Renal Cancer

5

Jalil Afnan, Jaclyn A. Therrien, and Christoph Wald

Renal Imaging

The most recent data for adult renal cancer estimate around 65,000 new cases of renal cancer annually within the United States in 2018, with a 2:1 male to female predominance and nearly 15,000 associated annual deaths [1]. The predominant type, renal cell carcinoma (RCC) usually clear cell type, is associated with multifactorial etiologies [2, 3], and incidence continues to rise at least in part due to increase in overall imaging utilization in the US and elsewhere, which has been observed in the inpatient as well as outpatient setting [4, 5]. Consensus guidelines for further evaluation of incidentally identified renal lesions have been updated, recommending use of multiphasic CT or MRI to further characterize [6]. Despite earlier reports of approximately 50% mortality at 5 years, the larger number of cancers detected at an earlier stage and often organ-confined disease is leading to a more favorable overall prognosis [7] most likely associated with a lead time bias, permitting earlier and possibly definitive treatment.

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Renal cancer is detected either during the evaluation of genitourinary tract-related symptoms such as flank pain and hematuria, or during workup of unrelated medical issues for a variety of abdomino-pelvic conditions or, for instance, during colon cancer screening with CT colonography. It should be noted that many computed tomography (CT) examinations of the chest may include at least a portion of the kidneys. Therefore, future potential risk population screening for lung cancer may lead to a further increase in incidental renal cancer discovery. Certain groups of patients, such as those with Von Hippel Lindau (VHL) and other hereditary renal cancer syndromes, may undergo active surveillance [8].

A variety of imaging techniques and modalities are at the clinician's disposal, to appropriately characterize and stage a renal tumor and subsequently use in disease surveillance. These range from basic grayscale ultrasound to advanced cross-sectional imaging, including CT and Magnetic Resonance Tomography imaging (MRI). The various modalities will be considered, together with the refinements necessary to maximize their respective strengths. Imaging may also play a central role in the treatment of renal cancer, high-intensity-focused ultrasound ablation (HIFU) [9, 10], and image-guided percutaneous ablation [11, 12]. These techniques and the functional radionuclide analyses will be reviewed separately.

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Intravenous Pyelogram (IVP)

Intravenous pyelography, or excretory urography, is a noninvasive, sequential fluoroscopic evaluation of the kidneys, ureters, and urinary bladder before and after administration of iodinated contrast. An initial X-Ray may identify an area of increased density, a density (mass) with irregular margins, or calcifications, which is intrinsic to the kidneys or resulting in local mass effect (Fig. 5.1).

However, soft tissue contrast resolution of plain radiography and fluoroscopy are limited and the resulting images are a two-dimensional representation of a three-dimensional object inherently subject to superimposition of anatomical structures interfering with detection and precise localization of structures of interest. Following administration of an intravenous contrast agent, usually an iodine-based dye, additional serial X-Rays are used to evaluate the same structures during excretory phase imaging (Fig. 5.2).

Sometimes, conventional tomography is employed to focus the examination on intrinsic abnormalities of the collecting system or portions of the bladder. As a result of these limitations, IVP is of limited value in context of renal cancer detection (especially of early stage, treatable disease), which is reflected in the low reported sensitivity and specificity of 60% and 48%, respectively [13]. As such, in current practice, an IVP alone cannot be considered sufficient for renal mass evaluation and will likely be complemented by an ultrasound or dedicated cross-sectional imaging. Even in terms of evaluating

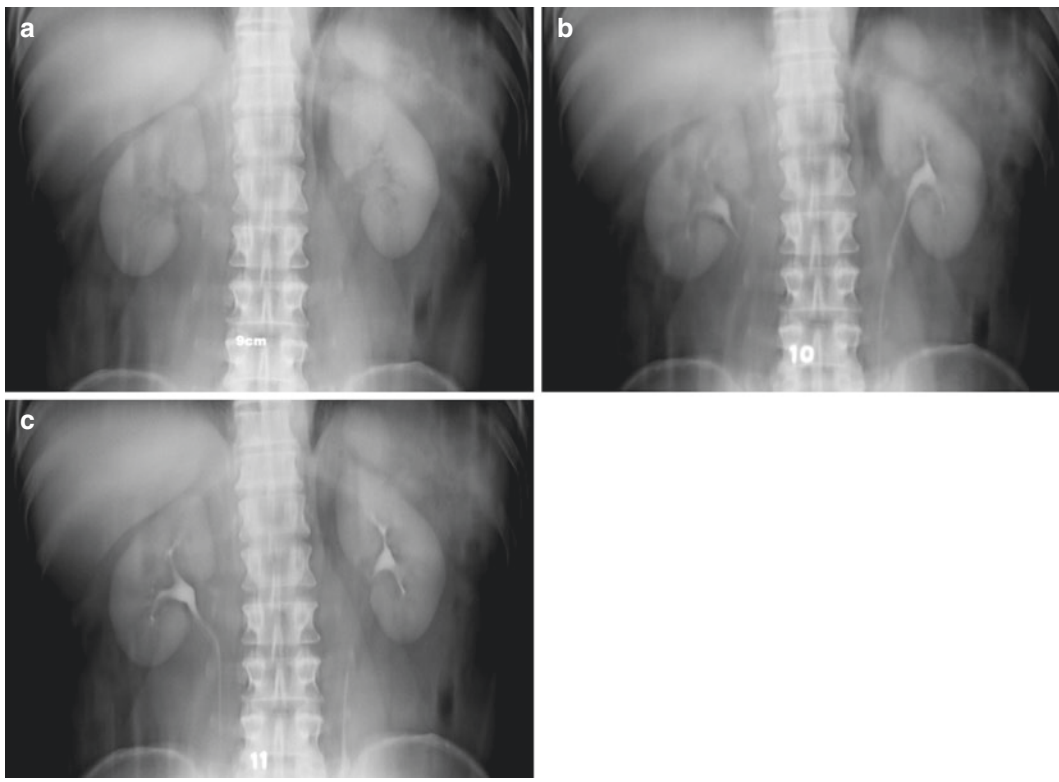


Fig. 5.1 Sequential frontal abdominal radiographs from an Intravenous Pyelogram (IVP), performed for hematuria, with no apparent abnormalities. Blurring of adjacent intra-abdominal structures while keeping the collecting system in focus is deliberately achieved with controlled tube-table translation during image acquisition. Distinct phases of contrast excretion typically evaluated are renal cortical phase (**a**) and calyceal opacification with early (**b**) and excretory phase (**c**)

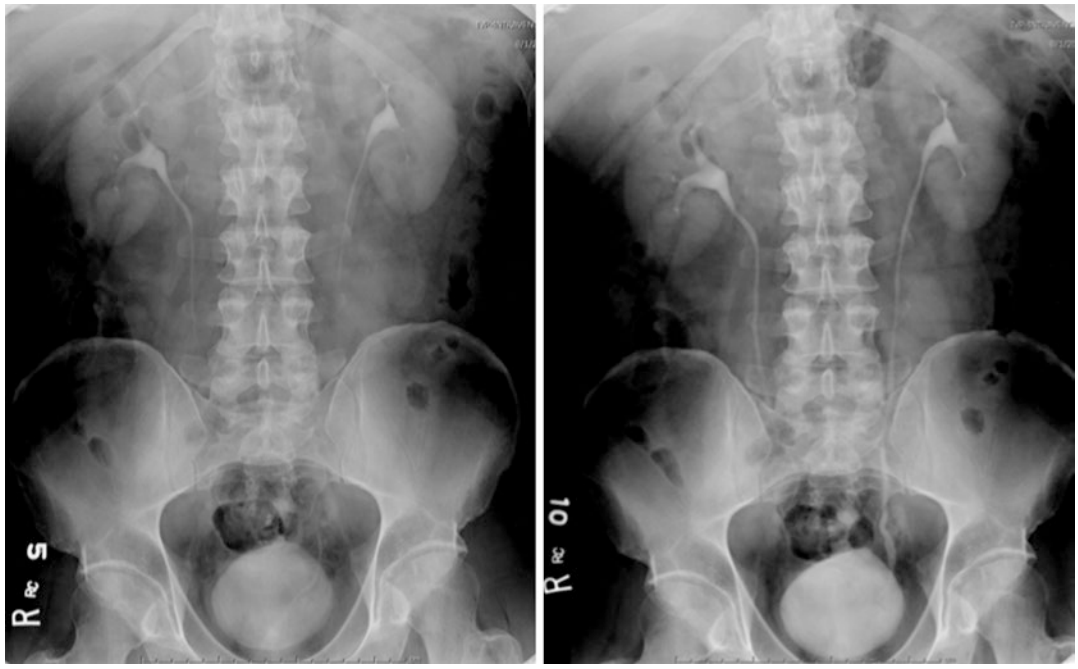


Fig. 5.2 KUB images in late excretory phase, to further delineate the ureters and bladder. Prone imaging may be helpful to show ureters to advantage. Post-micturition images are subsequently acquired

renal function and further characterizing the renal tract, CT or MR urography, or radionuclide-based tests are now more commonly performed in most practices. Finally, the use of ionizing radiation, albeit at low dose, and the use of an intravenous contrast agent are additional considerations when utilizing this test.

Ultrasound (US)

Since its introduction into the medical arena in the 1950s, ultrasound has distinguished itself as a readily available, cost-effective imaging modality relying on the differential penetrance and reflectivity of sound waves and notably being performed without the use of ionizing radiation. Ultrasonic waves are generated by mechanical oscillation of certain crystals and ceramics, typically generating frequencies in the range of 2–15 MHz. The ultrasound beam is focused either mechanically or electronically. The ultrasound wave is subjected to attenuation, reflection, scattering, refraction, and diffraction within human tissues due to the inherent differences in the acoustic impedance of the tissue components. Analysis of the reflected wave generates a predictable 2D or 3D grayscale image with information about the constituent elements of a lesion, its distance from the transducer, and degree of vascularity if Doppler is utilized (Fig. 5.3).

Certain processing techniques, such as harmonic imaging, may be employed to reduce background echoes, which can be helpful, for instance, when attempting to clarify borderline echogenic signal within a suspected (simple) cyst.

Ultrasound readily differentiates cystic from solid lesions, often the first step in assessing whether a renal lesion is likely benign or malignant. A typical benign renal cystic lesion is well-circumscribed and anechoic on US. The back wall of the lesion should appear sharp and smooth, and positive ‘through transmission’ or un-attenuated ultrasound waves should be observed beyond the lesion, from which the simple nature of the fluid within the lesion is inferred (Fig. 5.4).

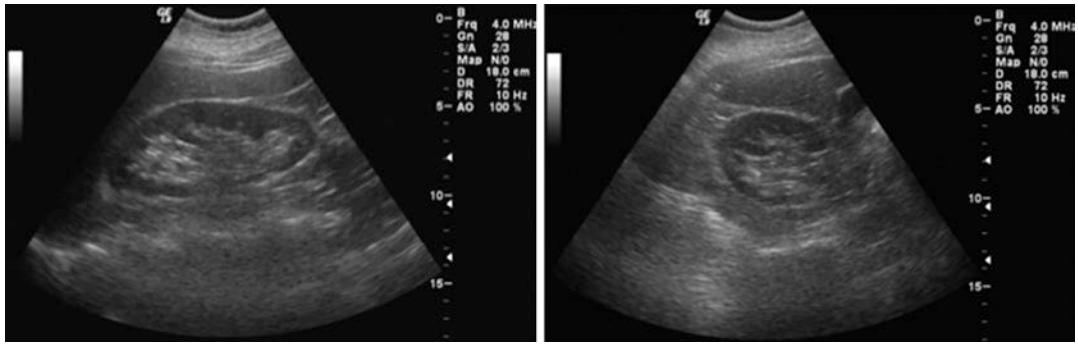


Fig. 5.3 Normal ultrasound images of the kidney, in sagittal and transverse planes. Grayscale ultrasound images were acquired with a 4.0 MHz curvilinear probe and demonstrate typical central echogenic structures of the renal sinus, and overlying hypoechoic, cortex

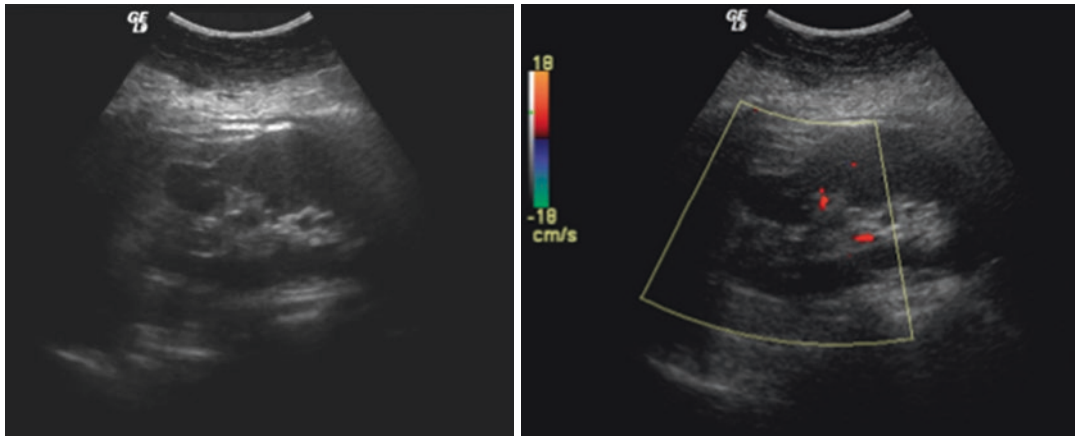


Fig. 5.4 Well-circumscribed, partially exophytic, anechoic, and thin-walled cortical cyst evident on grayscale ultrasound image on the left. Color Doppler evaluation (inside yellow-framed region of interest) confirms absence of abnormal blood flow in the cyst; findings are typical for simple renal cortical cyst

Complex features include debris indicative of proteinaceous content or prior hemorrhage and necrosis, thickened irregular septations, soft tissue mural nodularity, and the presence of calcifications (Fig. 5.5).

Renal cell carcinoma (RCC) may exhibit a variety of characteristics on grayscale ultrasound, usually hyperechoic or isoechoic to surrounding renal cortex with a hypoechoic rim or pseudocapsule. It is typically hypervascular around the periphery of the mass, although papillary type RCC is hypovascular and less locally invasive. Color Doppler may also evaluate renal vein and IVC patency, or the presence of tumor thrombus. Larger lesions often exhibit hypoechoic areas of central necrosis on ultrasound. Although renal cell carcinoma may be fat-containing, a typical solid, fat-containing renal mass is most likely a benign angiomyolipoma. Occasionally, renal carcinomas can exhibit predominantly cystic features [14] (Fig. 5.6).

Recent studies have matched ultrasound against CT and MRI in the evaluation of renal masses prior to surgical resection and found it to be equivalent in determining tumor size [15]. In another study of the ultrasound features of renal tumors, with the use of ultrasound contrast agents, it was possible to distinguish between clear cell

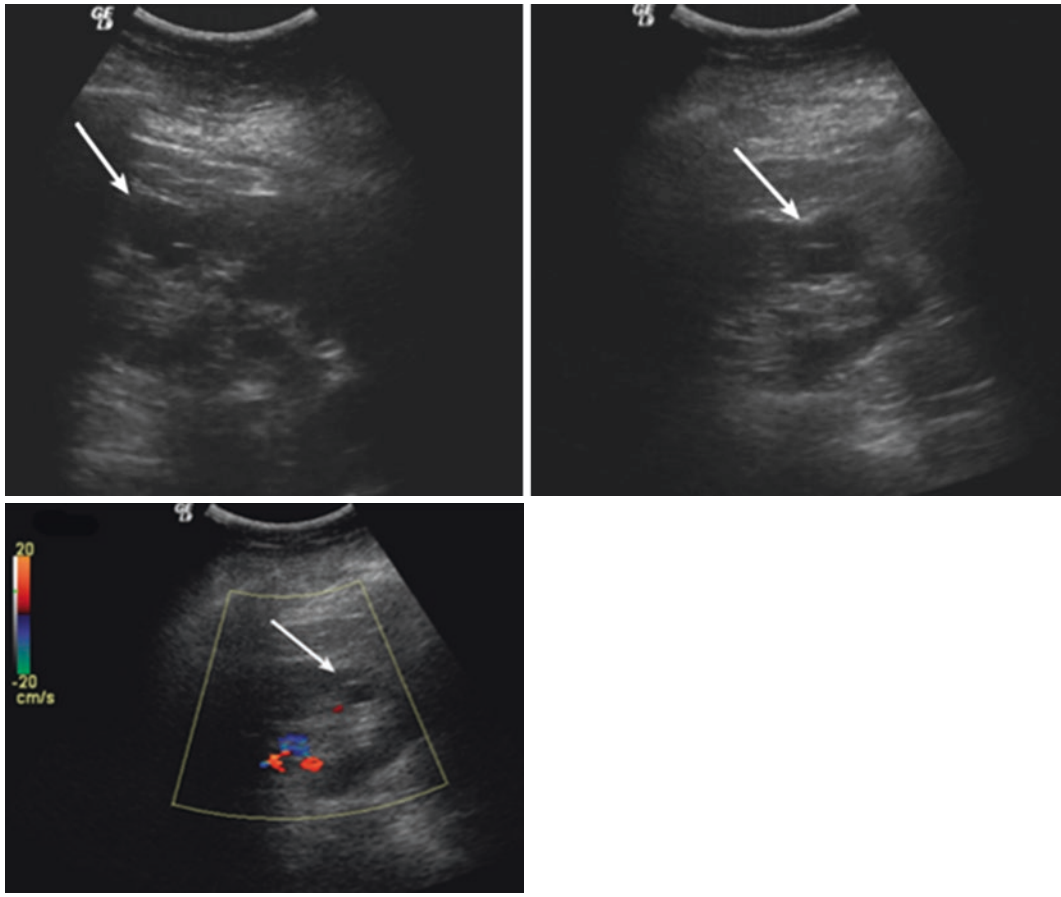


Fig. 5.5 Grayscale ultrasound images demonstrate a predominantly hypoechoic renal cortical lesion, containing a well-defined linear echogenic septation. There is no evidence of vascular flow within the septation, and no associated soft tissue mass or mural nodule. Findings are consistent with a minimally complex, septated cyst

carcinoma and non-clear cell renal tumors, based on grayscale heterogeneity, lesion washout, grade of contrast enhancement, and quantitative measure of peak intensity [16]. The utility of contrast-enhanced ultrasound (CEUS), employing injected intravascular microbubbles, may be an accurate diagnostic test for patients with chronic renal impairment in whom intravenous contrast is contraindicated [17]. In addition to sonographic evaluation of the lesion, CEUS permits vascular architectural analysis and multiphasic analysis of contrast enhancement and washout. A sensitivity of 96% and specificity of 50% have been demonstrated for malignancy in patients with normal renal function. The sensitivity, although slightly reduced in patients with chronic renal impairment, remains high at 90%, with a similar sensitivity of 55% [18].

Small renal lesions defined as geographic and less than 3 cm in size are more difficult to identify and characterize by ultrasound, with an approximate sensitivity of 79% [19]. The majority of such small renal masses are statistically likely to be benign [20]. Furthermore, analysis of a large prospectively collected population-based registry identified that small renal cell cancer less than 3 cm is likely to be an organ-confined disease with a limited malignant potential around 5% [21].

Although ultrasound may identify a variety of specific morphologic characteristics to aid

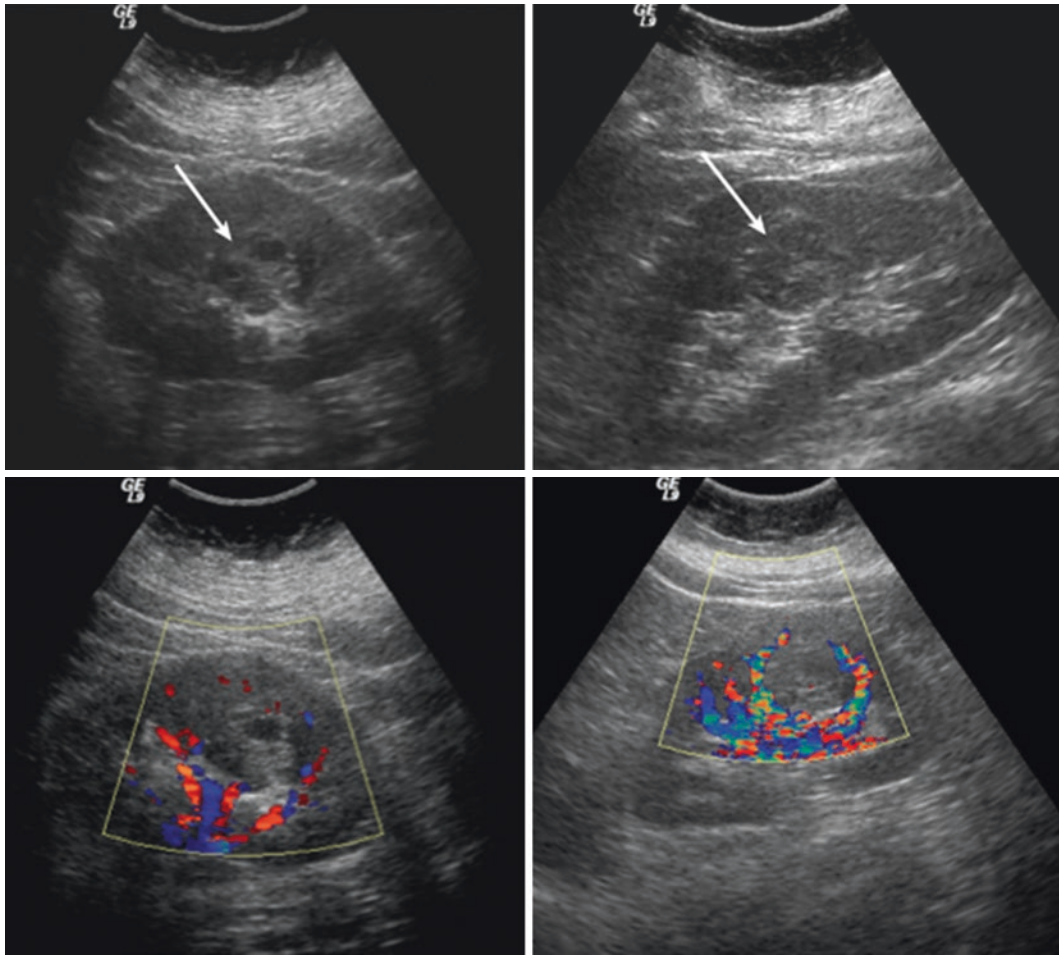


Fig. 5.6 Well-circumscribed mass of heterogeneous echogenicity is centered in the renal cortex. Trace vascular flow is seen on color Doppler images. Findings are consistent with a complex renal mass; multiphasic cross-sectional imaging would typically be recommended for further evaluation

diagnosis, it is incapable of categorizing tumor biology that may ultimately play a more significant role in predicting disease progression.

Ultrasound is also utilized to guide local thermal coagulation and cryoablation of renal lesions, both techniques requiring percutaneous puncture and direct placement of probes within the target tumor. A separate role for high-intensity focused ultrasound (HIFU) is well-described, whereby energy absorbed by biologic tissue in the path of a wave of ultrasound energy, focused on a specific location, results in temperatures exceeding the threshold level of protein denaturation, effecting coagulative necrosis [22]. The intraoperative use of ultrasound to assist with the guidance of nephron-sparing partial nephrectomy has become standard of care at Lahey Hospital and Medical Center and many other institutions (Fig. 5.7).

Ultrasound is, therefore, most commonly utilized as a screening tool for RCC, to document stability of known lesions over time and may be considered for ongoing surveillance following tumor resection. If a lesion is identified, initial further characterization and staging of disease by contrast-enhanced multiphasic cross-sectional imaging with either CT or MRI is recommended.

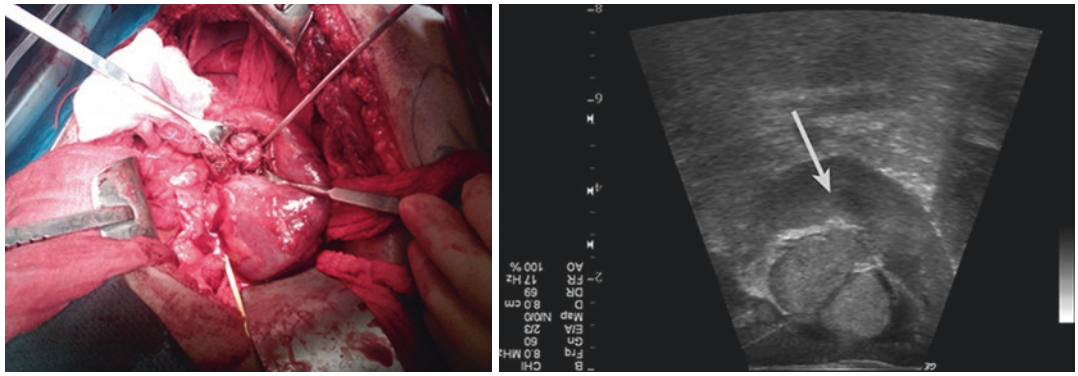


Fig. 5.7 Intraoperative photograph on the left, demonstrating open, partial nephrectomy for renal mass within the upper pole of the kidney. Intraoperative real-time ultrasound image on the right is used routinely to identify tumor and evaluate extent of local invasion during nephron-sparing surgery

Computed Tomography (CT)

It is estimated that, in 13–27% of abdominal imaging studies, at least one renal lesion is identified incidentally, unrelated to the patient's presenting illness or the known medical history [23, 24]. Furthermore, it is estimated that more than half of patients over 50 years of age will have at least one renal mass [23]. Since CT has become a widely utilized means of urgent assessment of abdominal and pelvic conditions, as well as a screening tool for colon cancer and lately lung cancer, many renal tumors will, therefore, come to light as an incidental finding during the evaluation of a separate clinical issue. Such incidental findings invariably present a diagnostic dilemma, not least because the findings are rarely found on studies with protocols optimized for evaluation of a renal mass. Furthermore, the clinical relevance of any asymptomatic, incidental small renal mass must be critically considered in the global clinical context for a given patient to temper any potential downstream diagnostic or therapeutic activity. Indeed, evidence that many incidentally identified renal masses, whether cystic or solid, are benign has emerged [25]. Guidelines are, therefore, necessary to strengthen confidence in identification of features concerning for a malignant versus benign process [6].

An optimized renal CT study is a multiphasic examination of the abdomen and pelvis, utilizing a precontrast and at least one postcontrast phase, often during the excretory or nephrogenic phase (80–100 seconds post-injection). An arterial phase (between 20 and30 seconds) may be considered, although this is usually not necessary to make a diagnosis of a renal mass, but rather aids depiction of the renal vasculature (Fig. 5.8a, b).

Thin section axial imaging sufficient to discriminate between lesions less than 3 mm in size should be employed on a multidetector CT, equipped to modulate patient dose and better, yet, capable of acquiring low-dose images of quality comparable to full-dose images through use of newer iterative image reconstruction techniques. Low KV imaging should also be considered in follow-up CT studies when a lesion has already been characterized. Studies have demonstrated that 1 mm thick axial images in multiphase acquisition have the capability of diagnosing stage I renal cell cancer with 96% sensitivity and 93% specificity in detection of perirenal fat infiltration, with 100% positive predictive value [26] (Figs. 5.9, 5.10a, b, and 5.11).

However, the benefit of multiphasic imaging data (requiring multiple imaging acquisitions) should be weighed against the associated increase in radiation dose to the patient. Post-processing technology should be available to construct dedicated 3-D models of the kidneys, identify tumor foci, and further characterize the renal hilar vasculature. Although not essential to diagnosis, additional information is provided for treatment planning, including operative approach. To

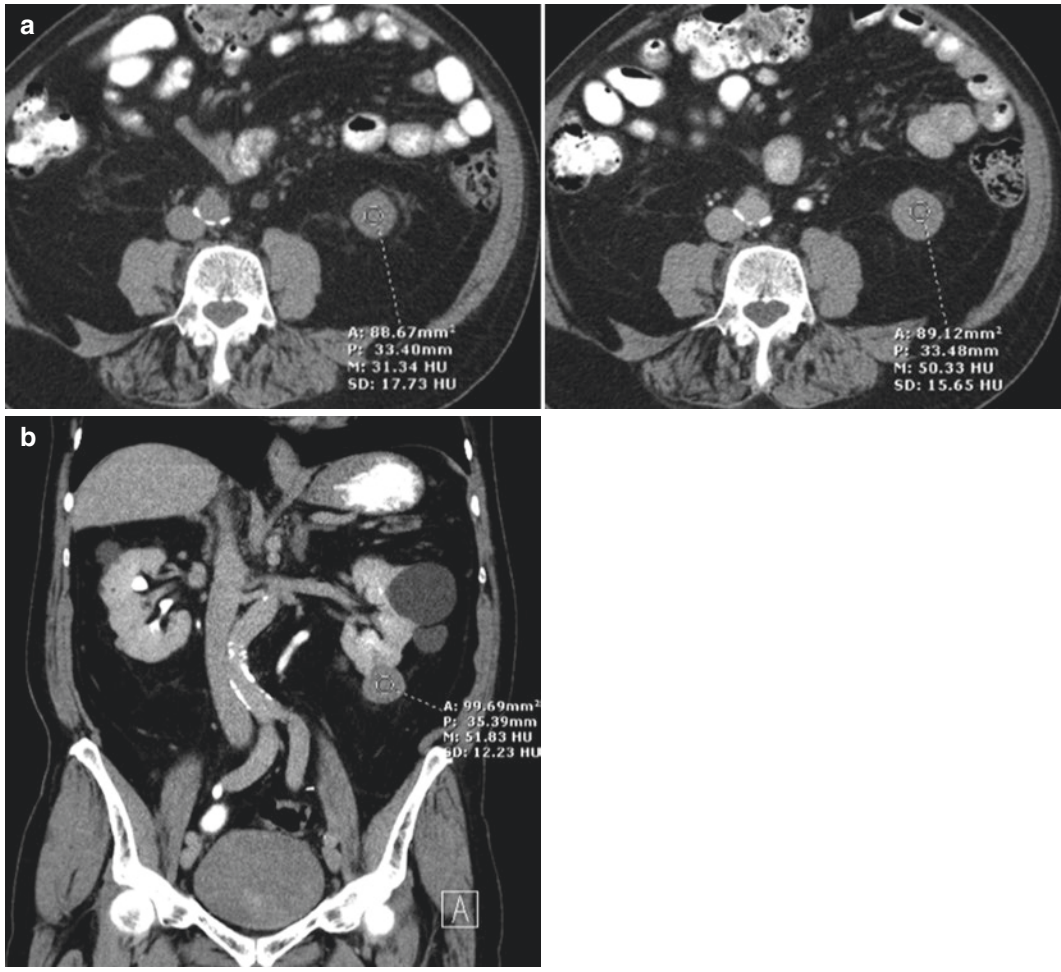


Fig. 5.8 (**a**) Precontrast and nephrogenic phase axial CT images of the left renal lower pole, demonstrate moderately enhancing lesion, quantified in Hounsfield units (HU), evaluated by manually placing a region of interest (ROI) on the target. Mean HU increased from 31 to 50, suspicious for neoplasm. (**b**) Coronal reformat from the same study, in nephrogenic phase, re-demonstrates the exophytic, well-circumscribed left lower pole mass, 51 HU. Incidental note of several benign appearing, non-enhancing upper pole renal cortical cysts

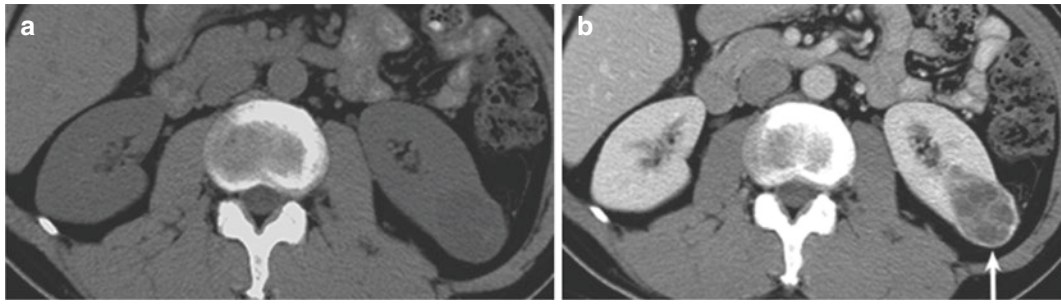
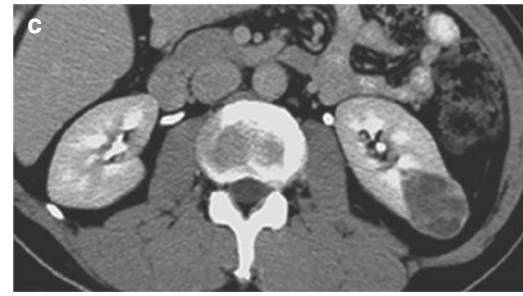


Fig. 5.9 Multiphasic CT study demonstrates precontrast (**a**), arterial phase (**b**) and nephrogenic phase (**c**) axial images of a well-circumscribed, exophytic renal cortical mass in the posterior left kidney. Septations seen on precontrast imaging demonstrate enhancement, a suspicious feature. The mass corresponded to a clear cell type renal cell carcinoma

Fig. 5.9 (continued)



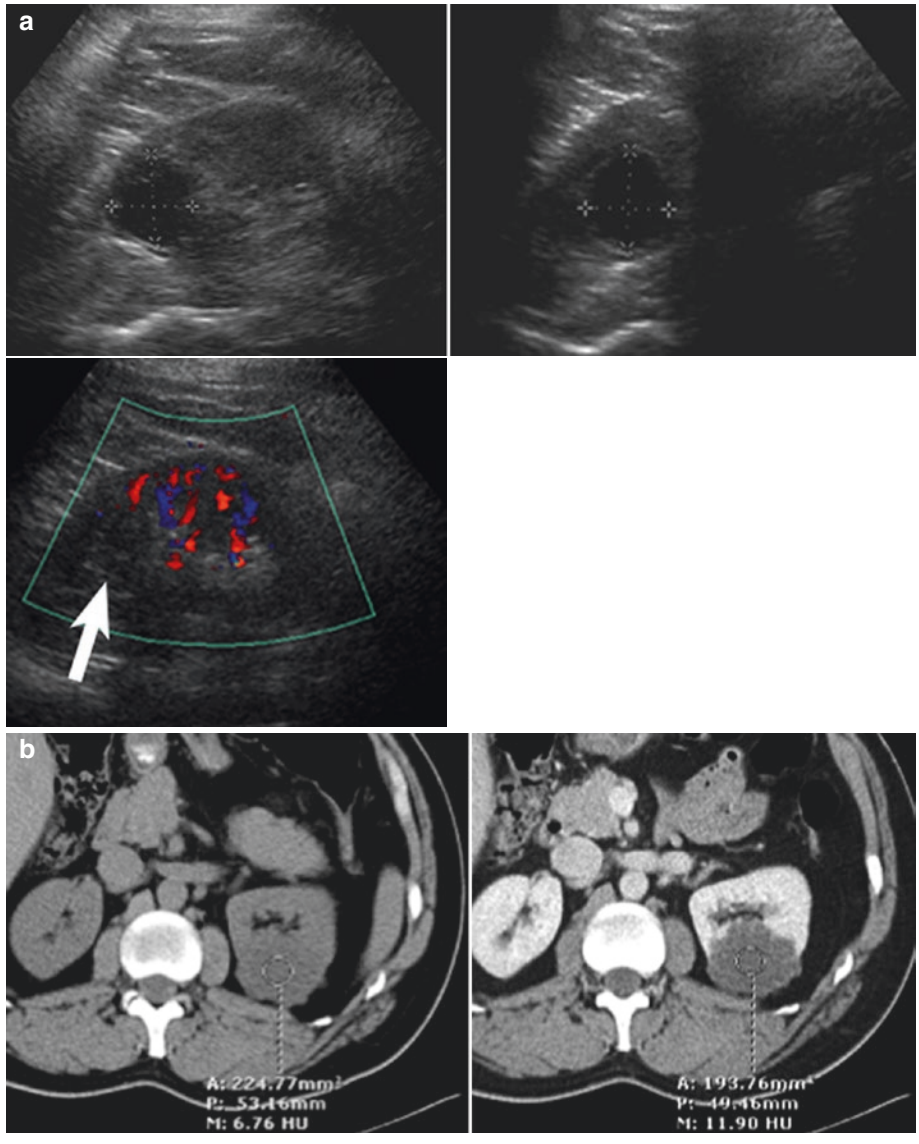


Fig. 5.10 (**a**) Grayscale ultrasound images in sagittal and transverse planes, of the left kidney, demonstrate a well-circumscribed, hypoechoic cortical lesion, no apparent vascularity. (**b**) Precontrast and late arterial phase axial CT image demonstrates a lobulated, hypodense lesion in the left posterior interpolar region, without significant enhancement (6 HU to 12 HU). The lesion was resected due to associated hematuria and pain; pathology demonstrated a renal cell carcinoma, clear cell type. Imaging features are atypical

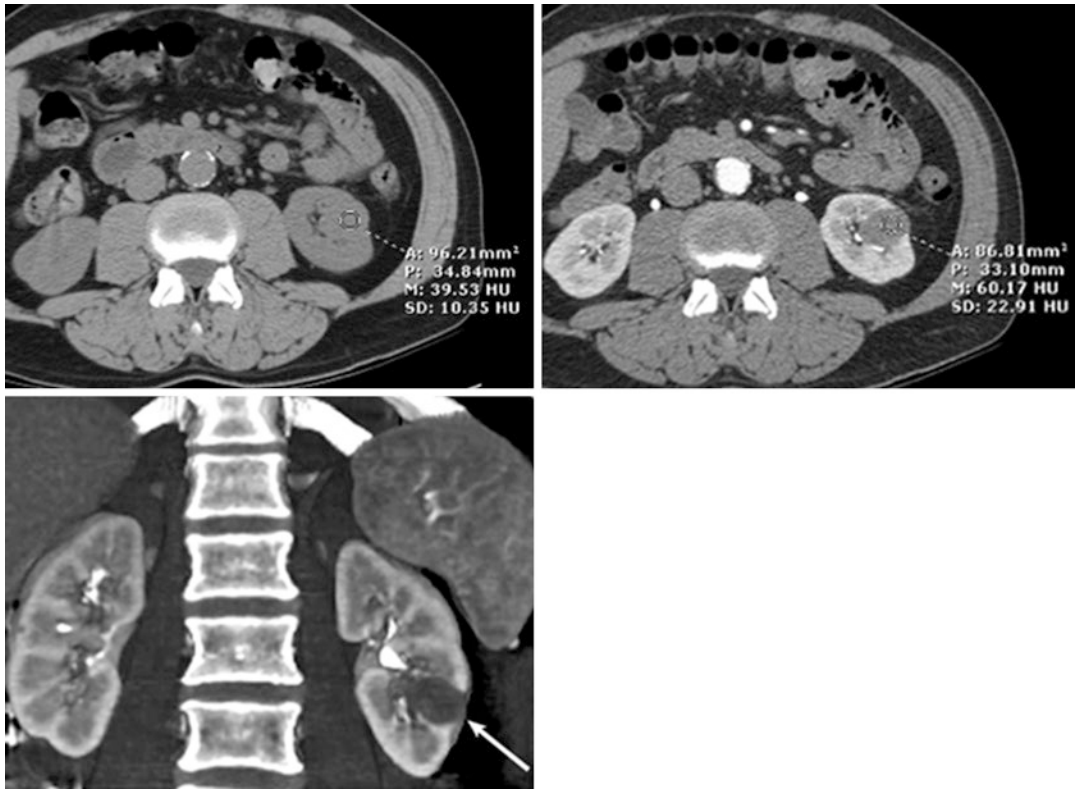


Fig. 5.11 Precontrast (left), nephrogenic phase (middle) and coronal reformat (right) demonstrate a hypodense, enhancing cortical lesion, abutting the collecting system. Significant differential enhancement of 21 HU is noted; pathology confirmed renal cell carcinoma, papillary type

complete disease staging, a CT scan of the chest and contrast-enhanced MRI of the brain may each be considered (Figs. 5.12, 5.13 and 5.14).

Staging for renal cell cancer was first introduced in 1958 [27] and revised in 1963 [28]. Following the introduction of the TNM system in 1978, and its subsequent iterations, the most recent American Joint Committee on Cancer (AJCC) guidelines on renal cancer staging from 2010 incorporate recent advances in survival characteristics between different groups. The framework allows for standardization of treatment, appropriate inclusion into research trials, and utilization of experimental therapies and provides more accurate prognostic indicators, all of which depend upon imaging.

The relative radiodensity of a region of interest on a CT image is defined according to the Hounsfield reference scale that measures the linear attenuation coefficient against that of water. Fluid and solid tissue are, therefore, given a relative positive numerical designation; fat and air are defined with relative negative values. The majority of adult renal cancers appear as a solid, enhancing, cortically based mass. An increase of at least 15 Hounsfield units (HU) measured within a representative region of interest (ROI) represents significant enhancement on a CT scan [29]. Enhancement of less than 10 HU strongly suggests a benign process, well-established criteria [30].

On precontrast imaging, and also on ultrasound, a simple cystic renal lesion, which is almost certainly benign, will demonstrate simple fluid density, Hounsfield units between 0 and 20, the upper end of this spectrum indicating proteinaceous or possibly hemorrhagic content. Cystic lesions are well-characterized by the eponymous Bosniak classification system, which has evolved particularly in the categorization of complex

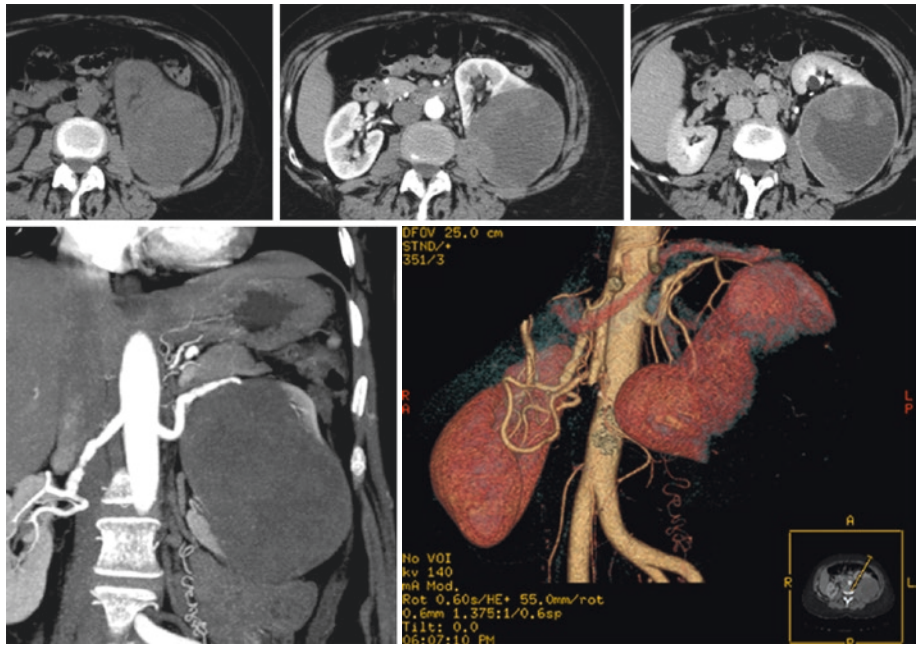


Fig. 5.12 Multiphasic axial CT images in precontrast (upper left), arterial (upper middle), and nephrogenic phases (upper right), demonstrate a large, heterogeneous mass arising from the left kidney, centrally cystic and peripherally nodular in appearance. Coronal reformat (lower left), and volume-rendered subtracted image (lower right) provide further information about the blood supply

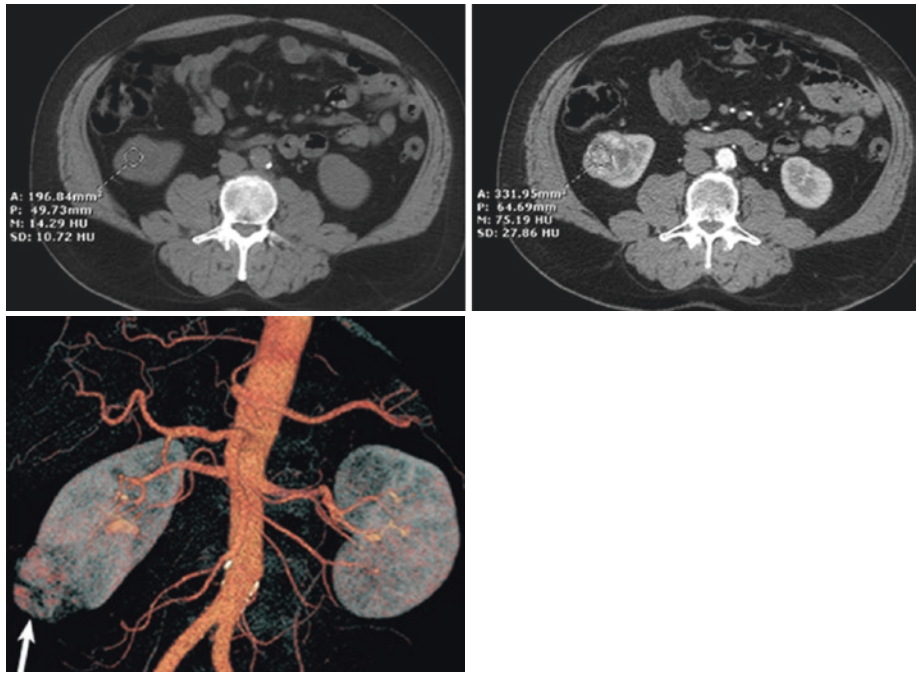


Fig. 5.13 Precontrast (left) and arterial phase (middle) CT images demonstrate a heterogeneous, right lower pole cortical tumor with avid enhancement of 61 HU. The tumor and vascular supply are well-demonstrated on the volume-rendered subtracted image (right), useful for operative planning

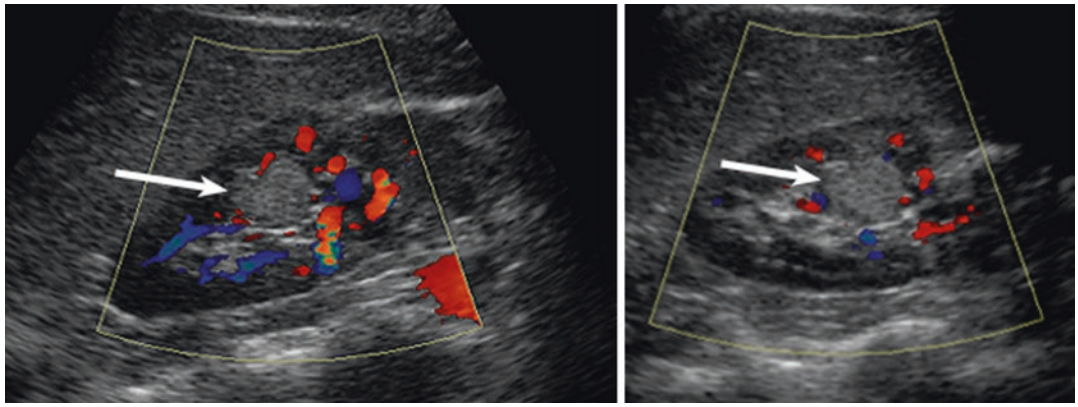


Fig. 5.14 Sagittal and transverse ultrasound images of the right kidney, with superimposed Doppler, demonstrate a well-circumscribed, heterogeneous slightly hyperchoic lesion. There is no significant vascularity

Table 5.1 The Bosniak Renal Cyst Classification. A classification system used worldwide, to evaluate and categorize cystic renal masses into one of five groups. It is not a pathological classification system, rather an imaging and clinical management system

Category	Criteria and management
I	A benign simple cyst with a hairline-thin wall that does not contain septa, calcifications, or solid components; it has water attenuation and does not enhance; no intervention is needed
II	A benign cystic lesion that may contain a few hairline-thin septa in which perceived (not measurable) enhancement may be appreciated; fine calcification or a short segment of slightly thickened calcification may be present in the wall or septa; uniformly high-attenuating lesions (<3 cm) that are sharply marginated and do not enhance are included in this group; no intervention is needed[a]
IIF[b]	Cysts may contain multiple hairline-thin septa; perceived (not measurable) enhancement of a hairline-thin smooth septum or wall can be identified; there may be minimal thickening of wall or septa, which may contain calcification that may be thick and nodular, but no measurable contrast enhancement is present [45]; there are no enhancing soft-tissue components; totally intrarenal nonenhancing high-attenuating renal lesions (>3 cm) are also included in this category; these lesions are generally well marginated; they are thought to be benign but need follow-up to prove their benignity by showing stability [46][a]
III	Cystic masses with thickened irregular or smooth walls or septa in which measurable enhancement is present; these masses need surgical intervention in most cases, as neoplasm cannot be excluded; this category includes complicated hemorrhagic or infected cysts, multilocular cystic nephroma, and cystic neoplasms; these lesions need histologic diagnosis, as even gross observation by the urologist at surgery or the pathologist at gross pathologic evaluation is frequently indeterminate
IV	Clearly malignant cystic masses that can have all of the criteria of category III but also contain distinct enhancing soft-tissue components independent of the wall or septa; these masses are clearly malignant and need to be removed

Adapted from [59]

[a]Perceived enhancement refers to enhancement of hairline-thin or minimally thickened walls or septa that can be visually appreciated when comparing unenhanced and contrast-enhanced CT images side-by-side and on subtracted MR imaging datasets. This "enhancement" occurs in hairline-thin or smooth minimally thickened septa/walls and, therefore, cannot be measured or quantified. The authors believe tiny capillaries supply blood (and contrast material) to these septa/walls, which are appreciated because of higher doses of intravenous contrast material and thinner CT and MR imaging sections

[b]"F" indicates follow-up needed

lesions, in large part due to outcomes since its initial introduction in 1986 [31, 32]. A recent systematic review demonstrated the Bosniak classification system to retain a high level of accuracy and efficacy for grading complex lesions (Bosniak class II, IIF and IV), while suggesting that intermediate Bosniak class III cystic lesions may be overcalled and thus overtreated [33] (Table 5.1).

Although definitive subtyping of renal cell cancer is not currently achievable by CT, certain characteristic features may be exhibited. Clear cell type tends to enhance, avidly and heterogeneously,

typically an increase of more than 80 HU on post-contrast imaging, differentiating this from non-clear cell type renal cell cancer, with a sensitivity of 74% and specificity of 100% [34]. Homogeneous enhancement and lower tumor to parenchyma enhancement ratio is noted in non-papillary type renal cell carcinoma, particularly in smaller tumors less than 3 cm [35].

Additional features include a peripheral enhancement pattern and decreased vascularity that have been noted in chromophobe tumors, although these characteristics are not always seen. Medullary renal cell cancer is usually central in location and exhibits a variable enhancement pattern, but is seen in young patients with concomitant sickle cell disease. Oncocytomas, although benign, cannot be readily differentiated from chromophobe renal cell cancer, or necrotic clear cell tumors, the latter subtype mimicking the central scar sometimes associated with oncocytomas. Treatment is thus usually surgical (Fig. 5.15).

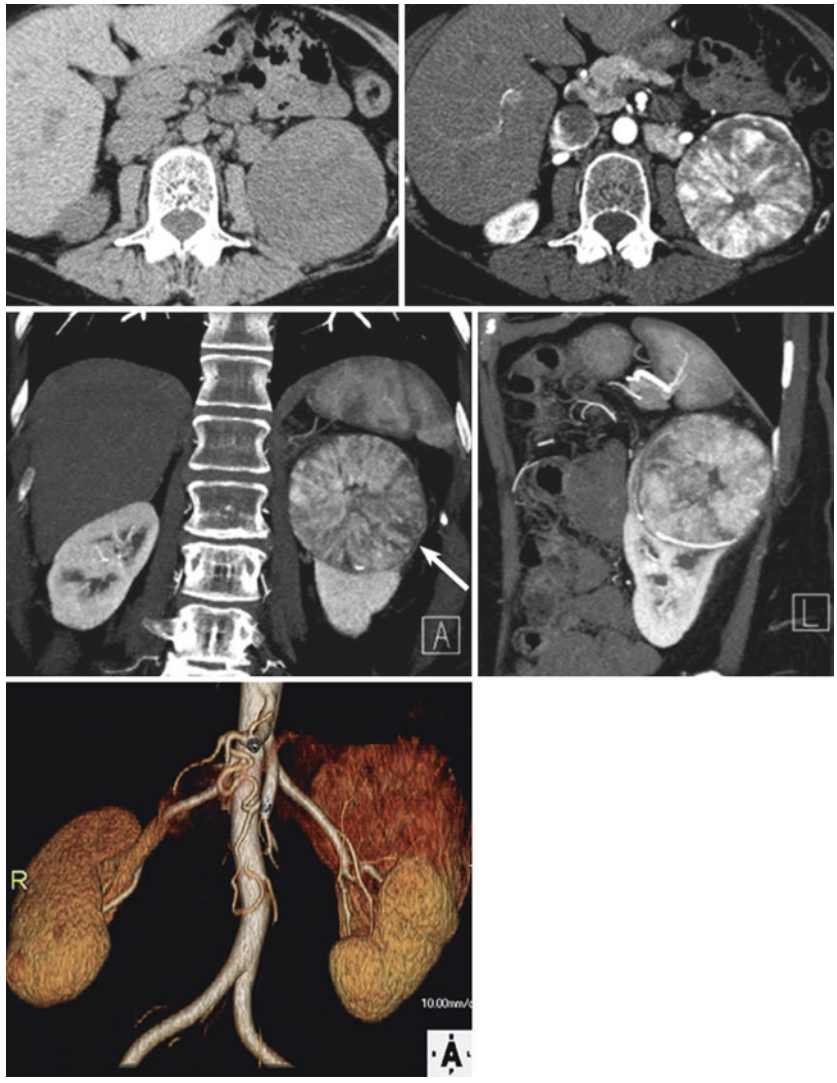


Fig. 5.15 Multiphasic axial CT images, including pre-contrast (upper left), arterial phase (upper right), coronal and sagittal reformatted images (middle row), demonstrate a large, heterogeneously enhancing mass in the upper pole of the left kidney. There is a "spokewheel" pattern noted on axial imaging. Imaging findings are typical for oncocytoma, a benign solid renal tumor, confirmed by pathology. However, this diagnosis is often rendered at time of surgery due to the common close resemblance of oncocytoma and renal carcinoma

A greater awareness of radiation dose associated with CT is reflected in the principles of ALARA enshrined in the American College of Radiology Appropriateness Criteria ensure minimum standards are established at all accredited imaging centers. Technical and hardware advances drive lower CT radiation dose, including dose modulation, lower tube current, and individualization of the kilovoltage to patient body habitus, all of which afford significantly lower doses of radiation administered with CT studies and the possibility of more focused examinations of the upper abdomen with decreased dose in follow-up studies. Furthermore, evolving hybrid (HIR) and model-based iterative reconstruction (MIR) algorithms have been established, in contrast to earlier adaptive statistical iterative reconstruction (ASIR) algorithms that permit lower radiation doses without sacrificing image quality. Finally, recent developments in dual-energy CT, which utilize different methodologies to generate low- and high-energy spectra, have demonstrated the potential to improve renal lesion and calcification characterization [36]. CT remains a mainstay of imaging in both the elective and emergent settings, generating images of high quality that guide diagnosis, therapy, and surveillance.

Posttreatment imaging remains an integral component of surveillance due to the risk of local or metastatic recurrent disease. The highest recurrence rate occurs in those with an initial tumor greater than 5 cm in size, higher Fuhrman grade, and stage at presentation. T1 tumors recur between 38 and 45 months, while T3 tumors recur between 17 and 28 months following initial nephrectomy [37]. Metastatic recurrence correlates directly with tumor stage and has been reported as 7.1% in stage T1 disease, 26.5% in stage T2 disease, and 39.4% in stage T3 disease [38]. Although the recurrence rate is close to 85% within the first three postoperative years, recurrence continues to occur up to and beyond 10 years posttreatment [39]. Although some variability in surveillance guidelines for metastatic disease exists [40], imaging is suggested at 6-month intervals for the first 3 years, followed by annual surveillance [41]. Recurrent renal cell carcinoma is typically seen as hypervascular lesions within the lung, liver, bone, and brain and is more commonly multifocal [42]. Surveillance strategies following surgery are considered in more detail in another chapter (Fig. 5.16).

Thermal ablation with either radiofrequency ablation (RFA) or cryoablation is an alternative treatment to partial nephrectomy in a patient population with comorbid conditions that preclude surgery, or in those who elect to undergo a minimally invasive procedure [42]. It is of paramount importance to correctly interpret the images of a renal tumor that has been subjected to thermal ablation and recognize its variable appearance. Immediately following thermal ablation, and up to 2 months later, an ablation cavity larger than the original tumor forms, particularly if the mass was less than $3cm^3$ in volume [43]. Between 12 and 24 months after thermal ablation, the ablation cavity reduces to less than half the original volume. The ablation cavity is typically of higher density than surrounding normal parenchyma, likely residual blood products. Postcontrast images demonstrate lower attenuation cavities due to lack of viable tissue. Perinephric stranding may persist indefinitely associated with the intense heat during RFA, resulting in a localized inflammatory response. The stranding is partially replaced by a halo of fibrous tissue within 1–2 months. Finally, later fat invagination, particularly with exophytic lesions, is seen [44] (Fig. 5.17a, b).

In cases where contrast-enhanced CT (or MR) imaging raises the suspicion for recurrent tumor but fails to unequivocally demonstrate its presence, examination with 18F FDG PET/CT or even combination thereof with a blood flow agent such as Rubidium PET/CT may provide clues to the diagnosis.

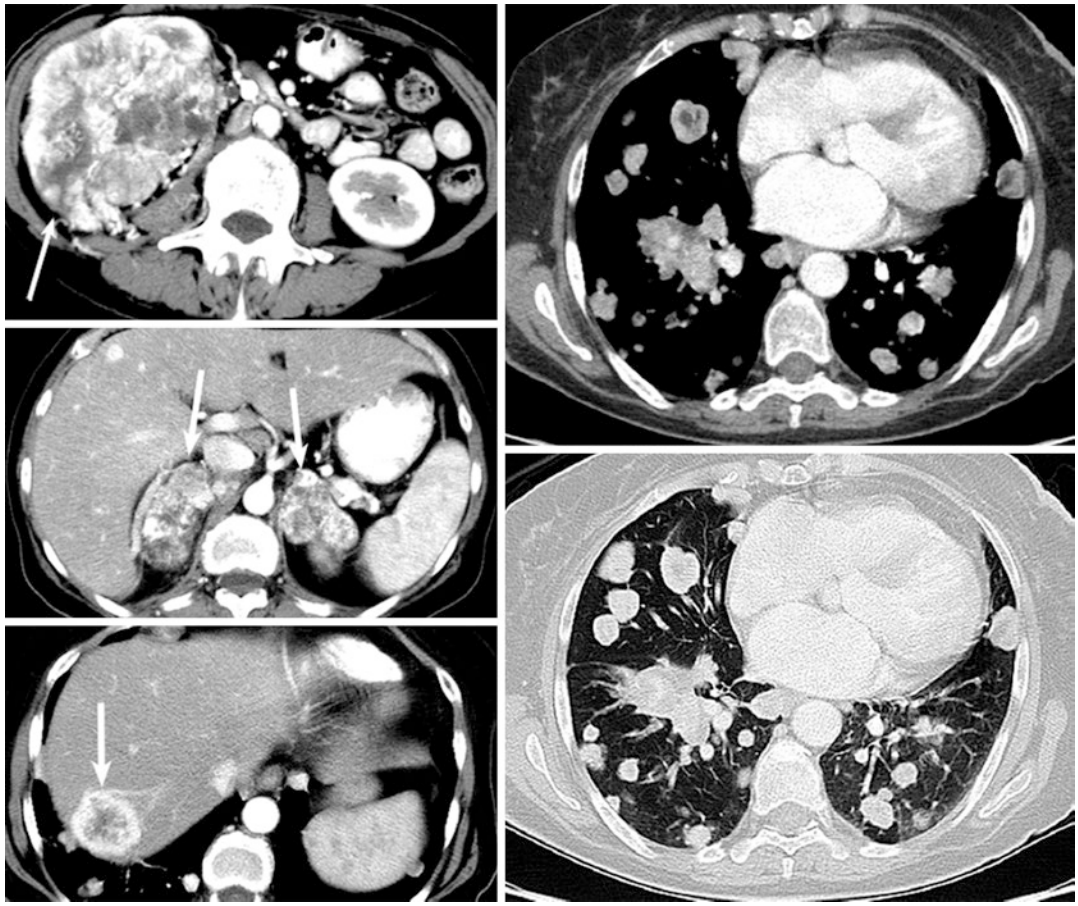


Fig. 5.16 Multiple contrast-enhanced axial CT images demonstrate evidence of numerous metastatic lesions from a renal cell carcinoma primary. The large, heterogeneous enhancing mass in the right kidney (upper left) was the primary tumor. Metastases to both adrenal glands are evident (middle left), and a hypervascular metastasis to the liver (lower left). Numerous large, hypervascular metastases are noted within the lungs

Magnetic Resonance Imaging (MRI)

MRI represents a powerful tool alongside ultrasonography and CT in the detection, characterization, and staging of renal masses. The intrinsic properties of MRI allow multiplanar soft tissue characterization, without ionizing radiation, and the available variety of imaging sequences is continually evolving to address specific questions.

A complete abdominal MR examination consists of many individual short component exams, often termed sequences which are named after the radiofrequency pulse schemas which drive each interrogation of the target tissue. Each sequence is designed to produce images which are optimized for the characterization of one or several tissue types of interest. MRI has a much higher intrinsic soft tissue contrast resolution, which means it is better suited to visualize subtle differences between tissue types. Furthermore, some MR sequences are exquisitely sensitive to the detection and degree of acuity of blood products or other fluid. Typical sequences used in renal imaging include T1, T2, in- and opposed-phase imaging, diffusion-weighted images (DWI), and postcontrast T1 sequences employing breathhold technique. The T2-weighted sequence may be used to evaluate renal cysts; simple cysts are T2 bright with thin walls, while

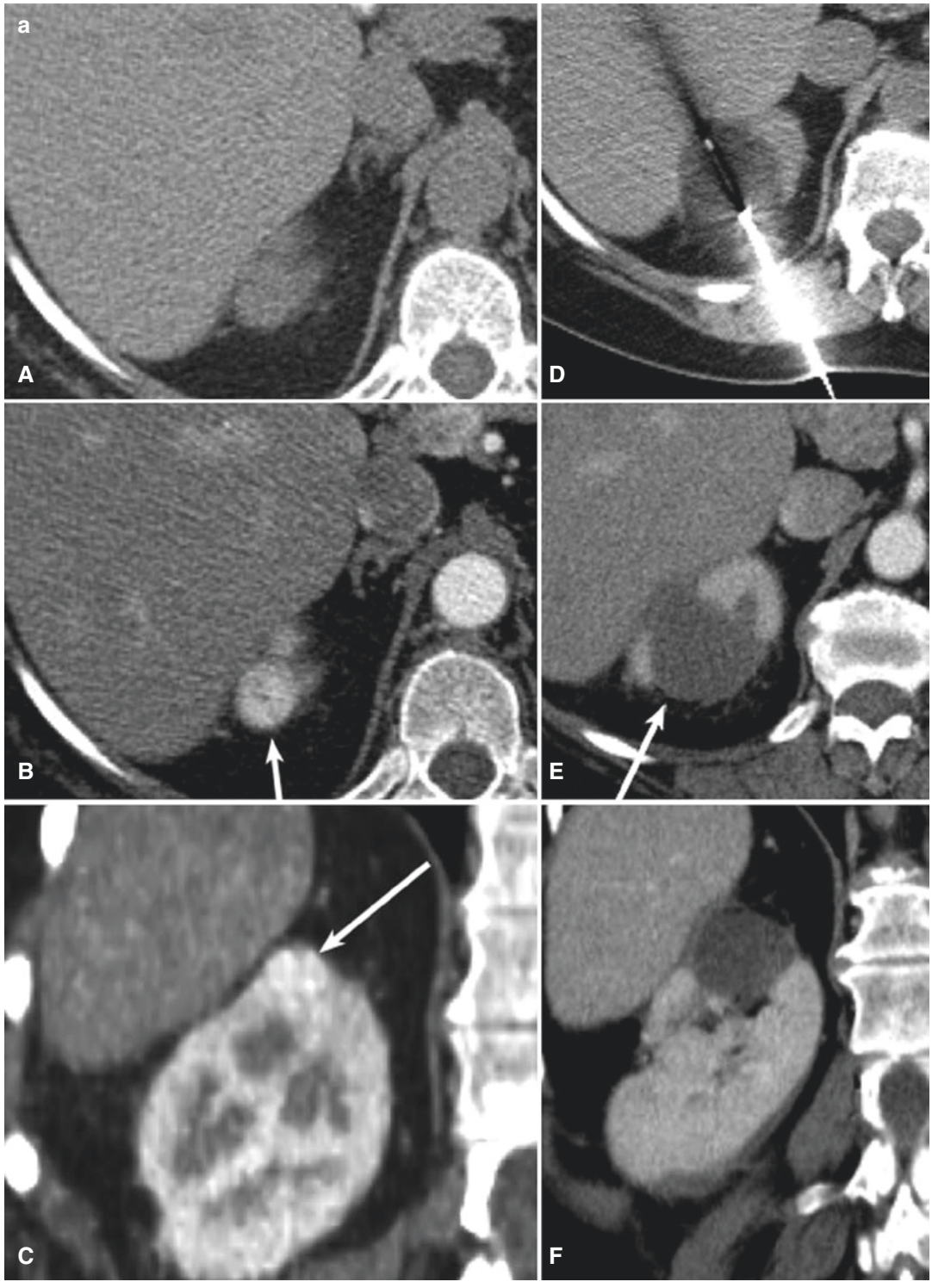


Fig. 5.17 (**a**) Axial precontrast (A) and postcontrast (B) CT images demonstrate a hypervascular upper pole lesion, better seen on coronal reformat (C). This was proven renal cell cancer by biopsy and treated with cryoablation (D). Post-ablation contrast-enhanced CT images in axial (E) and coronal (F) plane demonstrate infracted tissue, no definite evidence of recurrence. (**b**) Dynamic phase T1-weighted, subtracted precontrast (left) and postcontrast (middle and right) MR images demonstrate no evidence of recurrent disease

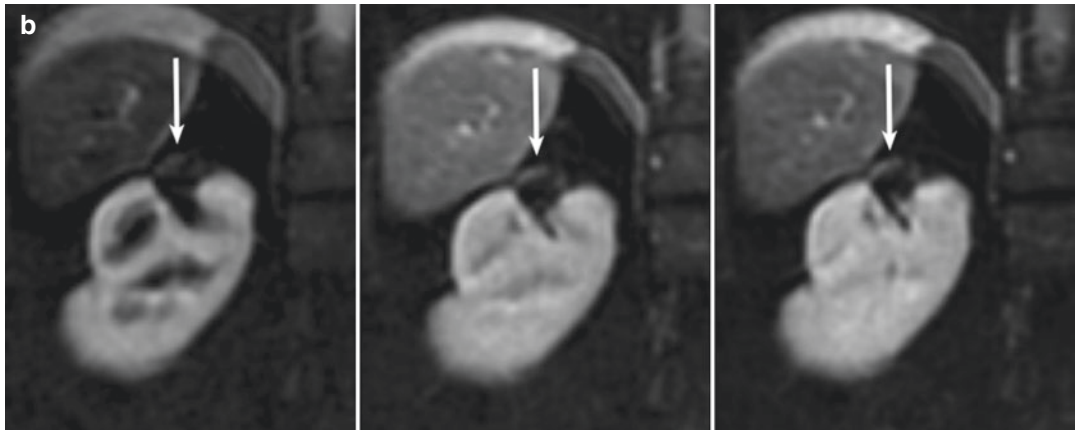


Fig. 5.17 (continued)

proteinaceous or hemorrhagic cysts will appear heterogeneous to low signal intensity. Septae and mural nodules are quickly identified against the fluid background. Precontrast images of proteinaceous or hemorrhagic cysts are intrinsically T1 bright. Chemical shift imaging is utilized to identify tumoral fat content and incidental findings such as hepatic steatosis and fat-containing adrenal lesions such as adenoma. Postcontrast imaging, typically following intravenous administration of an extracellular contrast agent such as gadopentetate dimeglumine, is acquired dynamically in corticomedullary, nephrographic, and excretory phases. Subtraction imaging may assist with identification of small lesions (Figs. 5.18 and 5.19).

The most common renal cell cancer subtype is clear cell, comprising up to 80% of all RCC, and associated with a poorer prognosis than papillary or chromophobe [45, 46]. Typical MR characteristics of clear cell include T1 isointense and T2 hyperintense with surrounding parenchyma, and signal drop on opposed phase imaging consistent with cytoplasmic fat is seen in 60% of clear cell tumors. Central necrosis and intratumoral hemorrhage are common and may appear different on T1- and T2-weighted images, depending on the age of the hemorrhage. Subacute hemorrhage is T1 and T2 hyperintense, while chronic hemorrhage is T1 and T2 hypointense from hemosiderin. Postcontrast images demonstrate a hypervascular tumor. A surrounding T1 and T2 pseudocapsule is often identified and, if interrupted, may indicate capsular extension.

The second group of RCC is papillary type, comprising up to 15% of all RCC, and may appear necrotic and hemorrhagic (type 1) or more heterogeneous (type 2). Enhancing papillary projections at the periphery of a cystic, hemorrhagic mass is noted, together with a fibrous capsule.

The third main type of RCC is chromophobe, which appears as a solid mass with central cystic areas. Certain macroscopic features may be similar to clear cell RCC, although it carries a more favorable prognosis. In addition, chromophobe type RCC may appear very similar to an oncocytoma, as mentioned in the description of CT imaging (Fig. 5.20).

Benign entities within the kidneys include angiomyolipoma (AML) and oncocytoma. AML is the most common benign renal lesion and is a hamartomatous mass that can be associated with life-threatening hemorrhage if greater than 4 cm in size. Fat suppression pulse sequences are based on a technique which nulls signal arising from tissue areas composed of macroscopic fat, and opposed phase imaging demonstrates classic "India-ink" artifact surrounding the kidney, indicating a fat-water interface. Since RCC may rarely be fat-containing [47], the presence of macroscopic fat is not entirely pathognomonic for AML. It is suggested that central necrosis is a feature of RCC and not AML [48] (Figs. 5.21 and 5.22).

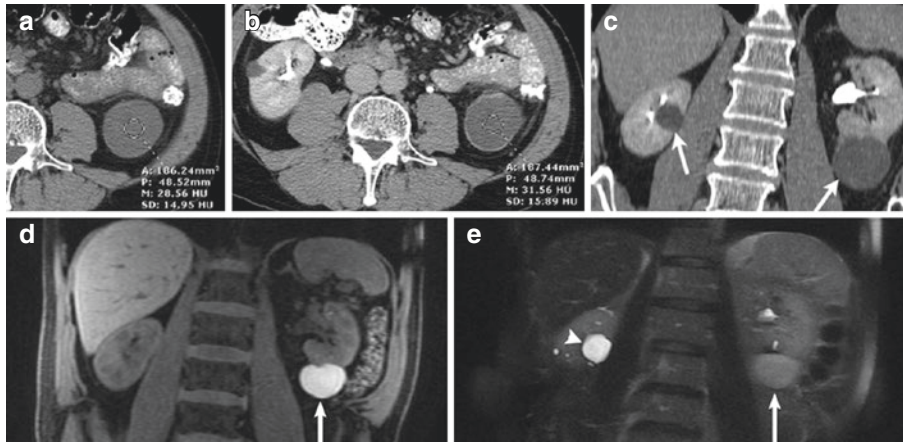


Fig. 5.18 Prominent exophytic left lower pole hypodense lesion seen on precontrast CT (**a**). Lesion is measured at 28 HU, more than would be expected for simple fluid. There is no significant enhancement on nephrogenic phase axial (**b**) or coronal (**c**) images. T1-weighted, fat-suppressed coronal MRI (**d**) confirms bright signal, likely proteinaceous rather than hemorrhagic content, given the CT appearance. Fluid-sensitive T2-weighted sequence (**e**) demonstrates isointense left lower pole lesion, and more typical simple fluid-density cyst in the right kidney (arrowhead). Interpretation of images from different modalities by an expert radiologist often yields the most specific lesion characterization

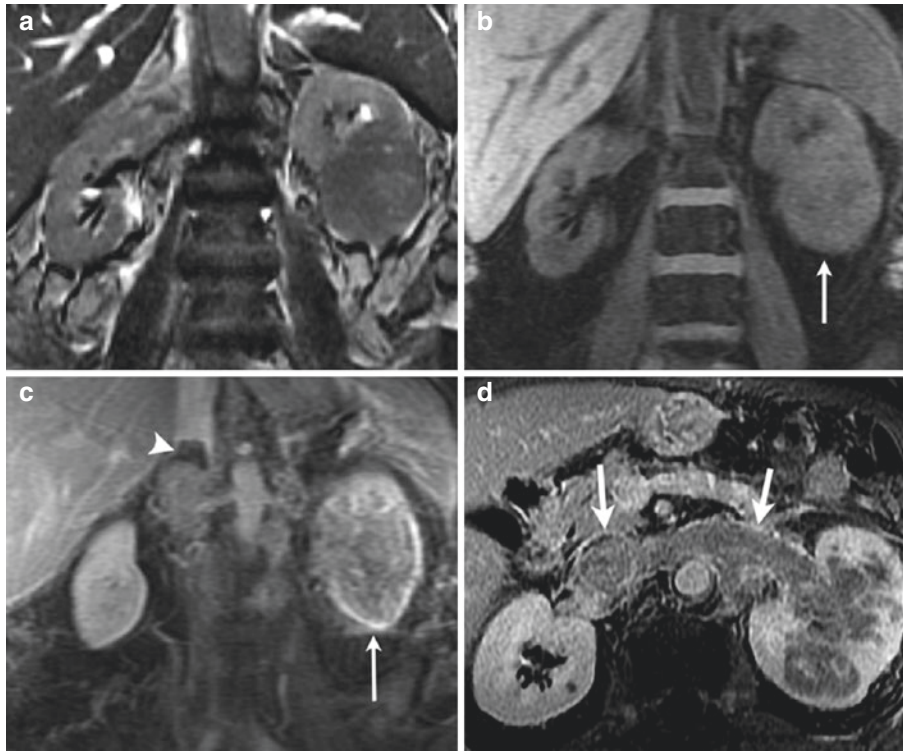


Fig. 5.19 Coronal T2-weighted sequence (**a**) demonstrates hypointense lesion in the left lower pole. This appears to be heterogeneously enhancing on T1-weighted, fat-suppressed precontrast (**b**) and postcontrast (**c**) coronal images. Note is made of a filling defect within the suprarenal IVC (arrowhead), better seen on the postcontrast, T1-weighted fat-suppressed axial image (**d**), with enlargement and apparent occlusion of the left renal vein, through to the IVC

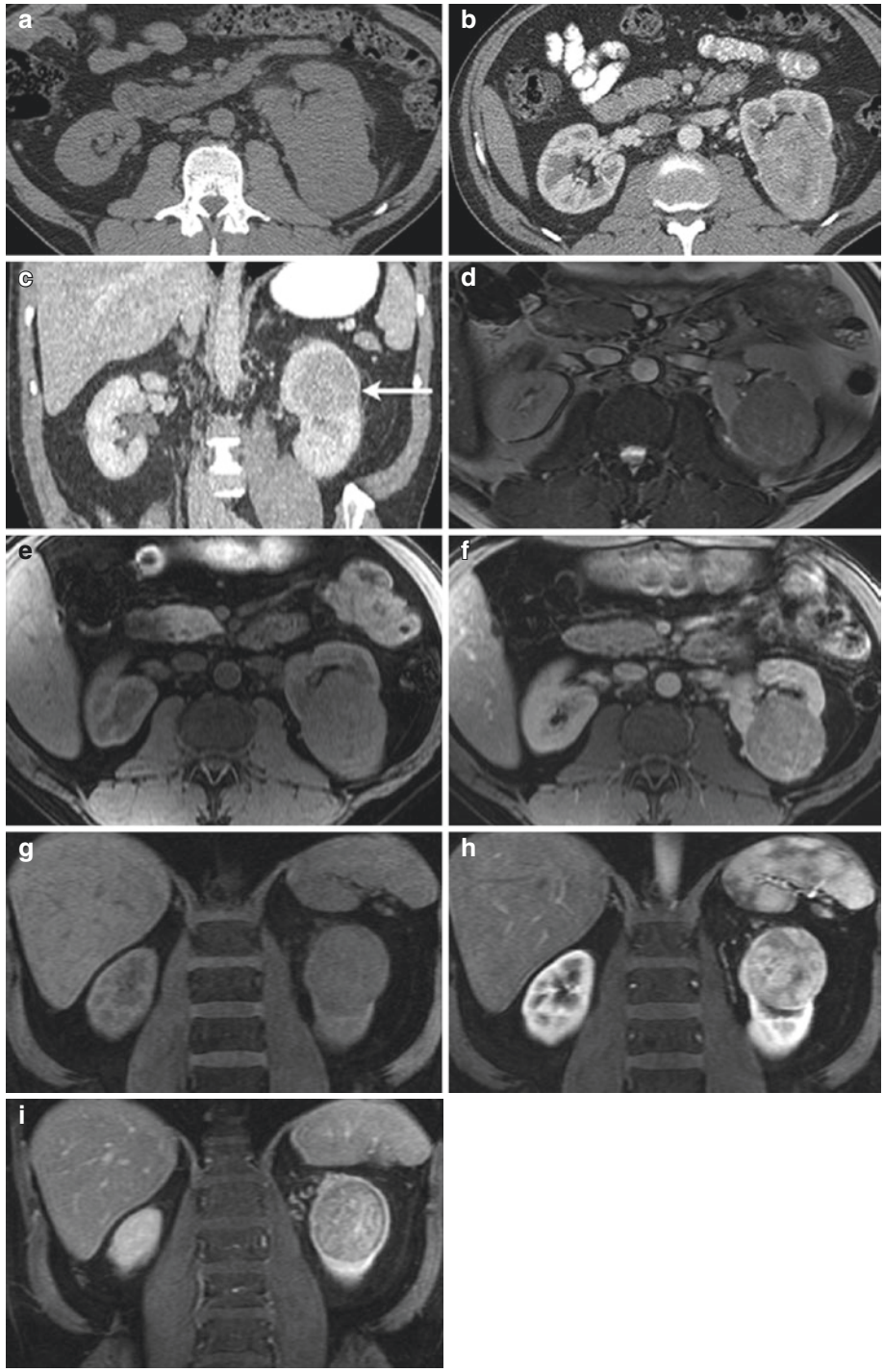


Fig. 5.20 Multiphasic CT images, including axial precontrast (**a**), nephrogenic phase (**b**), and coronal postcontrast (**c**), demonstrating a lobular, hypointense mass with heterogeneous enhancement. Axial T2-weighted (**d**), T1-weighted precontrast (**e**) and postcontrast (**f**) images confirm the left interpolar mass with heterogeneous enhancement. Coronal precontrast T1-weighted (**g**), early (**h**) and late (**i**) T1-weighted postcontrast images demonstrate heterogeneous enhancement with delayed washout. Imaging findings are similar to those of an oncocytoma, pathologically proven chromophobe type, renal cell carcinoma

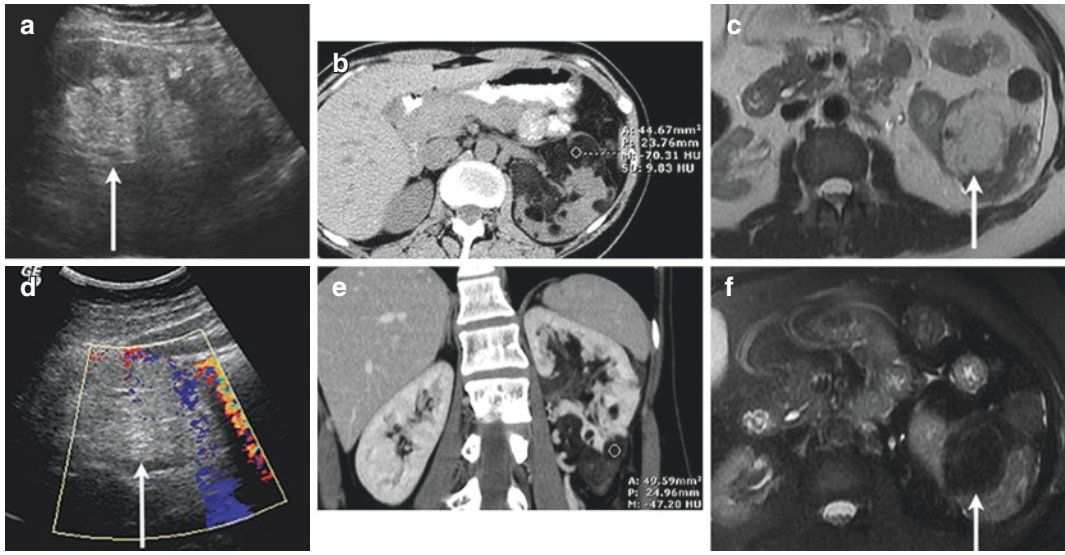


Fig. 5.21 Grayscale (**a**) and Doppler (**d**) images demonstrate an echogenic renal mass without vascular flow. Axial (**b**) and coronal (**e**) CT images demonstrate multiple fat-density lesions (between −40 and −70 HU) within the left kidney. T1-weighted axial MR image (**c**) demonstrates T1 hyperintense left renal mass, which loses signal on fat-suppressed image (**f**), consistent with angiomyolipoma

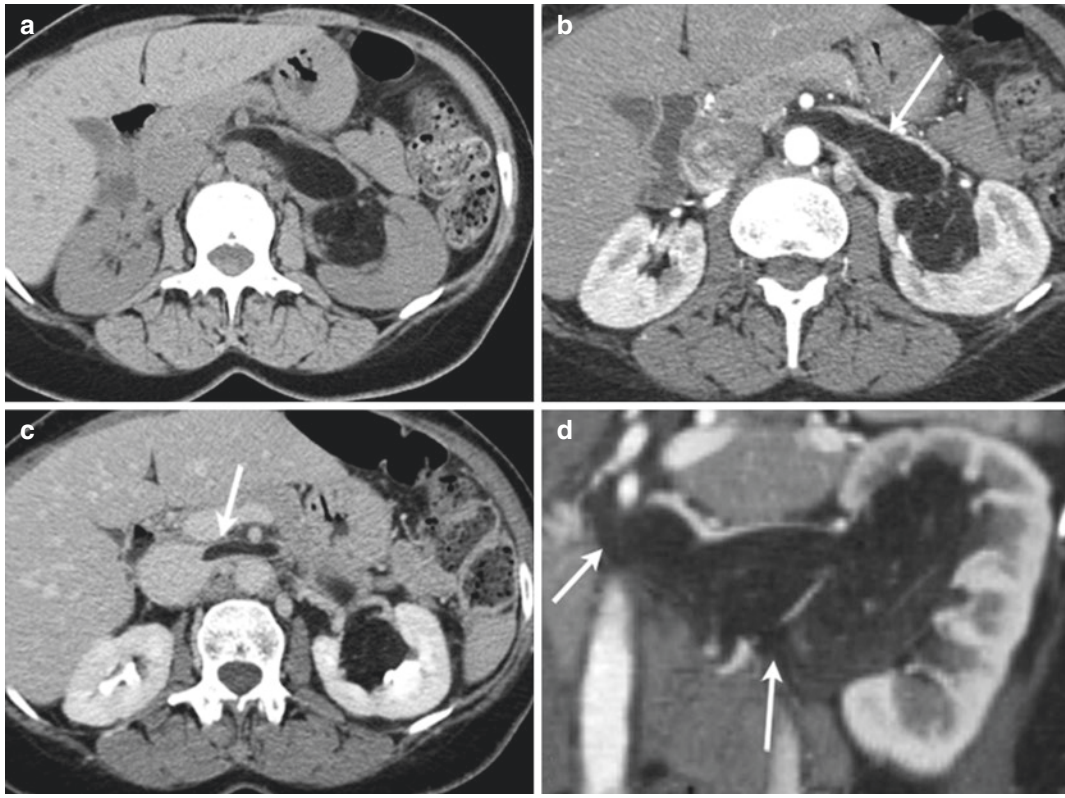


Fig. 5.22 Multiphasic axial CT images, precontrast (**a**), arterial phase (**b**), and nephrogenic phase (**c**) demonstrate a homogeneous, non-enhancing, fat-density mass within the left kidney with extension to the IVC, consistent with a large renal AML

Renal oncocytoma is the second most common benign renal neoplasm, after angiomyolipoma, and is found in up to 7% of solid renal masses; morphologically appearing spherical and well-defined, often peripheral in location, with mildly decreased signal on T1-weighted sequences, slightly T2 hyperintense in comparison with surrounding parenchyma. These lesions may be heterogeneous, although less likely to contain cysts, subacute hemorrhage, hemosiderin, and microscopic fat. There is often a stellate, central scar that enchances on delayed postcontrast imaging. These various imaging features are shared with chromophobe type renal cell cancer, the third most common subtype; both lesions sharing a common origin renal progenitor cell. Another distinctive feature of an oncocytoma is termed 'segmental enhancement inversion' in reference to areas of hyalinized stroma, resulting in relative hypovascularity in comparison with the renal cortex at the start of each phase of imaging. This may also be seen in chromophobe RCC. Although a capsule is seen in up to 50% of oncocytomas, it is also seen in an equivalent number of renal cell cancers [49].

Diffusion-weighted imaging (DWI) is an increasingly utilized sequence in abdominal imaging to evaluate inflammatory and neoplastic processes. Malignant tumors often cause relative impedance to unrestricted diffusion and transit of water molecules, normally seen as a function of Brownian motion. Apparent diffusion coefficients (ADC) values are derived as a measure of diffusion and ranges can be established that may be used to evaluate for benign versus malignant mass. ADC values typically range from 1.0 to 4.0×10^{-3} mm^2/s; lower values indicative of higher grade tumors [50]. The ADC value should be independent of MR scanner field strength, but may be affected by field inhomogeneities, such that a lower ADC value will be recorded in a 3 Tesla MRI scanner, as compared with a 1.5 Tesla scanner. DWI sequences provide additional functional information, conferring improved diagnostic accuracy and detection of neoplastic processes without requiring intravenous contrast administration [51] (Figs. 5.23 and 5.24).

Differentiation between solid and cystic renal masses has been demonstrated based on ADC values. Mean ADC values of 2.18×10^{-3} mm^2/s were obtained for normal renal parenchyma. Solid renal tumors demonstrate significantly lower ADC values, with a median of 1.16×10^{-3} mm^2/s, compared with a median of 2.73×10^{-3} mm^2/s for cystic tumors. Bosniak category I simple cysts had a mean ADC value of 3.09×10^{-3} mm^2/s. Furthermore, different histologic subtypes exhibited significantly different ADC values; chromophobe cell carcinoma 1.41×10^{-3} mm^2/s, clear cell carcinoma 1.23×10^{-3} mm^2/s, and papillary cell carcinoma 0.90×10^{-3} mm^2/s [50].

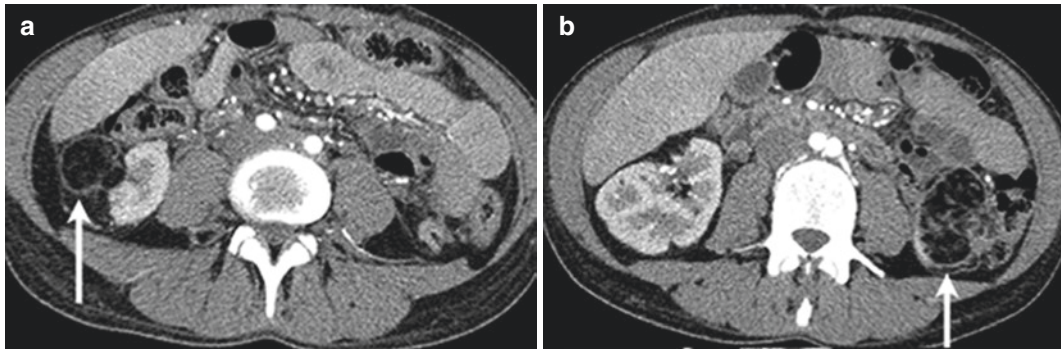


Fig. 5.23 Axial (**a**, **b**) and coronal (**d**) postcontrast images demonstrate multiple fat-density lesions within both kidneys. Corresponding lucent masses are seen on the volume-rendered image (**e**). Evaluation of the lung parenchyma (**c**, **f**) demonstrates innumerable thin-walled cysts and small pleural effusions. The unifying diagnosis is tuberous sclerosis, associated with multiple renal angiomyolipomas (AML) and lymphangioleiomyomatosis (LAM)

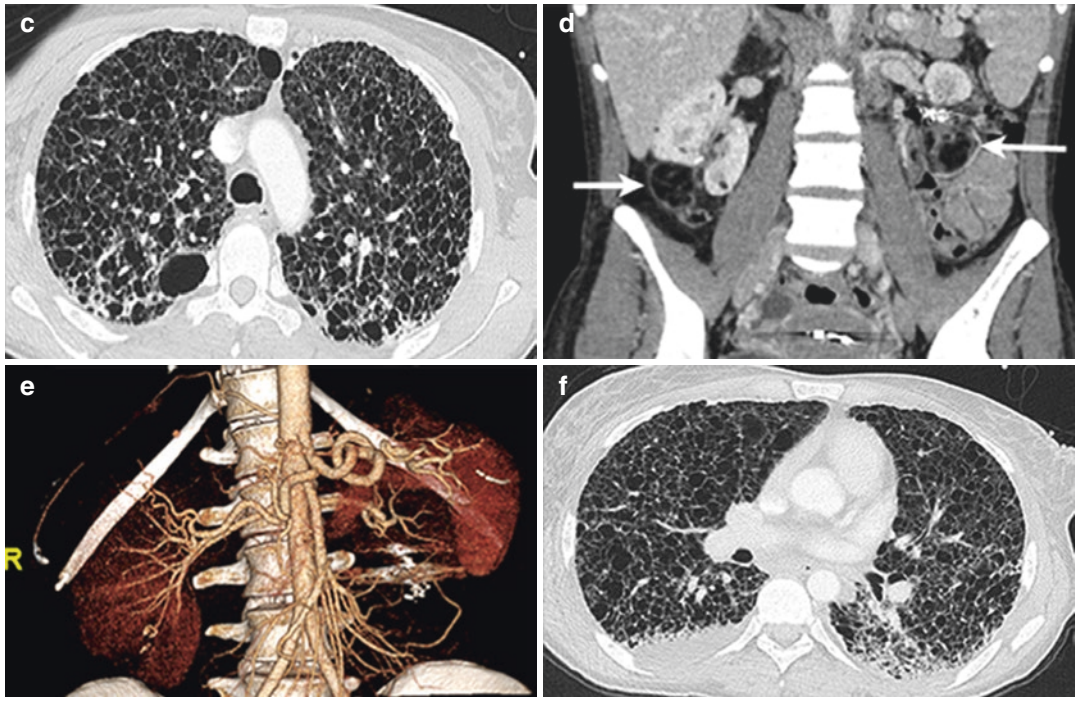


Fig. 5.23 (continued)

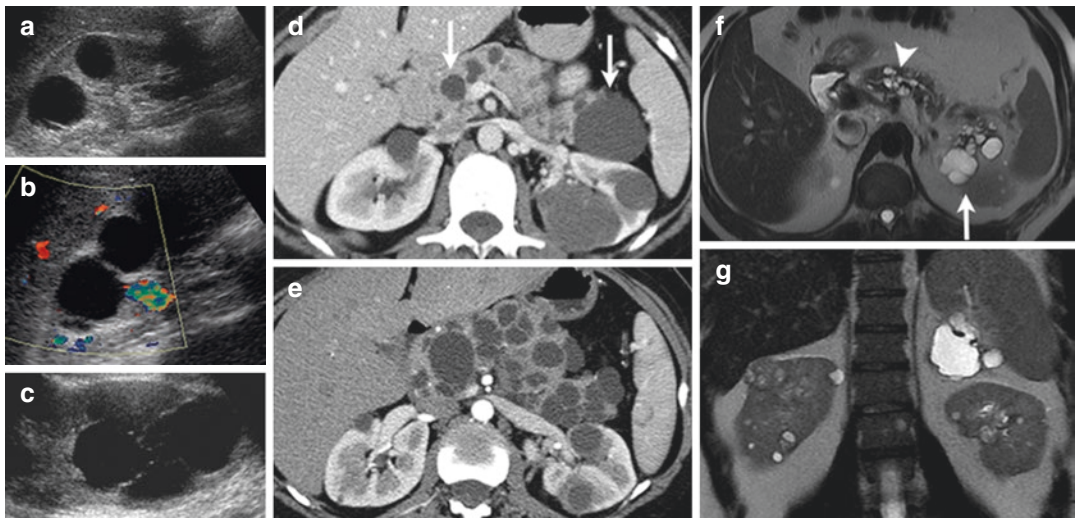


Fig. 5.24 Multiple well-circumscribed, anechoic, avascular cysts are seen within both kidneys on grayscale and Doppler ultrasound (**a**–**c**). Axial CT images in arterial phase demonstrate multiple non-enhancing, thin-walled renal and pancreatic cysts of varying sizes (**d**–**e**). These findings are also seen on T2-weighted axial and coronal images (**f**–**g**). The underlying condition is Von-Hippel-Lindau disease

In a different study, analysis of a variety of renal masses prior to surgical resection with subsequent pathologic histological correlate noted that, in clear cell type RCC, ADC values greater than 2.12×10^{-3} mm^2/s indicated low-grade tumor, less than 1.50×10^{-3} mm^2/s indicating high-grade cancer. An ADC value of 1.87×10^{-3} mm^2/s or less corresponded to high-grade, clear cell type renal cell cancer, with a sensitivity and specificity of 90% and 71%, respectively [52]. These findings have been corroborated in more recent retrospective analysis, which identified a moderate diagnostic role for DWI in distinguishing high- from low-grade clear cell renal cell carcinoma, which may assist with a treatment plan [53].

Further refinement and standardization in the acquisition of DWI sequences and generation of ADC maps may provide information on the histologic subtype and degree of differentiation of a renal tumor with increased accuracy.

Future Directions

Functional or molecular imaging continues to remain the next big frontier of imaging, targeting a physiologic pathway or mechanism. The field of radiomics initially gained traction combining liver cancer imaging with gene expression and has continued to develop reflecting the allied strength of radiologic imaging and various adjunct diagnostic tools, including, among others, genomics, proteomics, and metabolomics. The current methodology may provide a role for artificial intelligence to assist with computer analysis of data integration, classification, statistical, and mining processes [54].

Active targeting of renal cancer with nanoparticles for the purpose of diagnosis or treatment, including antibody and antibody fragment-based imaging, remains an area of interest, resulting from passive or active tumoral uptake [55]. Monoclonal antibody recognition of a determinant on carbonic anhydrase IX (CA-IX), which has near ubiquitous overexpression in clear cell type renal cell carcinomas and not expressed in benign tumors, has been proven successful in animal models and may provide future direction as a form of radio immune-therapy combined with tyrosine kinase, for treatment of both primary and metastatic renal cell carcinoma [56]. Additional evidence supporting the role of CA-IX as a surrogate marker for tumor hypoxia, and thus, a theranostic target (integrating diagnostic information with pharmaceutical therapy for safe, targeted delivery of cancer treatment) has been demonstrated within the research arena [57] and in ongoing clinical trials [56].

Novel pharmaceutical agents may be used in conjunction with positron emission tomography (PET), combining the highly sensitive and specific antigen-antibody reaction (that may be further tailored by altering the Fc binding domain) with the high resolution of PET imaging [58]. Although ^{18}Fluorine is the most commonly utilized metabolic tracer, its short half-life limits its role in immunoPET. Alternative PET isotopes include ^{124}Iodine, ^{73}Strontium, ^{89}Zirconium, and ^{89}Zr-girentuximab.

Although still largely in the research domain, optical imaging via fluorescence or bioluminescence may have a utility during intraprocedural detection of tumor. Following resection of a primary renal mass, the necessary enzymatic reaction such as between a luciferase enzyme and its substrate will elicit photons that may pinpoint additional foci of disease ensuring clear surgical margins.

Also within the research field are Quantum dots (QD) or semiconductor nanocrystals, essentially light-emitting colloidal nanocrystals, with a broad excitation spectrum and narrow range of emission wavelengths. QD may be linked to antibodies, or antibody fragments, and based on their unique spectral properties and enhanced stability, may offer significant advantages in the realm of bioimaging agents.

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Molecular Imaging for Renal Cell Carcinoma

6

Jian Q. Yu and Yamin Dou

Introduction

Molecular imaging such as positron emission tomography (PET) has been widely used in clinical oncology. Currently, F18-labeled fluorodeoxyglucose (18F-FDG) PET/CT is accounted for the majority of all molecular imaging procedures. Accurate and reliable imaging studies are needed to proper stage cancer patients for treatment plans and to provide imaging parameters and biomarkers for optimal assessment of therapeutic response. Immunotherapy and targeted therapies have become the standard of practice for oncology treatments. Molecular imaging such as PET is likely to play an even greater role in the treatment selection and monitoring treatment response. Success of FDG PET is also recognized with certain limitations. Special attention has been devoted to the development of new tracers for better evaluation of tumor burden and immunotherapy response. In this chapter, we will outline the clinical utility of FDG PET (PET/CT) and provide a brief discussion of new radiotracers for renal cell carcinoma (RCC).

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Renal cell carcinoma (RCC) accounts for about 3% of all adult cancers and 85% to 90% of all primary renal tumors. It is the seventh most common cancer in men and the ninth most common in women. The incidence of RCC is rising over time, partially attributable to the success of modern imaging technologies. Choudhary and colleagues estimated 50–60% of RCCs are found incidentally when diagnostic imaging is performed for an unrelated indication [1]. Characterization of a small renal mass can be done through tissue biopsy, which is invasive with known procedural complications, potential sampling errors, and concern of track metastasis. It is not commonly performed due to inaccuracy and ineffectiveness in clinical management. Noninvasive imaging modalities are useful in diagnosing, staging, and monitoring therapy response. To date, the role of FDG PET in the initial detection and diagnosis of RCC is still limited, controversial, and discordant. It is not recommended by NCCN guidelines. However, FDG PET seems to show some promise for the detection of distant metastases and local recurrence, and may be complementary to other cross-sectional imaging techniques. Semi-quantitative FDG PET/CT imaging may be helpful to predict tumor differentiation and prognosis. Immunotherapy with checkpoint inhibition has revolutionized the treatment of many cancers. Standard criteria for response assessment of immunotherapy are limited due to delayed response and initial pseudoprogression occurring in some patients. Few data

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are available using FDG PET/CT for the assessment of immunotherapy response for mRCC. Alternative targeted therapies for mRCC such as tyrosine kinase inhibitors (TKIs) are aimed at specific biologic molecules or processes to modify response or signal transduction. These drugs act as a cytostatic and inhibit growth rather than induce tumor regression. Conventional imaging techniques such as CT and MRI are size based and are not optimal in evaluating early changes after therapy. Molecular imaging has become more important in evaluating response for these cytostatic agents. The change in FDG uptake on PET scans before and after therapy is a strong indicator of biological response to TKIs.

In this chapter, we will examine the current application of FDG PET (PET/CT) for detecting primary RCC, locoregional metastasis evaluation, and distant metastasis assessment including liver, lung, and bone. We will also discuss the prognostic value of FDG PET/CT and the utility of FDG PET/CT for monitoring therapeutic response for mRCC.

Primary Renal Cell Carcinoma Diagnosis

Kidney cancer used to be considered a single disease many years ago. It is now known that renal cell carcinoma has different histological patterns and variable clinical courses that appear to respond differently to therapy [2]. The Heidelberg classification identifies five distinct malignant subtypes: clear cell, papillary, chromophobe, collecting duct, and RCC unclassified. Benign tumors have been subclassified into metanephric adenoma and adenofibroma, papillary renal cell adenoma, and renal oncocytoma [3]. Approximately 54% of renal masses are more aggressive clear cell carcinoma [2].

The initial diagnosis of a renal mass is usually made with ultrasound, CT, or MRI. Most cases are discovered incidentally during procedures for other indications [4]. CT is currently the imaging modality of choice to stage and detect metastasis in patients with RCC. These are essential for prognostic evaluation and surgical planning. Surgical resection by either partial or radical nephrectomy remains the standard of care for the localized disease.

FDG PET provides unique information about molecular pathways of disease. It has gained increasing acceptance for the diagnosis of cancer. Early studies using FDG PET reported a broad range of accuracy for detecting primary RCC. Ramdave et al. [5] studied 17 patients with known or suspected primary tumors and found true positive in 15, one true negative, and one false negative. The accuracy of FDG PET and CT was identical (94%). Similar results were also reported by Goldberg et al. [6]. Two other studies [7, 8] with larger sample of 53 and 66 patients showed different results. Aide et al. [7] reported a sensitivity, specificity, and accuracy of 47%, 80%, and 51%, respectively. Kang et al. [8] reported a sensitivity of 60% and a specificity of 100% for PET versus 91.7% sensitivity and 100% specificity for CT. Kang and colleagues concluded that the role of FDG PET in the detection of primary RCC is limited by low sensitivity. But the superior specificity of the PET may have a complementary role in equivocal cases on conventional imaging [8]. Several factors may explain the large ranges of variation of sensitivity. First, due to the heterogeneity of RCC, some have low FDG uptake due to low glucose transporter-1 expression [9]. In a study with 44 primary clear cell RCC, SUVmax (maximum standardized uptake value) ranges from 2.5 to 18.4, with average SUVmax 6.8 [10]. Second, the kidneys and collecting system are the route for radiotracer FDG excretion; this makes the diagnosis of small parenchymal mass difficult, even with hydration and diuretics [11]. Third, due to the limited resolution and the lack of anatomic (CT) correlation of old generation non-hybrid PET-only scanners, small lesions are very difficult to detect. The main disadvantage of FDG PET for RCC is the relatively high false-negative results. Another drawback of the FDG PET is the lower spatial resolution of PET images when compared to a CT scanner. There is known false-positive uptake in infection and inflammation for PET as well. It is worth noting that most articles published regarding RCC were based on

PET-only scanners, which may lower the sensitivity and specificity by about 5–10%. The newer generation of hybrid PET/CT scanners with improved resolution has markedly improved the localization of lesions and diagnostic accuracy compared to either CT or PET stand-alone applications. A more recent study with FDG PET/CT by Kayani et al. detected 41/43 of primary RCC with the smallest tumor measuring less than 2.5 cm [10].

There is limited data regarding the ability to predict the histological diagnosis based on anatomic imaging findings [12]. Clear cell RCC is the most common type of renal malignancy. It can be hypodense, isodense, or hyperdense on pre-contrast CT studies. Post-contrast CT usually enhances significantly and can be heterogeneous due to necrosis [13]. No correlation of FDG uptake has been found between benign and malignant renal tumors. Most of the clear cell RCC demonstrate increased FDG uptake above the background renal parenchyma activity (Fig. 6.1). SUVmax (maximum standardized uptake value) has been reported ranging from 2.5 to 18.4 with an average of 6.5 [10].

Oncocytoma is considered a benign tumor. On unenhanced CT, it usually appears isodense or hypodense to the renal parenchyma and shows enhancement on post-IV contrast CT images. On PET, oncocytoma normally shows no appreciable FDG uptake as previously reported [14]. However, a case report described intense uptake in a renal oncocytoma [15]. A typical appearance of oncocytoma is shown in Fig. 6.2.

Angiomyolipoma is the most common benign tumor of the kidney. These lesions characteristically contain variable amounts of abnormal blood vessels, adipose tissue, and smooth muscle elements. The majority of angiomyolipomas can be accurately diagnosed on unenhanced CT as the lesions contain macroscopic fat (Fig. 6.3). There is limited literature on the role of FDG PET in the diagnosis of angiomyolipoma. Kochhar et al. [14] showed a renal angiomyolipoma without significant FDG uptake similar to our case in Fig. 6.3.

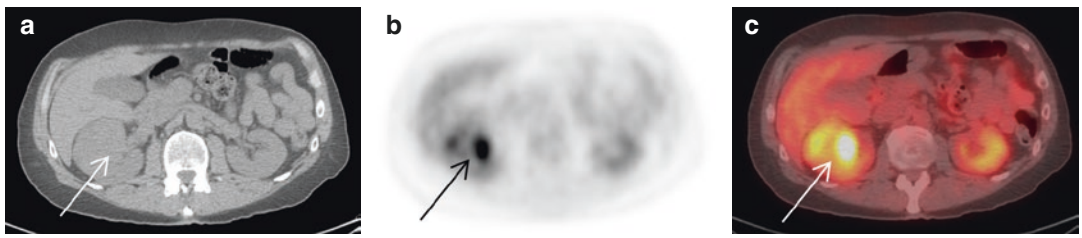

Fig. 6.1 Clear cell renal carcinoma. (**a**) Non-contrast CT shows a 5-cm right renal mass. (**b**) FDG PET demonstrates heterogeneous increased uptake in right renal mass. SUVmax 5.7. (**c**) Fused PET/CT image

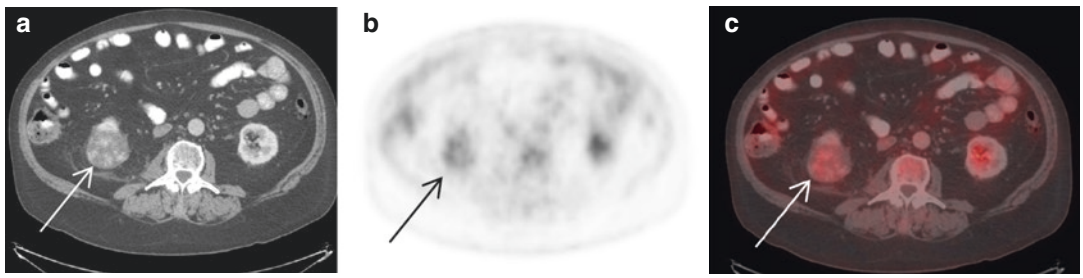

Fig. 6.2 Oncocytoma. (**a**) CT with IV contrast shows a well-defined 5-cm mass with mild heterogeneous enhancement. (**b**) FDG PET shows mild increased uptake. SUVmax 2.9. (**c**) Fused PET/CT image

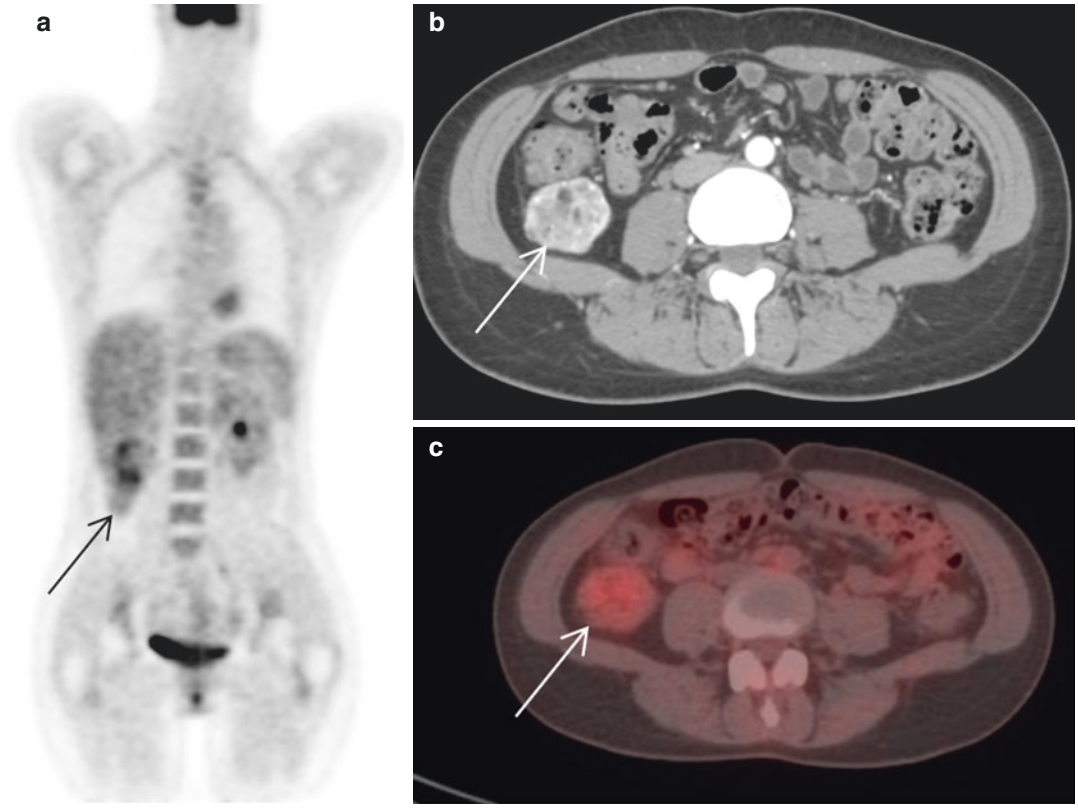

Fig. 6.3 Angiomyolipoma of the kidney. (**a**) FDG PET shows focal mild uptake equal to or less than background renal parenchymal activity. SUVmax 1.9. (**b**) A well-marginated tumor with fatty attenuation seen on CT scan (arrow), highly suggestive of angiomyolipoma. (**c**) Fused PET/CT image

Locoregional Metastasis

Approximately 18% of patients with RCC have metastasis at the time of diagnosis [16]. CT and MRI are currently the study of choice to provide important information about tumor extension, vascular invasion, and regional metastasis. MRI has a special role to assess thrombus extension. Lymphadenopathy remains a major challenge for cross-sectional imaging. Current cross-sectional imaging criteria for suspicious lymph nodes include a short-axis diameter of 1 cm or more and loss of kidney shape and fatty hilum. Yet, some of the enlarged lymph nodes were related to hyperplastic and inflammatory change. FDG PET provides an alternative to contrast-enhanced CT by showing the metabolic activity of the disease. In RCC, both CT and PET data for local extension and regional nodal metastases are limited at the current time and believed to be similar [17].

FDG PET helps detect small metastatic nodes (Fig. 6.4). Kang et al. [8] reported 75% sensitivity and 100% specificity for retroperitoneal lymph node metastases and/or local recurrence by PET while abdominal CT showed 92.6% sensitivity and 98.1% specificity. Aide et al. [7] reported two patients with local nodal metastasis. FDG PET detected one of them; with IV contrast, CT correctly identified both. Kocher et al. [18] compared the results of FDG PET with histology in patients with suspected RCC. They found true regional lymph node metastasis in three patients and true negative in seven. Ramdave et al. [5] reported two cases of locoregional lymph node metastasis detected on FDG PET but not on CT.

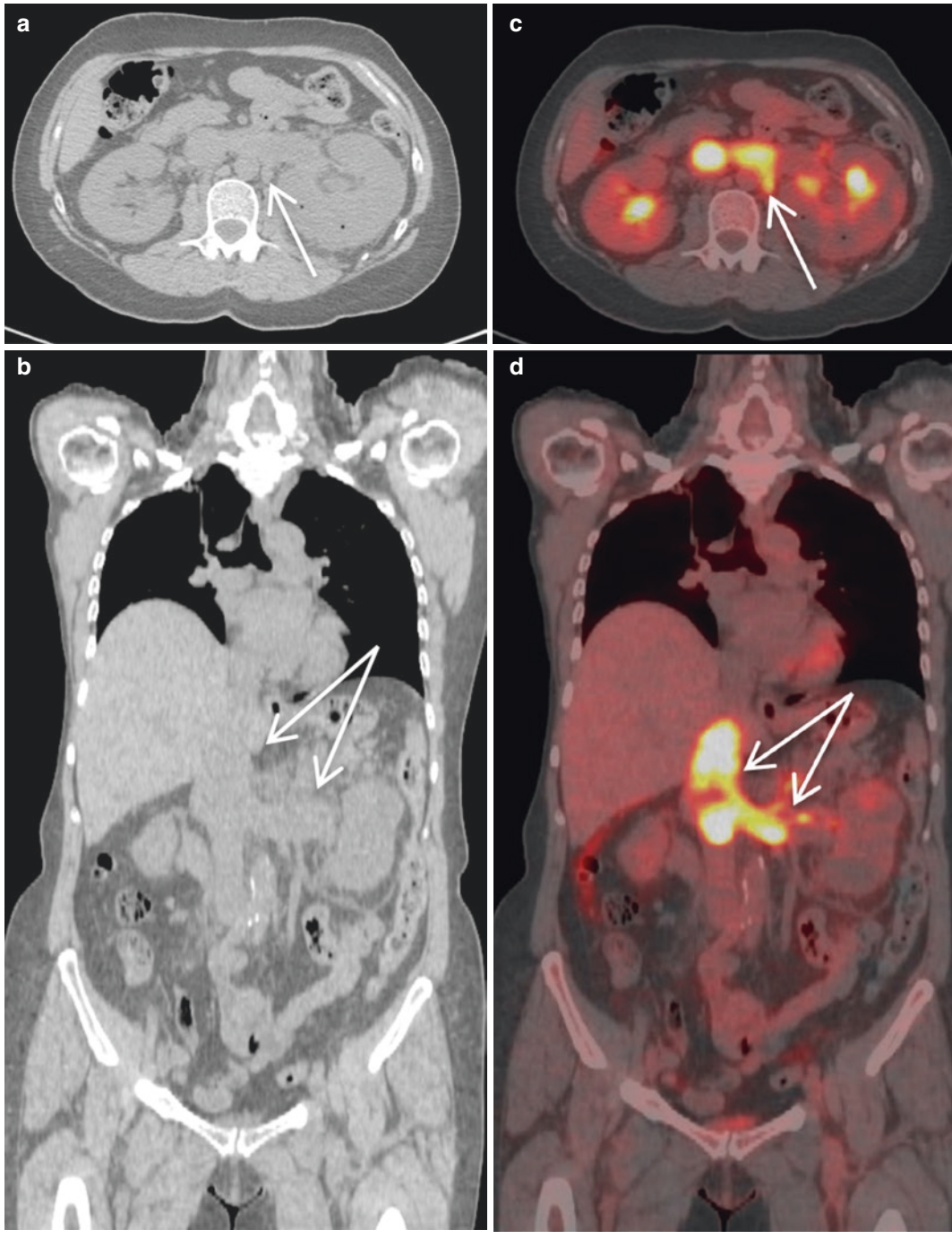

Fig. 6.4 Papillary renal cell carcinoma with local small nodal metastasis and tumor invading renal vein and IVC. (**a**) Staging FDG PET/CT demonstrates a large left renal mass and a 10-mm left para-aortic node (arrow) on non-contrast CT. (**b**) There is a markedly dilated left renal vein and IVC (arrows). (**c**) Fused FDG PET/CT images demonstrate heterogeneous uptake in the left renal mass, SUVmax 11, and corresponding uptake in a10-mm left para-aortic lymph node (arrow), suggesting metastatic disease. (**d**) There is intense FDG uptake in left renal vein and IVC (arrows), consistent with tumor extension

Although some publications have suggested that only tumor and infected thrombi show increased FDG uptake, a few reports showed that bland thrombus may have this appearance as well, a finding consistent with the acute inflammatory phase of aseptic deep venous thrombosis [19]. It seems that FDG PET is not useful in recognizing the cause of the thrombus because FDG uptake relies on the degree of reactive inflammation, which is variable and does not correlate with bland or tumor thrombus. However, there is generally accepted consensus that tumor thrombi have higher uptake than bland thrombus. A case with tumor thrombosis is shown in Fig. 6.4.

The incidence of local recurrence ranges from 1.8% to 27% after nephrectomy [20]. CT interpretation of the renal bed is difficult because of migration of the adjacent normal organs into the renal fossa, postoperative scar, and artifacts from surgical clips. In addition, patients may develop renal failure after nephrectomy which makes IV contrast injection relatively contraindicated. The metabolic activity of tumor is not altered by these factors. Therefore, FDG PET may be superior for evaluation of renal bed recurrence (Fig. 6.5). Ramdave et al. [5] showed that in the eight patients referred for this condition, PET was able to clearly differentiate tumor recurrence from fibrosis or necrosis. The diagnostic accuracy of FDG PET was calculated to be 100%. In comparison, the diagnostic accuracy of CT was 88%.

Distant Metastasis

FDG PET/CT is very useful in evaluating distant metastases, partially attributable to the length (routine skull base to mid thigh) of the scan. It has shown promising results with RCC, with sensitivity range from 60% to 100% and the specificity close to 100% for the majority of cases [7, 17, 21–25]. Majhail et al. reported two cases of unsuspected distant metastasis detected by FDG PET not seen by CT in 17 patients evaluated for primary RCC [21]. In another study [26], FDG PET detected 77/112 of the metastatic lesions. Of those, 32 lesions had not been detected by any other anatomic imaging. The results of CT and FDG PET for detecting distant metastases from RCC were comparable, with sensitivities of 70% and 69%, respectively. Safaei et al. [27] reported a study of 20 patients with 25 lesions biopsied. FDG PET accurately identified 21/25 metastases and demonstrated a sensitivity of 87% and a specificity of 100%. Park et al. [17] evaluated FDG PET/CT for the postoperative surveillance of advanced RCC and found that it has 89.5% sensitivity, 83.3% specificity, 77.3% PPV, 92.6% NPV, and 85.7% accuracy in detecting local recurrent and distant metastasis. A study by Aide et al. [7] showed no metastases detected by CT that were missed by FDG PET. In fact, FDG PET was able to detect additional metastatic sites, leading to better accuracy compared with CT.

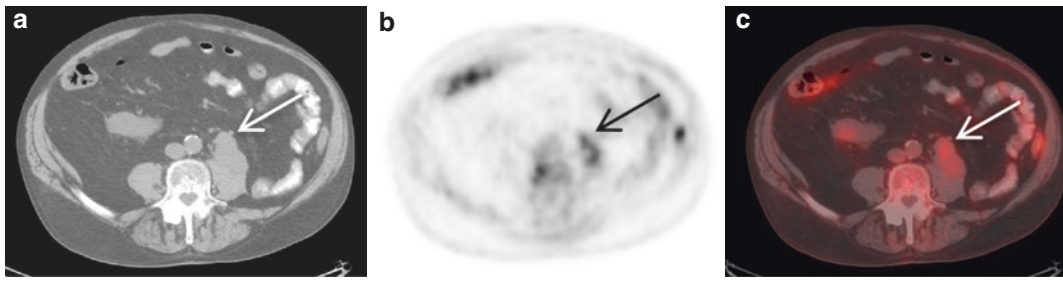

Fig. 6.5 Chromophobe renal cell cancer with local recurrence. (**a**) Re-staging FDG PET/CT demonstrates a left retroperitoneal soft-tissue mass on non-contrast CT, question of post-surgical change vs local recurrence. (**b**) FDG PET demonstrates focally increased uptake, SUVmax 2.5, consistent with recurrent disease. (**c**) Fused FDG PET/CT image

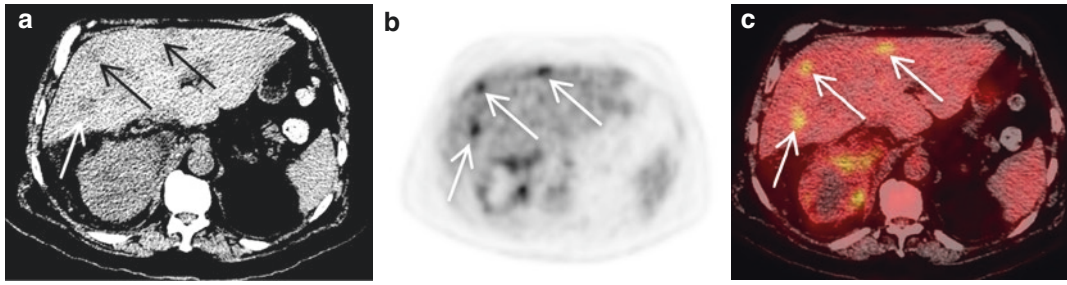

Fig. 6.6 Clear cell renal cancer with liver metastases. (**a**) CT shows a large right renal mass and subtle liver lesions (arrows). (**b**) FDG PET shows intense heterogeneous uptake in the right renal mass and clearly multiple foci of liver uptake (arrows). (**c**) Fused FDG PET/CT

Liver Metastasis

Liver is the third most common site of metastasis for RCC after lung and bone and accounts for 15–20% of metastasis in RCC [28, 29]. Liver metastasis is associated with poor prognosis [30]. CT is the mainstay of imaging in the detection of intra-abdominal metastases. On CT, liver metastases can appear as ill-defined low attenuation lesions that may show peripheral enhancement or appear as hypervascular masses with or without central necrosis [31]. On a non-IV CT contrast FDG PET/CT scan, lesions on the CT component can be subtle. In general, there is high target to background ratio of uptake seen on FDG PET, which makes it easier to detect (Fig. 6.6). Study by Kang et al. [8] showed FDG PET has a sensitivity of 61.5% and a specificity of 100% for liver metastases. In contrast, CT has a sensitivity of 76.9% and a specificity of 94.1%. FDG PET detected 2/13 metastases that were negative on CT. In the study by Park et al. [17], FDG PET/CT has a sensitivity of 100% for liver metastasis.

Lung Metastasis

Lung is the most common site of mRCC and accounts for 50–60% of metastasis [28, 29]. Patients with lung-only metastases have a better survival rate than patients with other sites of metastases [30]. Pulmonary metastases usually appear as well-defined round or ovoid nodules on both chest radiography and CT. They can be solitary or multiple and typically range in size from 0.5 to 2 cm in diameter. They are one of the well-known causes of "cannonball" metastases [31]. CT with IV contrast is the current study of choice to evaluate lung metastases with high sensitivity. However, CT has limitation due to its low specificity to differentiate benign from malignant nodules. FDG PET assesses the metabolic process of the lesions and is useful in evaluating malignant potential. A large study of 585 patients by Bryant and colleagues showed the higher the SUV, the more likelihood of malignancy [32]. Fortes et al. [33] evaluated 83 patients with metastatic pulmonary nodules from different primaries and found that FDG PET is positive in only 67.5% of them. Nodule size and grade affect the sensitivity of FDG PET. For nodules ranging from 1 mm to 5 mm, the sensitivity of FDG PET was 23.5% (4/17); however, for nodules greater than 25 mm in diameter, the sensitivity of FDG PET was 88.5% (23/26).

With FDG PET, Majhail et al. [21] reported a sensitivity of 63.2% and 100% PPV in detecting pulmonary metastasis from RCC. The mean size of lung metastases in patients with true-positive FDG PET was 2.0 cm (95% CI, 1.3 to 2.7 cm) compared with 0.8 cm (95% CI, 0.5 to 1.2 cm) in patients with false-negative FDG PET.

A dual modality hybrid PET/CT scanner takes advantage of the high sensitivity from CT and the greater specificity of FDG PET which results in

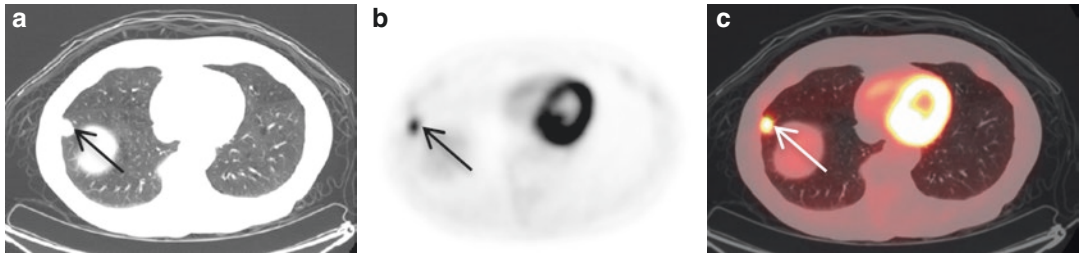

Fig. 6.7 Clear cell renal cancer with lung metastasis. (**a**) CT component of FDG PET/CT scan shows a 2-cm solitary right lower lobe pulmonary nodule. (**b**) FDG PET demonstrates intense uptake. SUVmax 6.4. (**c**) Fused FDG PET/CT

Fig. 6.8 Metabolic negative lung metastases from clear cell renal cancer. FDG PET/CT in a 63-year-old female with clear cell renal cancer and biopsy-proven pulmonary metastases. (**a**) Multiple lung nodules, largest measuring 10 mm (arrow) on CT. (**b**) No significant FDG uptake corresponding to these small nodules on PET. (**c**) Fused FDG PET/CT

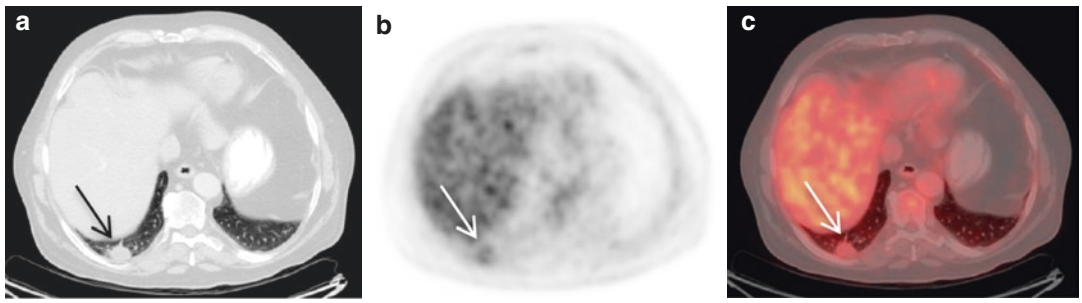

Fig. 6.9 False-positive lung metastasis from clear cell renal carcinoma. (**a**) CT component shows a large lung nodule, measuring 2.7×1.7 cm (arrow). (**b**) FDG PET demonstrates increased uptake corresponding to the large nodule, SUVmax 2.7. (**c**) Fused FDG PET/CT. Biopsy of this nodule shows inflammation and necrotic tissue

increasing accuracy as compared to either modality alone. Small pulmonary metastasis from RCC even without significant metabolic activity can be seen by CT (Fig. 6.7). A pulmonary nodule with corresponding FDG uptake is highly suspicious for metastasis in a patient with history of RCC (Fig. 6.8). Due to overlapping FDG uptake between inflammatory cells and cancer cells, false-positive metastasis is not uncommonly seen on FDG PET/CT (Fig. 6.9).

Bone Metastasis

Osseous metastasis accounts for 30–40% of distance metastasis in RCC [34]. Bone metastases classically appear as large expansile lytic lesions on plain radiography, most commonly in the axial skeleton [31]. Contrast-enhanced CT shows bone destruction with or without the presence of an enhancing soft-tissue mass. Bone scan is not routinely performed for RCC patients

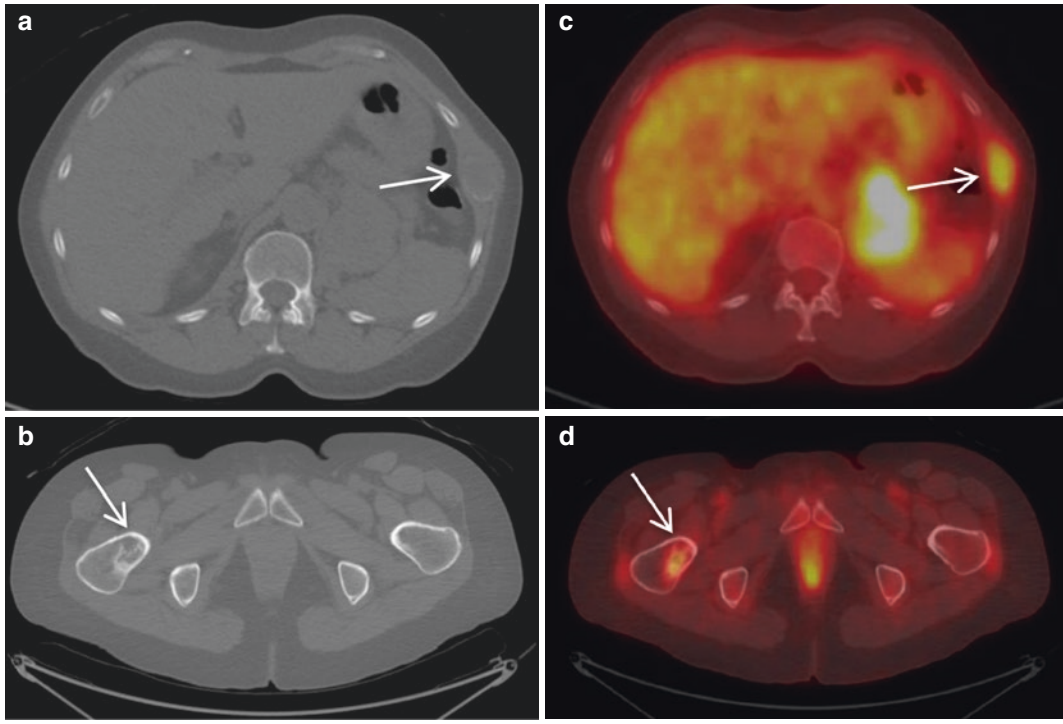

Fig. 6.10 Multiple bone metastases from clear cell renal carcinoma. (**a**, **b**) Re-staging scan demonstrates destructive and lytic bone lesions on CT component (arrows). (**c**, **d**) PET/CT fused images demonstrate moderate increased uptake corresponding to these bone lesions

due to the mainly lytic nature of the bone metastasis, which is commonly negative in conventional bone scan. The general consensus is to order a bone scan only for patients with symptomatic bone pain and elevated serum alkaline phosphatase [27, 35].

FDG PET has been reported to be very accurate to stage bone metastasis in breast and lung cancers [36, 37]. FDG PET may offer improved specificity over bone scintigraphy in the detection of bone metastases (Fig. 6.10). Another advantage of PET over bone scan is the evaluation of both bone and soft tissue in one setting. Solitary bone metastasis from RCC is not uncommon, and a subtle bone lesion is not easily seen on CT scan (Fig. 6.11). Wu et al. [38] showed that for detecting bone metastasis, FDG PET had both sensitivity and accuracy of 100% compared with 77.5% and 59.6%, respectively, for bone scintigraphy. Kang et al. [8] showed that positive predictive value and negative predictive value for bone metastases were 99% and 93.2%, respectively, and indicate that FDG PET is the most sensitive test for imaging bone metastasis of RCC.

Recently a study has demonstrated that NaF-18 PET is more accurate than ^{99m}Tc-diphosphonate SPECT for identifying both malignant and benign lesions of the skeleton [39]. Combining the NaF-18 PET with CT using a PET/CT scanner can improve the specificity and overall accuracy of detecting skeletal metastasis.

Surveillance

Chae et al. found that after resection of RCC, the mean time of tumor recurrence was 17 months, and 83% of recurrence occurred within 2 years [29]. Thus, they recommend follow-up imaging should be performed intensively the first 2 years after surgery. Most guidelines use anatomical and conventional imaging to monitor relapse and recurrence. FDG PET has been shown to identify

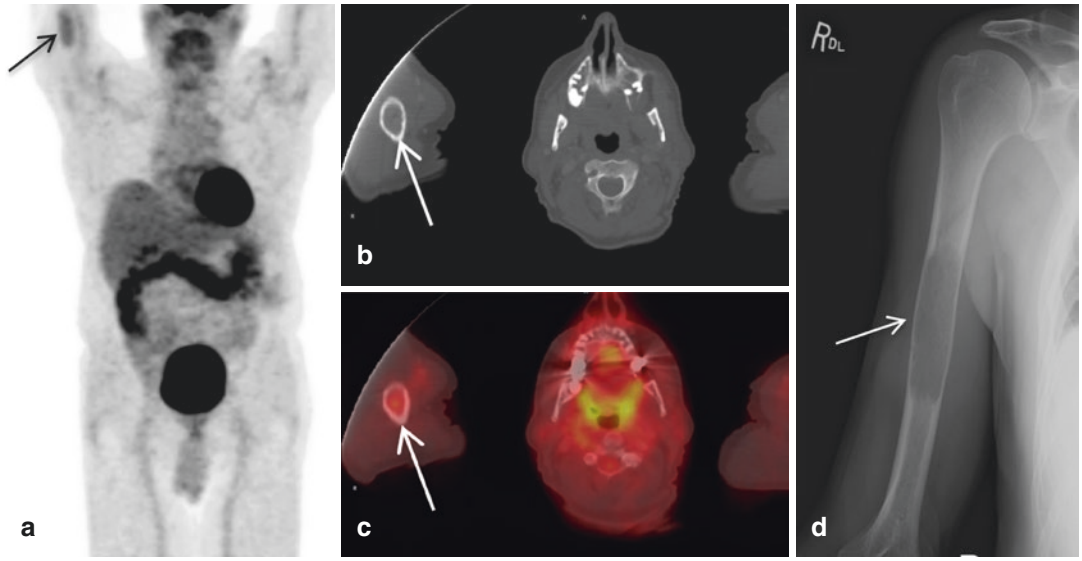

Fig. 6.11 Solitary bone metastasis from clear cell renal carcinoma. (**a**) Re-staging FDG PET/CT in a 63-year-old male with clear cell renal carcinoma. PET demonstrates a focal moderate uptake in the right humerus. (**b**) On the corresponding CT, there is an easy to miss lesion with subtle cortex thinning. (**c**) Fused image clearly demonstrates abnormal uptake in the bone and marrow. (**d**) Follow-up plain film shows lytic lesion in the right humerus

relapse and/or recurrence more readily than conventional imaging with higher sensitivity and specificity [17]. One advantage of FDG PET/CT imaging is that IV contrast is not essential to perform the study, thus avoiding potential renal damage, which is very important for the renal preservation of RCC patients. Nakatani and coworkers [40] reviewed 28 scans in 23 patients who had undergone FDG PET scans after surgery. They correlated the FDG PET findings with other imaging and histology or by clinical follow-up at least 6 months and reported overall sensitivity, specificity, and diagnostic accuracy of 81%, 71%, and 79%, respectively. FDG PET correctly detected local recurrence and metastases in all cases in the peritoneum, bone, muscle, and adrenal gland. Their experience suggested FDG PET would be useful for postoperative surveillance in patients with RCC.

Prognostic Values of FDG PET for RCC

A prognostic model has been developed by Motzer et al. [41]. Patients were categorized into favorable, intermediate, or poor prognostic groups based on five risk factors: Karnofsky performance status, elevated lactate dehydrogenase (> 1.5 times the upper limit of normal), low hemoglobin (less than normal), high corrected calcium, and absence of prior nephrectomy. Patients with no risk factors (favorable risk) had a median survival of 20 months; with one to two risk factors (intermediate risk), 10 months; and with three or more risk factors (poor risk), 4 months. Furthermore, Motzer et al. [42] performed a retrospective study to identify prognostic factors for survival in previously treated patients with advanced RCC. They found risk factors for shorter survival were low Karnofsky performance status, low hemoglobin level, and high corrected serum calcium. The median time to death in patients with zero risk factors was 22 months. The median survival in patients with one of these prognostic factors was 11.9 months. Patients with two or three risk factors had a median survival of 5.4 months.

Studies have shown the metabolic tumor burden (MTB) and/or metabolic tumor volume (MTV) on FDG PET/CT is an independent prognostic factor in lung, head and neck, and esophageal cancers [43–45]. Other studies showed that SUVmax (maximum standardized uptake value)

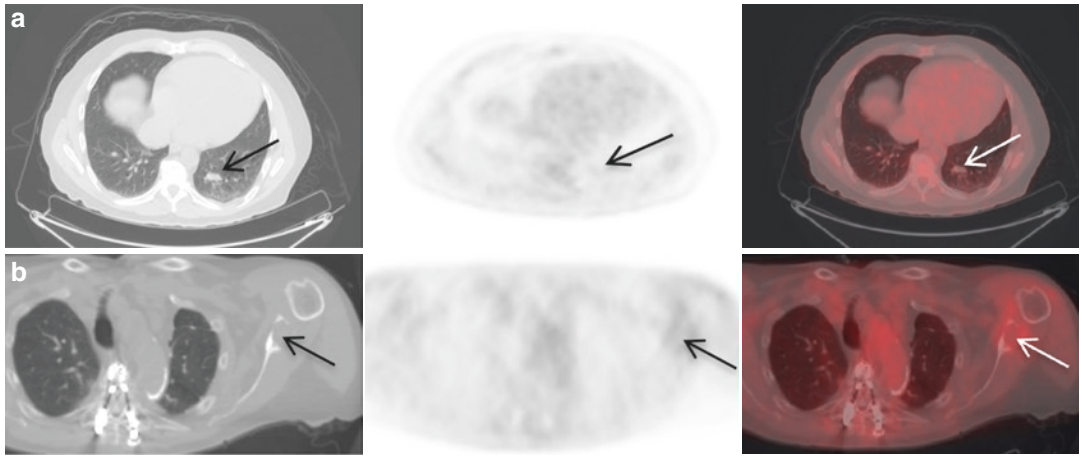

Fig. 6.12 Low FDG uptake in metastatic mRCC lesions demonstrates long-term survival. This 75-year-old male was diagnosed with clear cell renal carcinoma in 2001 and developed a left lower lobe nodule (**a**). FDG PET/CT showed minimal uptake. He underwent wedge resection of this nodule which was later confirmed as metastatic renal cell carcinoma. Subsequently, the patient developed multiple new low FDG avid metastases. He survived more than 10 years after the initial diagnosis of mRCC. The most recent FDG PET/CT showed a lytic bone lesion in the left scapula with mild FDG uptake (**b**)

of FDG predicts prognosis in various cancers [46–48]. The role of FDG uptake such as SUVmax or MTB as a prognostic factor has not been fully established in RCC, but it is generally accepted that a more aggressive tumor has a higher SUV. One study showed that RCC patients with SUVmax equal or above 8.8 demonstrated poor prognosis [49]. Kayani et al. [10] showed a SUVmax of 7.1 was the most significant level to predict overall survival. In another study, Revheim et al. [50] found that patients with relatively low FDG uptake before treatment (defined as a SUVmax <5) had significantly longer progression-free survival than those with relatively high initial 18F-FDG uptake (SUVmax >5). Patients with low FDG uptake in their metastatic lesions are favorable for longer survival (Fig. 6.12). These findings suggest that SUVmax should be considered as a criterion to incorporate in future prognostic models.

Monitoring Therapeutic Response

Immunotherapy has become a cornerstone treatment for mRCC. Based on the CheckMate-214 trial [51], the European Association of Urology has recommended the combination of two immune checkpoint inhibitors ipilimumab and nivolumab as the first-line therapy for mRCC [52]. Conventional standard criteria for response assessment are not suitable to immunotherapy based on the fact that early pseudoprogression of existing lesions and small new lesions can occur in these late responders [53]. Therefore, immune-related response criteria were proposed by Wolchok et al. [53]. It is hypothesized that the initial pseudoprogression in some patients treated with immunotherapy is due to inflammatory cell infiltrates. Given that both cancer and immune infiltrates can be FDG avid, it is a challenge for FDG PET/CT to differentiate cancer progression with pseudoprogression. Several studies have been conducted to explore the role of non-FDG radiotracers, the "immuno-PET" for the evaluation of immunotherapy [54, 55]. Nevertheless, a negative FDG PET/CT after immunotherapy indicates good response to therapy (Fig. 6.13).

Alternative therapies are also used for the treatment of mRCC. These include TKIs such as sorafenib and sunitinib, inhibitors of mammalian target of rapamycin (mTOR) such as temsirolimus and everolimus, and other biologic agents such as bevacizumab. Currently, TKIs are still agents of

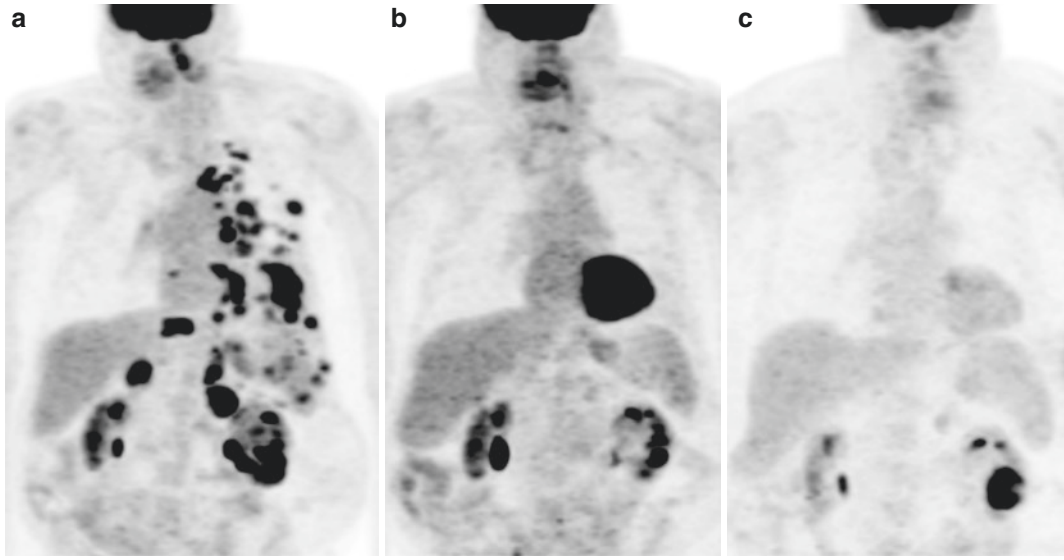

Fig. 6.13 Monitoring of immunotherapy response by FDG PET/CT. A 75-year-old male presented with a large left renal clear cell carcinoma with extensive metastasis to bilateral adrenal, right lung, right pleura, and bone with negative PD-1 expression (**a**). He was treated with combined checkpoint inhibitors (Nivo + Ipi). After 4 cycles of therapy, restaging FDG PET/CT showed dramatic response to therapy (**b**). Follow-up scan demonstrated continued treatment response of metastatic disease. Worsening of uptake in the primary left renal lesion may represent pseudoprogression (**c**)

choice for favorable-risk patients with mRCC [52]. These agents block cell signaling through various mechanisms and demonstrate better outcomes in patients with advanced clear cell RCC compared with standard therapies [19, 56].

Most and near all of these new agents can induce stabilization of RCC. A decrease in primary tumor diameter >30% while on targeted therapy is rare [57]. Since these therapies induce tumor necrosis with little tumor shrinkage, an unchanged residual mass does not necessary imply poor therapeutic responses. This makes anatomic imaging less suitable for monitoring treatment response for mRCC. In addition, differentiation between vital tumor and fibrosis or necrosis is difficult using anatomic imaging. Thus, molecular imaging such as FDG PET can be an attractive alternative to morphological imaging for this purpose. The new RECIST 1.1 now adds functional imaging in the response assessment [58, 59]. Data is now available on the monitoring of the therapeutic response of mRCC using FDG PET and FDG PET/CT [60–62]. A recent study [50] demonstrated that in patients with metastatic RCC, a high baseline FDG uptake indicates aggressive disease, and patients with a partial metabolic response or stable metabolic disease after two courses of sunitinib had improved prognosis as compared with those with progressive metabolic disease. They concluded that the inclusion of the PET results seems to improve the clinical counseling of patients with advanced disease.

Early metabolic response monitoring is possible with molecular imaging since the signal change at the cellular level takes quite some time to translate into size change (Fig. 6.14). Interestingly, in a multicenter phase II study, Kayani et al. [10] found that after 4 weeks of sunitinib, metabolic response occurred in 24/42 (57%) patients, but this did not correlate with progression-free survival (PFS) or overall survival (OS). After 16 weeks of treatment, disease progression on FDG PET/CT occurred in 28% of patients which correlated with a decreased OS and PFS.

FDG PET might be useful to identify nonresponding patients early in the treatment phase of TKIs (Fig. 6.15). This can guide a personalized treatment plan and avoid unnecessary

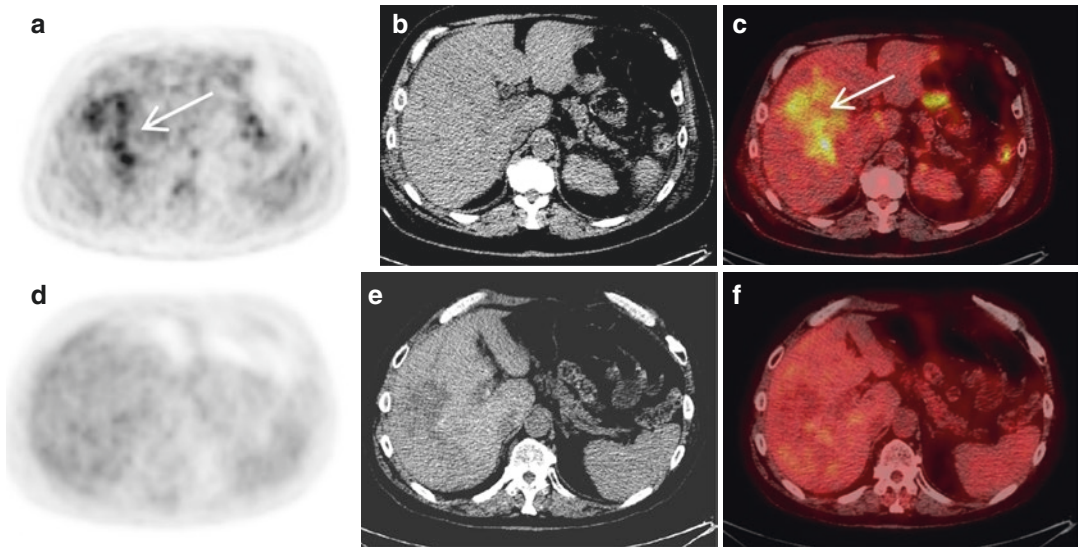

Fig. 6.14 Good response to therapy. FDG PET/CT in a 61-year-old male with bilateral renal cell cancer and liver metastasis. Top row: (**a**) Pre-therapy staging scan shows large focus of abnormal uptake in the right hepatic lobe (arrow). SUVmax 6.5. (**b**) Subtle hypodense lesion noted on non-contrast CT. (**c**) Fused PET/CT image. Bottom row: (**d**) 6 months after sorafenib treatment, there is marked improvement of uptake in liver metastasis. (**e**) Large lesion in the liver is now easily seen on CT with contrast. (**f**) Fused PET/CT image. Patient's disease is stable with sorafenib treatment 4 years after initial diagnosis

therapy; the potential benefits to patients, the medical community, and the economy could be enormous.

Influence on Management

It is very important to know whether FDG PET scan has an impact on patient management in terms of clinical decision making. Studies have shown that FDG PET altered the management of patients with mRCC. In one study [5], FDG PET was completed in 25 patients with known or suspected primary RCC and/or metastasis, and the results were compared to those that received conventional imaging techniques. Normally all patients would go to surgery post-conventional imaging, but PET scan altered the treatment plan for 6 (35%); 3 could be treated with partial nephrectomy rather than radical surgery, and 3 avoided surgery owing to confirmation of benign pathology or detection of unsuspected metastasis leading to systemic therapy. Similar results were reported by others as well [7, 8, 27, 35].

National Oncologic PET Registry (NOPR) conducted a large study to evaluate the impact of FDG PET on Medicare cancer patients. The results of the NOPR were published in several high impact journals through a peer review process [63–65]. The first paper was published in the *Journal of Clinical Oncology* in May 2008 with over 22,000 studies analyzed [63]. This large, prospective, nationally representative registry of elderly cancer patients found that physicians often change their intended management on the basis of PET scan results across the full spectrum of its potential uses. In this article, there were 1600 cases of kidney and other urinary tract cancer patients, which account for 7% of total cases. Overall, physicians changed their intended management in 36.5% (95% CI, 35.9 to 37.2) of cases after FDG PET scan.

Another article was published in the *Journal of Nuclear Medicine* by the same group at the end of 2008 with similar findings and more details [65]: including 895 cases for initial staging of RCC, with a 41.1% change in management; 979 cases for RCC restaging, with a 34.4% change in management; and 1003 cases for monitoring

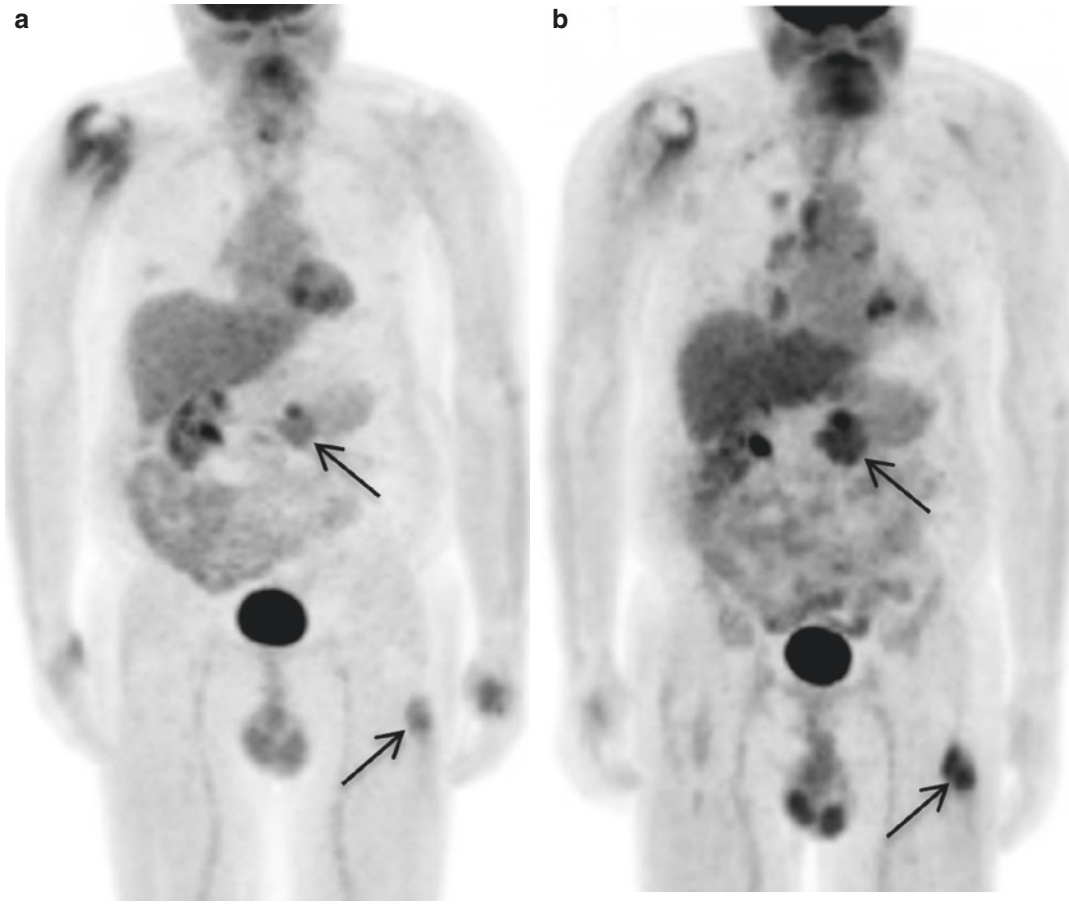

Fig. 6.15 Progression of metastatic disease. FDG PET/CT scans in a 70-year-old male with metastatic clear cell renal cancer. (**a**) Pre-therapy FDG PET/CT scan shows disease in peri-spinal soft tissue and left thigh (arrows). There is post-surgical/radiation uptake in right humeral metastasis. (**b**) Post-therapy with sunitinib, FDG PET/CT scan shows interval increased in size and intensity of FDG uptake in peri-spinal mass and left thigh soft-tissue mass (arrows). There are multiple new pulmonary and mediastinal metastases, indicating progression of the disease

response, with a 32.4% change in management. Given the evidence-based large population study results, FDG PET was approved by CMS for virtually all cancer types as the initial treatment strategy in mid-2009.

Novel Tracers and Future

124I-cG250 for Clear Cell RCC

Preoperative identification of tumor type could have important implications for the treatment choice for RCC. Carbonic anhydrase IX (CA IX), a membrane protein over-expressed in clear cell RCC, was found in 94% of clear cell carcinomas, and decreased CA IX levels are independently associated with poor survival in advanced RCC [66]. G250, a monoclonal antibody to carbonic anhydrase IX (CA IX), has extreme high affinity binding to clear cell RCC with tumor uptake approaching 0.5% of injected dose per gram of tumor tissue [67]. G250 was originally labeled with 131I [68]. Later on, positron emitters such as 89Zr [69] and 124I were labeled to cG250 [70]. A chimeric form of the antibody (cG250) has been generated with a less immunogenic response. A study using 124I-cG250 to target clear cell RCC showed great results from the phase 1 trial. Divgi and his group [70] demonstrated that 124I-cG250 PET could accurately distinguish clear cell RCC histology from other renal lesions with a sensitiv-

ity of 94% and a specificity of 100%, indicating the potential clinical utility of this tracer in the non-invasive molecular evaluation and subtyping of RCC. A renal tumor with a positive 124I-cG250 scan is found to be almost 100% a clear cell type (Fig. 6.16), while a negative scan is suggestive of non-clear cell type with 90% accuracy (Figs. 6.17 and 6.18). A false-negative scan has

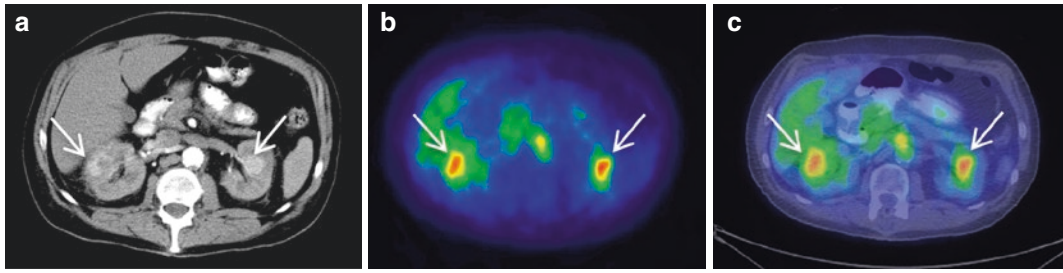

Fig. 6.16 Bilateral clear cell renal carcinoma. 124I-cG250 PET/CT in a 65-year-old male with bilateral renal masses. (**a**) Triphasic CT shows a 5-cm enhancing lesion in the right kidney and a 2-cm enhancing lesion in the left kidney (arrows). (**b**) 124I-cG250 PET shows intense uptake in both renal lesions, indicating clear cell renal carcinoma. (**c**) Fused PET/CT image

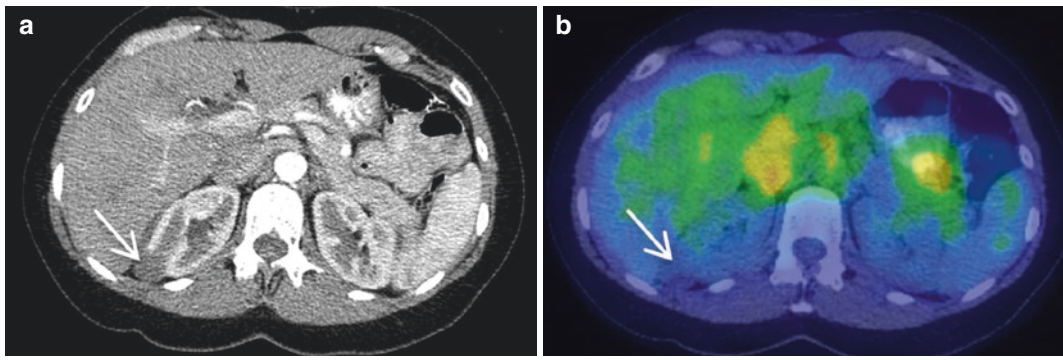

Fig. 6.17 Papillary renal cell carcinoma. 124I-cG250 PET/CT scan in a 49-year-old female with right kidney mass. (**a**) Triphasic CT scan demonstrates a non-enhancing lesion in right lower pole (arrow), HU 41. (**b**) No significant 124I-cG250 uptake corresponding to this renal mass, suggesting non-clear cell renal tumor

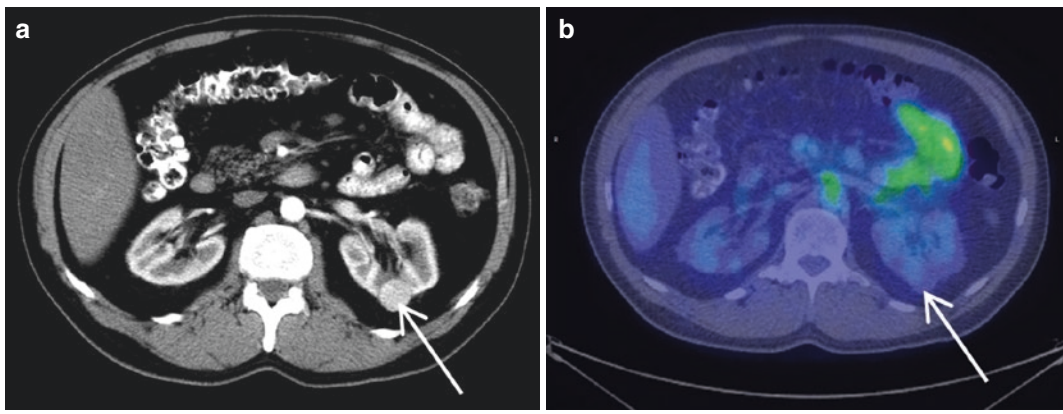

Fig. 6.18 Left renal oncocytoma. 124I-cG250 PET/CT scan in a 59-year-old male with a left renal mass. (**a**) Triphasic CT shows a 2-cm enhancing lesion (arrow), HU 120. (**b**) 124I-cG250 fused PET shows no significant corresponding uptake in the lesion, ruling out clear cell carcinoma

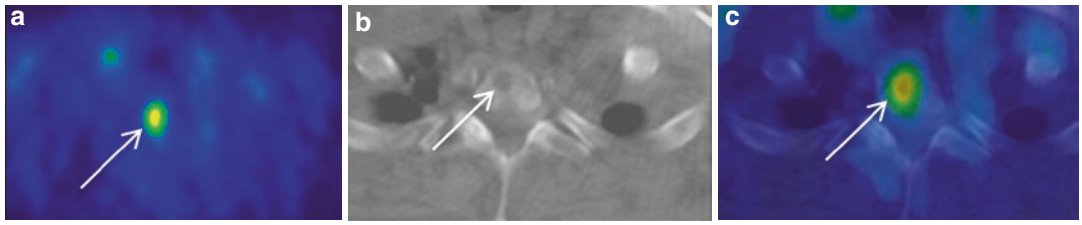

Fig. 6.19 Bone metastasis from clear cell renal cancer detected by 124I-cG250. 124I-cG250 PET/CT scan in a 65-year-old male with bilateral clear cell renal carcinoma. (**a**) PET shows a focal abnormal uptake (arrow). (**b**) There is a small corresponding lytic bone lesion in T1 vertebral body on CT (arrow). (**c**) Fused PET/CT image

been seen in tumor with extended necrosis and a small size (less than 1 cm). In addition, metastatic lesion(s) can also be seen on the scan with high confidence (Fig. 6.19).

Based on this phase 1 result, a comprehensive and multicenter comparative study for pre-surgical detection of clear cell RCC using 124I radiolabeled cG250 antibody was performed and completed in late 2009, and the results of the trial were published in JCO in early 2013 [71]. 124I-cG250 may improve the decision making for RCC treatment. For example, due to high possibility of clear cell RCC identification, patients with positive scans might need more aggressive therapy. Patients with negative scans may be candidates for active surveillance. The detection of metastasis may alter the treatment management plan from surgery to systematic medical therapy. More research is needed to fully evaluate the potential of this tracer in the future.

Other Novel Tracers

There are many targets and/or disease control points for new tracer development. The ideal tracer should target a specific disease process to provide patients with optimal care. The common targets or disease control points include metabolism, proliferation, hypoxia, angiogenesis, and apoptosis. Metabolism has been extensively studied by FDG PET with adequate data, and is well incorporated into the daily practice of clinical oncology.

18F-labeled thymidine (FLT), an analog of the nucleic acid thymidine, is a tracer that evaluates cellular proliferation. In a recent study, 18F-FLT was used to characterize and quantify changes in RCC tumor proliferation during sunitinib exposure and temporary withdrawal [72]. Data regarding the clinical use of 18F-FLT in RCC is still limited.

Hypoxia is another phenomenon commonly studied with novel PET tracers and PET imaging. 18F-FMISO appears to be the most commonly used tracer for imaging hypoxia. In a study, 18F-FMISO was performed in 17 patients with presumed RCC and showed only minimal increased uptake in RCC compared to normal renal tissue [73]. The mean SUV for RCC was 1.3, while that in the normal contralateral kidney was 1.1. A more recent study [74] with 53 patients evaluated the relationship between initial hypoxia-induced metastasis and after 1 month of sunitinib treatment using FMISO-PET scans. They concluded that sunitinib reduced hypoxia in hypoxic metastases but did not induce significant hypoxia in non-hypoxic lesions.

18F-labeled choline has been used for PET imaging of other tumors [75–78] such as lung and prostate. Middendorp and coworkers [79] published their initial experience with 18F-fluoroethylcholine PET/CT in staging and monitoring therapy response of advanced renal cell carcinoma. 18F-fluoroethylcholine PET/CT detected 56% of mRCC lesions on the baseline scan. Further study, ideally in comparison with FDG PET, should be investigated.

Acetate is another compound of interest. 11C-acetate has shown increased uptake in primary RCC and metastasis [80] as well. But another study showed low uptake [81]. 11C-acetate has been used for early prediction of sunitinib response in metastatic RCC with some success [80]. The use of this agent is limited due to the short half-life of 11C (20 minutes) requiring the need for an on-site cyclotron or one very near to the imaging

facility to produce. Recently available 18F-labeled acetate makes the delivery and commercialization of this tracer possible.

Conclusion

FDG PET offers limited advantage over conventional imaging in initial diagnosis of primary RCC. FDG PET is complementary to anatomic imaging in detecting locoregional and distant RCC metastasis. FDG PET/CT has the advantage of detecting small nodal metastasis and locoregional recurrent disease after nephrectomy. FDG PET/CT is the most accurate method used to study for bone metastasis from RCC.

Monitoring immunotherapy response of metastatic RCC by FDG PET/CT requires further studies to validate. FDG PET/CT has proven its usefulness in monitoring targeted therapies. These targeted therapeutic agents inhibit tumor growth rather than kill the tumor cells. This limits the use of conventional imaging modalities that are based solely on tumor size criteria. The information provided by molecular imaging such as maximum standardized uptake value (SUVmax) has shown to be an independent prognostic factor for RCC. SUVmax should be considered to be incorporated into future prognostic models.

There are limitations for FDG PET/CT as a diagnostic tool for RCC. New tracers focusing on disease processes such as hypoxia, angiogenesis, and apoptosis might be of value in RCC as well. Immuno-PET may help better assess the immunotherapy response. If we could find a specific tracer for each disease process, we might improve our patient care significantly and provide true individualized therapy for our patients.

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7 Interventional Radiology and Angioinfarction: Embolization of Renal Tumors

Sebastian Flacke and Shams Iqbal

Indications for Renal Artery Embolization

The key indications for renal artery embolization include the following:

- Angioinfarction or tumor infarction prior to resection or ablation
- Palliation of unresectable renal malignancies
- Management of renal angiomyolipomas
- Life-threatening or debilitating hematuria
- Arteriovenous fistulas (spontaneous or iatrogenic)
- Vascular malformations
- Renal artery aneurysm or pseudoaneurysm
- End-stage renal disease [5, 6]
- Uncontrollable hypertension [7, 8]

Technical Details

The techniques and materials used for the embolization of the kidney vary depending on the level of occlusion within the renal vascular tree [1–8]. The selection of the site and the material used to achieve vascular occlusion will determine the degree of complexity of the procedure and potential risks.

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All endovascular procedures have in common the vascular access in the femoral, brachial, or radial artery with the insertion of a catheter sheath. In a patient with very tortuous iliac arteries, a longer (35–45 cm) 5- or 6-French sheath can be positioned in the infrarenal aorta facilitating the access to the renal artery ostium. Embolization procedures are performed under strict aseptic conditions, and prophylactic administration of antibiotic is recommended for permanent embolization of larger areas of renal parenchyma. All endovascular procedures bear the risk associated with the access into the arterial system. As imaging during the procedure relies on the injection of iodine contrast, poor renal function may further deteriorate [9]. It is, therefore, beneficial if the patient is sufficiently hydrated prior to the procedure.

In principle, four types of occlusion can be differentiated based on the level of occlusion within the arterial system.

Central Occlusion

A central occlusion is usually achieved by deployment of larger platinum coils, a vascular occluder device, or a detachable balloon in the main renal artery through a 5-French or larger guiding catheter in hockey-stick or cobra configuration. The shape and size of the coils vary according to the size of the vessel to be occluded. Coils may contain small pieces of textile to enhance clot formation after deployment.

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In the presence of renal artery aneurysm, detachable microcoils, which can be introduced through a 3-F or smaller microcatheter, are used to occlude the diseased area while preserving flow to the kidney. Coil deployment within an aneurysm may be facilitated with balloon or stent-assisted coiling (Fig. 7.1).

Multiple coils are usually needed to obtain complete stasis in the main renal artery. Complete stasis can be documented with the injection of iodine contrast through the guiding catheter. The catheter is placed sufficiently deep into the renal artery to avoid inadvertent dislodgement of a coil into the aorta. If main renal artery embolization is performed prior to surgery, the coils should be deployed at least about 2 cm distant from the branching point of the aorta to allow for surgical ligation without the risk of coil displacement into the aorta.

A vascular occluder (Amplatzer Vascular Plug, AGA Medical Corporation, Plymouth, MN) is comprised of a nitinol cage filled with thrombogenic polyester filaments. The size of the occluder is chosen according to the size of the vessel to be occluded. A vascular occluder provides very rapid occlusion and is ideal for high flow situations.

Detachable balloons have been largely replaced by coils and plugs, despite the fact that they provide large volume occlusion with great precision. However, deployment is difficult and shape and persistence of the inflation of these balloons are variable and change over time.

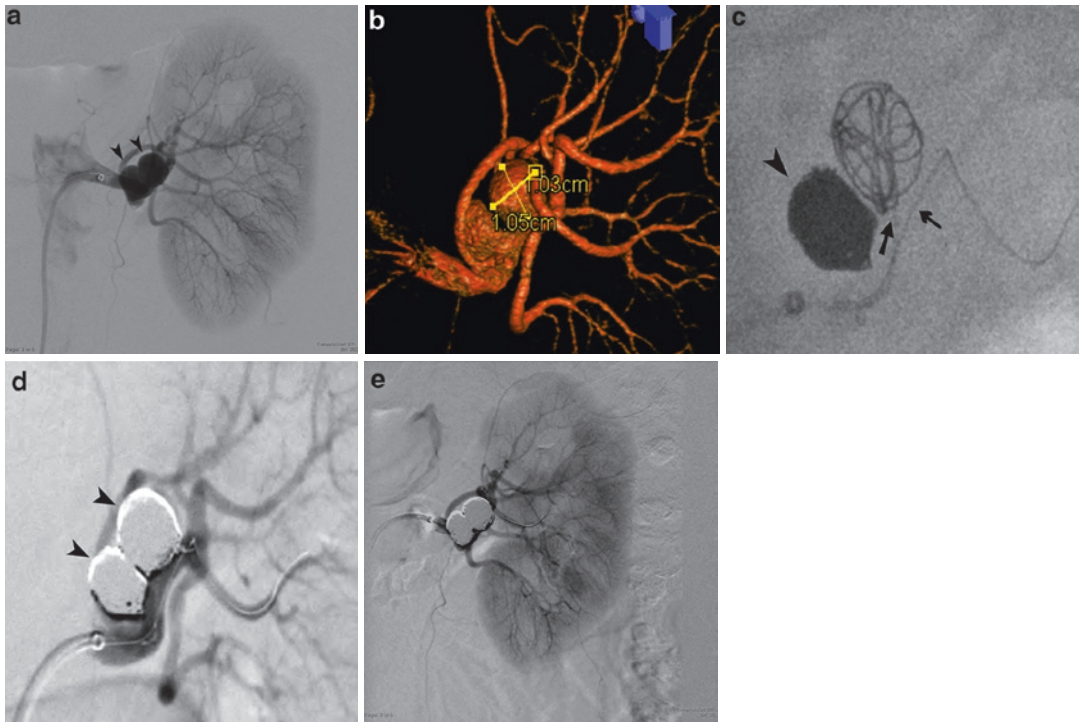

Fig. 7.1 Saccular aneurysm arising from the main renal artery in a 73-year-old patient with a planned contralateral partial nephrectomy for renal cancer. Both aneurysms were detected on cross-sectional imaging, and selective coil embolization was performed prior to surgery. Initially, a 6-French vascular sheath was positioned in the proximal portion of the main renal artery. This sheath secured safe access in the main renal artery during the entire procedure. Both aneurysms are seen as saccular outpouching of the main renal artery (**a**, arrowheads). A rotational angiogram and three-dimensional surface rendered reconstructions are obtained which helped to determine the dimensions of the aneurysm and the best projection angle of the C-arm (**b**). Balloon-assisted coiling of both aneurysms was performed using detachable microcoils. After embolization of the fist aneurysm (**c**, arrowhead), the microcatheter used for coil delivery is entered into the second aneurysm (**c**, arrow). A second microcatheter holding a balloon is inserted into the main renal artery (**c**, rounded arrow). The balloon is inflated if portions of the coils protrude into the main renal artery. An arteriogram of the main renal artery after dense packing of both aneurysms (**d**, arrowhead) shows patency of the main renal artery. These angiograms are obtained by injecting into the guiding sheath. The parenchymal phase (**e**) shows patency of the entire vascular tree without embolic events

Combined Central and Peripheral Occlusion

This type of embolization aims to occlude the renal artery and first- and second-order branches. A coaxial catheter system using a 3-French or smaller microcatheter and a guiding catheter is positioned in the main renal artery to reach the second-order branches. The use of a coaxial catheter system provides additional safety as the inner catheter can be withdrawn at any time without losing access to the renal artery and the added option to inject iodine contrast through the guiding catheter. A variety of embolic material can be used.

Micro- and macrocoils can be deployed by either pushing the coil with a guidewire or flushing the coils into the artery with a small bolus of saline injected using a 1-ml syringe.

A multitude of prefabricated inert embolic particles are available ranging from 40 to 1200 μm. Particles larger than 100 μm will not reach the capillary bed and may be used for this type of embolization. Different types of particles are available: polyvinyl alcohol (Ivalon, Unipoint Laboratories, High Point, NC), acrylic polymer microspheres (Embosphere Microspheres, Biosphere Medical, Rockland, MA), polymer-coated particles with a hydrogel core (Embozene Color-Advanced Microspheres, CeloNova Biosciences, Newnan, GA), and polyvinyl alcohol microspheres (Bead Block, Biocompatibles Inc., Oxford, CT). These particles can be dry or diluted in aqueous solution. They are usually mixed with iodine contrast prior to injection to facilitate visualization. Care must be taken to carefully assess for large arterio-venous shunting which bears the danger of embolizing into the renal vein and from there into the lungs. With the reduction of forward flow during embolization, the risk of reflux increases. A control angiogram after embolization with particles should be performed with care (Fig. 7.2). A gentle injection may confirm stasis of blood flow; a more forceful injection may wash out some of the injected particles leading to inadvertent nontarget embolization.

Embolization with resorbable material is another inexpensive option for this type of embolization. Sterile synthetic gelatine sponge is a biodegradable material, which is resorbed within 2 weeks to 3 months after the embolization. Various commercial preparations are available: Gelfoam (Pharmacia & Upjohn Company, MI), CuraSpon (CuraMedical BV, Amsterdam, The Netherlands), and Gelita-Spon (Gelita Medical BV, Amsterdam, The Netherlands). The foam

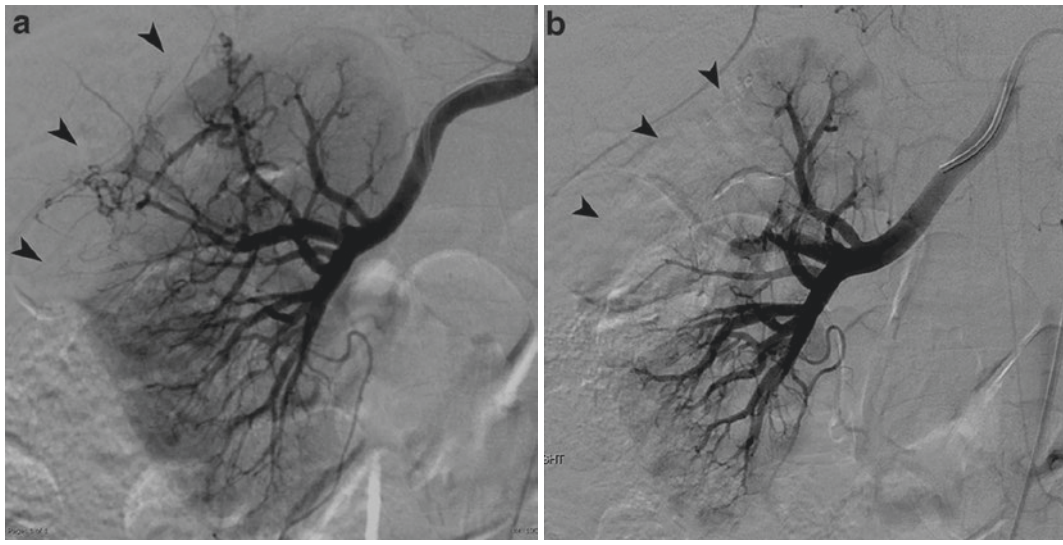

Fig. 7.2 Preventive embolization of a large angiomyolipoma in a 54-year-old female with recurrent hematuria. A selective angiogram of the left kidney shows a rounded poorly defined mass of approximately 5 cm in diameter in the left upper pole of the kidney (**a**, arrowheads). Superselective embolization of three segmental branches using a 3-French microcatheter and 300–500-μm microspheres was performed to completely devascularize the mass (**b**, arrowheads). Final angiography shows the preserved portions of the kidney

particles can be cut to appropriate size by the operator. They are then mixed with saline and contrast and can be injected into the target area. Although immediate occlusion can be achieved relatively quickly, there is a chance of recanalization of the targeted vessel territory over time as the Gelfoam particles may be reabsorbed.

Capillary Occlusion

Capillary occlusion aims to occlude the entire arterial compartment from the capillary bed to the main artery to create an infarct of a portion of the entire organ or total angioinfarction with permanent occlusion of all glomeruli.

Capillary occlusion can be achieved using small caliber inert embolic particles of about 40–100 μm. Small particles are the preferred agents for smaller parenchymal areas, such as a small tumor, due to the ease of administration.

Liquid embolic agents are an alternative and the preferred agents for the embolization of a larger vascular bed. N-Butyl-2-cyanoacrylate biological glue (Histoacryl, B/Braun, Tuttlingen, Germany) can be injected through a microcatheter using a coaxial approach. Prior to the injection, cyanoacrylate is mixed with ethiodized oil (Ethiodol/Lipiodol, Guerbet, Bloomington, IN), a poppy seed oil used as radiopaque contrast agent and diluent of the tissue glue. The speed of embolization is influenced by the quantity of added Ethiodol. In a mixture containing 0.5 ml tissue glue and 0.5 ml of Ethiodol, the polymerization of the tissue glue occurs within 0.5–1 s [10]. Mixtures of 1:1 to 1:3 ratios of biological glue and ethiodized oil are favored for capillary occlusion. The microcatheter is flushed with concentrated glucose or dextrose, which binds anions by osmosis prior to the injection of the biological glue to avoid polymerization within the microcatheter. If injected in small aliquots using a 1-ml syringe, adhesion of the microcatheter tip to the vessel wall can be avoided. However, it is recommended to withdraw the microcatheter into the guiding catheter after each injection as a small portion of the tissue glue may stick to the tip and require an exchange of the catheter. The use of a coaxial catheter approach is warranted. The advantage of the use of tissue glue is the fact that it will create immediate vascular occlusion even in the presence of impaired clotting. Complications related to inadvertent displacement of tissue glue are scarce and mostly related to an inappropriate technique, often due to not relying on a coaxial catheter set-up. Tissue glue can create a foreign body giant cell reaction within the first weeks of administration but does not lead to the development of secondary tumors.

Onyx (EV3 Endovascular, Plymouth, MN), another liquid embolic agent, is comprised of EVOH (ethylene vinyl alcohol) copolymer dissolved in DMSO (dimethyl sulfoxide) and suspended micronized tantalum powder to provide contrast for visualization under fluoroscopy. It can be injected as a liquid in a very controlled fashion and solidifies in contact with ionic solutions from the outside to the inside. It has potential application in vascular disease, but experience in the renal vasculature is still limited [11].

The most widely used liquid embolic agent to create a complete renal infarction is highly concentrated alcohol [12]. The injection of alcohol into the renal artery for complete infarction requires the use of an occlusion balloon, which is positioned in the proximal renal artery to avoid a spillover of the injected alcohol into the aorta and controls the blood flow through the kidney. If a coaxial approach is chosen, a sheath can be positioned in the aorta close to the ostium of the renal artery, and the balloon catheter is inserted through the sheath. The coaxial approach has the benefit to allow verification of the tightness of the inflated balloon with the injection of iodine contrast through the sheath (Fig. 7.3). If only a small region of the kidney is targeted, a coaxial approach using a microcatheter is sufficient. Alcohol can be injected in a single fast injection or in fractionated smaller doses. If a single fast injection is used, 10–15 ml of alcohol is injected through the tightly inflated occlusion balloon. The balloon remains inflated for at least 10 minutes before iodine contrast is injected to document secondary thrombosis of the arterial system. If the degree of occlusion is not satisfactory, the procedure will be repeated. In the fractionated approach, 4–10 ml is injected over several minutes. The degree of thrombosis will be documented with the injection of iodine contrast after each alcohol injection until com-

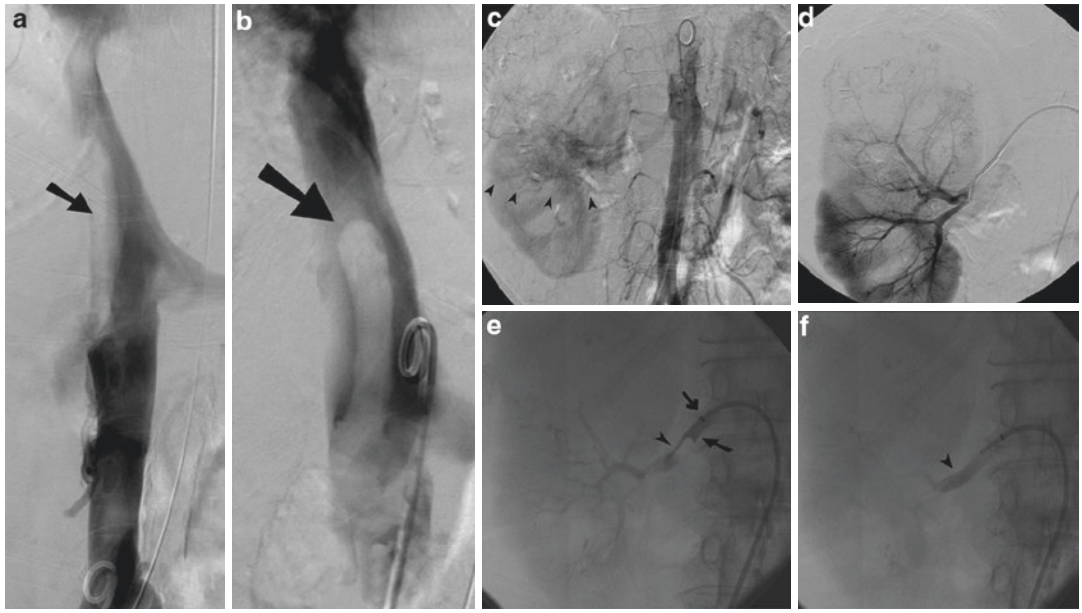

Fig. 7.3 Angioinfarction of a large left renal mass with extension into the inferior vena cava. An initial venogram of the inferior vena cava obtained after injection of a pigtail catheter placed at the level of the common iliac vein shows a filling defect in the IVC (**a**, arrow). A second injection with the pigtail catheter placed in the supra renal IVC delineates the large tumor thrombus (**b**, arrow) extending into the intrahepatic segment of the IVC. An aortogram shows the extent of the large renal mass which has replaced the upper 2/3 of the kidney (**c**, arrowheads). The uninvolved portion of the kidney fed by the lower pole segmental artery is better appreciated with a selective injection (**d**). Angioinfarction with high concentrated alcohol is performed through a balloon occlusion catheter (e, arrowhead). The balloon occlusion catheter is introduced through a 6-French guiding sheath placed into the proximal main renal vein (**c**, rounded arrow). Once the balloon occlusion catheter is inflated, blood flow through the main renal artery into the kidney is completely blocked. A contrast injection into the guiding sheath allows verifying the tightness of the occlusion. The injected contrast remains in the proximal stem of the main renal artery (**e**, arrow). After injection of 15 ml of alcohol and an occlusion of 15 minutes, the balloon was deflated. The injected contrast filled the space occupied by the balloon (**f**, arrowhead), but secondary thrombosis of the renal vasculature had already occurred and prevented the contrast from flowing into the kidney

plete stasis is reached. Both techniques require the same amount of time and approximately 20 ml of alcohol; however, in few cases up to 50 ml can be used. A total dose of 0.5 ml/kg bodyweight of alcohol should not be exceeded. Many complications associated with the embolization of the kidney with alcohol have been reported in the early days of embolization. The complications were mostly related to reflux of the embolic material into other vessel territories resulting in necrosis of colon, skin, and spinal cord [12–14]. The appropriate use of an occlusion balloon has drastically reduced complications.

Capillary occlusion of the kidney requires appropriate pain medication during and after the procedure. We usually use intravenous analgesics and opioids for 12 hours after the embolization procedure. The anticipated degree of pain is inversely correlated to the degree of tumor infiltration of the renal capsule. Embolization of a large tumor that has replaced the kidney will be better tolerated than whole kidney embolization for small tumor burden. A more targeted approach to smaller tumors is often more appropriate (Fig. 7.4).

Moderate hematuria may be observed after embolization as a result of hemorrhagic infarction in first days after embolization.

A post-embolization syndrome with flank pain, fever, paralytic ileus, nausea, vomiting, and headache can be observed in about 4% of patients after whole kidney embolization. Laboratory assessment shows an increased white blood cell count and increased level of plasmatic lactate dehydrogenase. The leading symptom is the flank pain

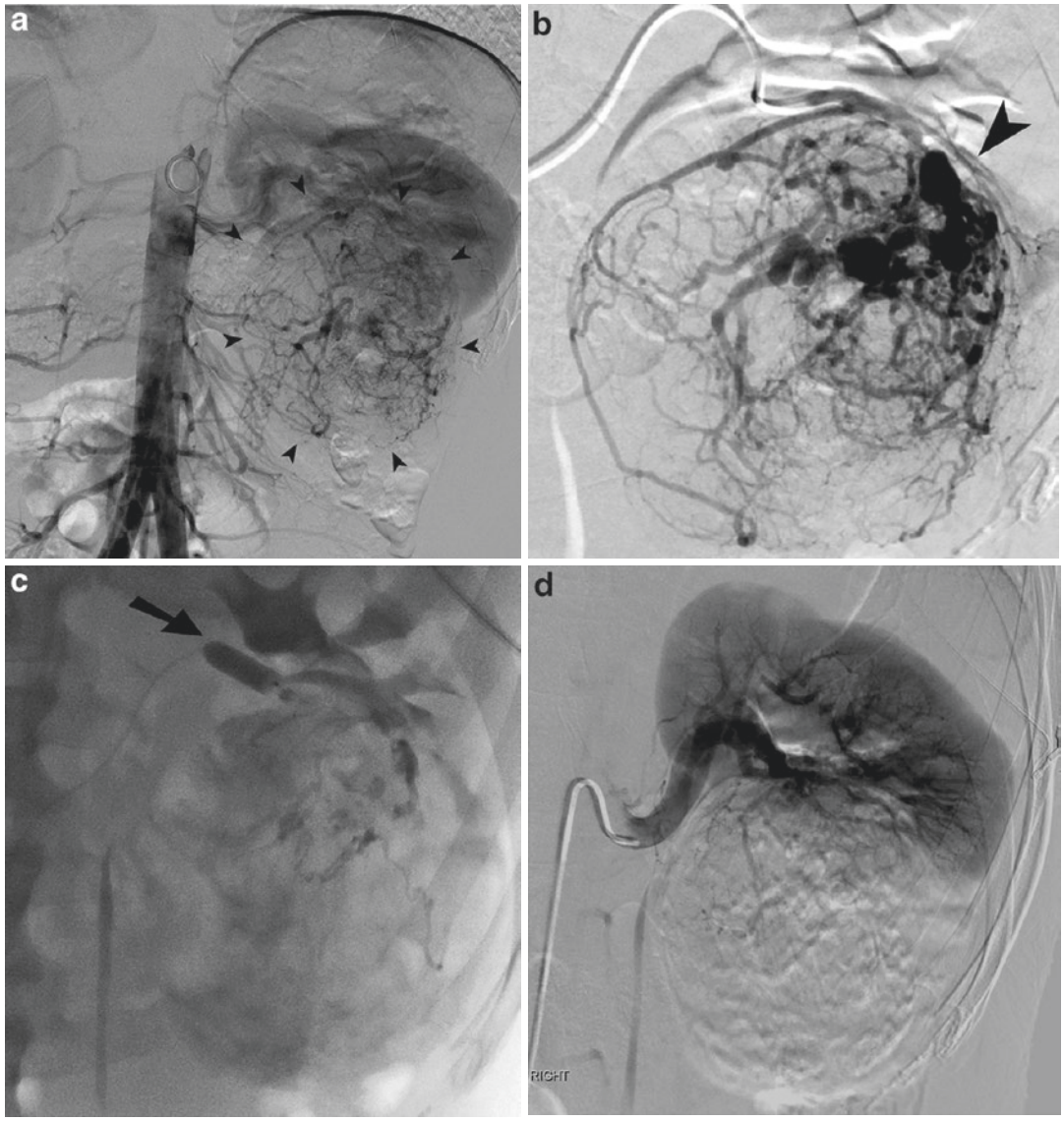

Fig. 7.4 Embolization of large angiomyolipoma in a 32-year-old female with recurrent retroperitoneal bleeding prior to intended partial nephrectomy. The initial aortogram shows a large, 7.6 cm in diameter, exophytic right lower pole renal mass (**a**, arrowheads) with pathological vessels. Aneurysmal dilatation of the intratumoral vessels (**b**, arrowhead) is better appreciated with a selective angiogram. A small PTA balloon was advanced into the tumor feeding segmental artery. After inflation of the balloon catheter, 12 ml of concentrated alcohol was injected. The PTA balloon remained inflated for 20 minutes. A final selective angiogram shows complete devascularization of the tumor with preserved perfusion of the uninvolved upper pole

which should be controlled with appropriate pain medication. Increased temperature may be present for hours or days but usually subsides shortly after the procedure. The syndrome generally resolves with symptomatic treatment in a few days.

Transient increases in arterial blood pressures are frequent during and immediately after the procedure, which could be associated with the increasing level of pain. Persistent arterial hypertension may indicate the presence of residual ischemic but not infarcted tissue [15].

During follow-up, small gas inclusion within the necrotic area can be found in cross-sectional imaging. These bubbles are not of a septic origin

but represent normal aseptic necrosis and usually do not require treatment as an abscess [16, 17].

Superselective Embolization

Superselective embolization is performed through a microcatheter which is introduced in coaxial technique through 5-7F guiding catheter. The microcatheter is advanced as close to the target area as possible prior to the injection of the embolic material. Microcoils, particles, tissue glue, alcohol, or onyx may all be used in various circumstances. The choice of the embolic material is depended on the blood flow and target. High blood flow with the chance of false embolization into the venous system usually requires the placement of microcoils, detachable balloons, or tissue glue. Microcoils are among the safest embolic material in these situations (Fig. 7.5). The selective deployment of such coils in small branches up to the interlobular artery level allows for a very selective embolization spar-

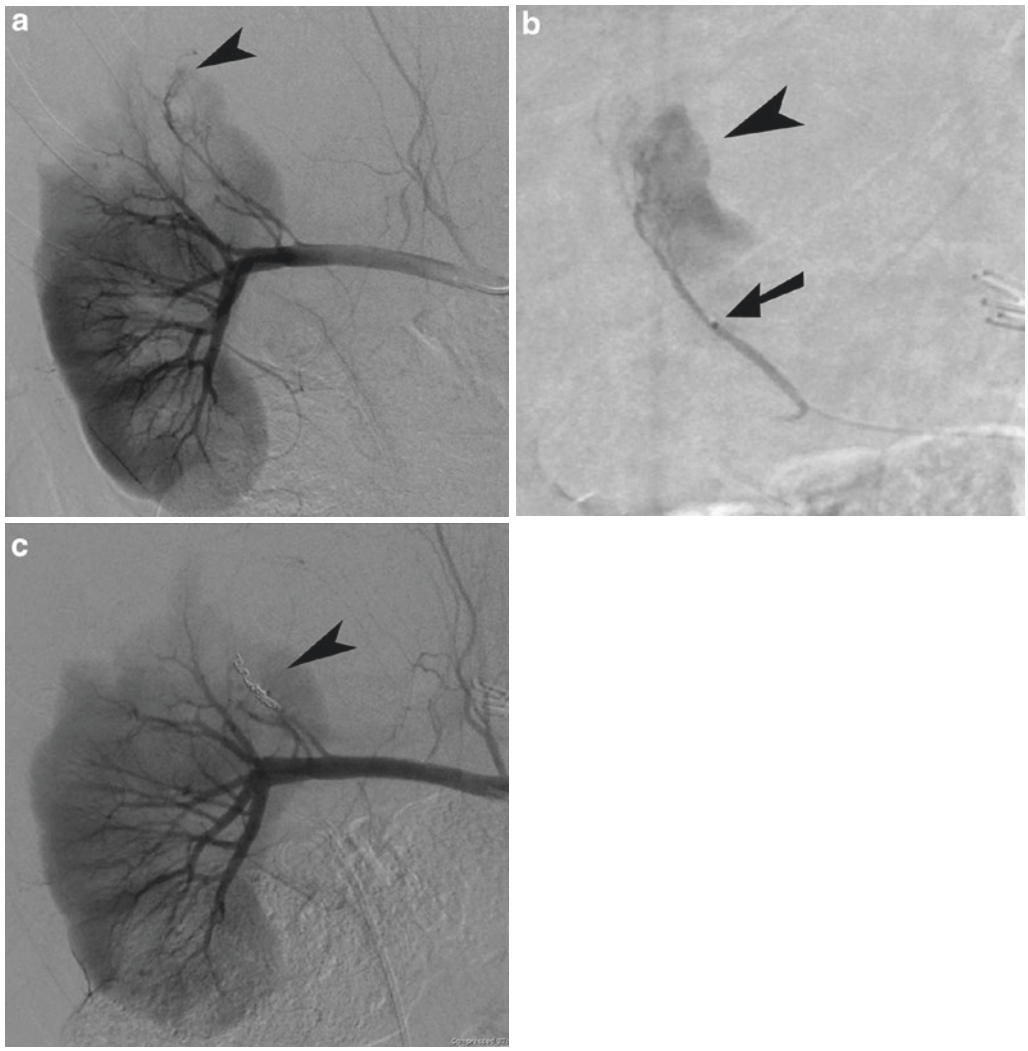

Fig. 7.5 Superselective embolization of a bleeding segmental artery after partial nephrectomy in a 67-year-old male. A selective angiogram of the left kidney shows a faint blush (**a**, arrowhead) next to an upper pole segmental artery after resection of a portion of the upper pole. A 2.3-French microcatheter (**b**, arrow) was placed close to the bleeding site. The superselective angiogram delineates the full extent of the bleeding (**b**, arrowheads). Placement of two microcoils into this artery (**c**, arrowhead) occluded the vessel and stopped the bleeding with minimal parenchymal damage

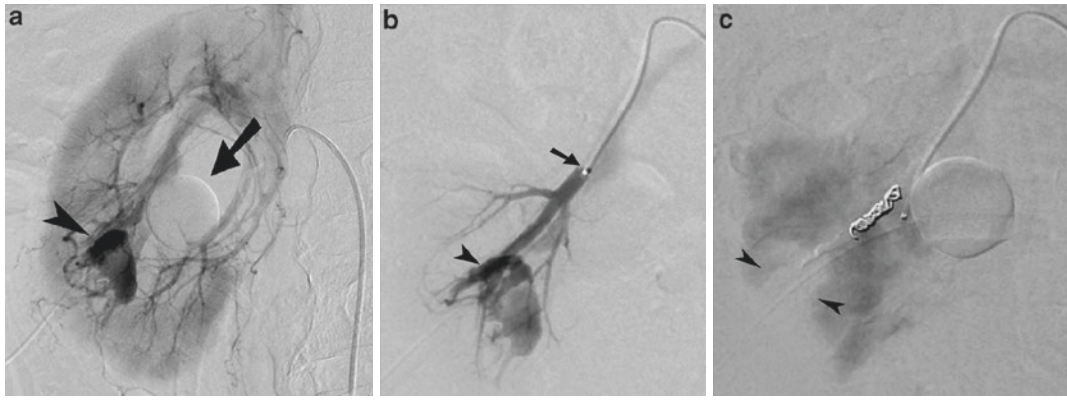

Fig. 7.6 Embolization of a false aneurysm after percutaneous nephrolithotomy. A selective angiogram of the left renal artery shows a false aneurysm (**a**, arrowhead) arising from the access site into the kidney. A Foley catheter (**a**, arrow) was placed initially to tamponade the bleeding. A 3-French microcatheter (arrow) was advanced into the bleeding segmental artery. A superselective angiogram using the microcatheter demonstrates the vascular injury to the artery (**b**, arrowhead). Coil embolization of the artery using three microcoils was performed leading to a small cortical defect (**c**: arrowheads)

ing the remaining parenchyma (Fig. 7.6). Care must be taken not to overestimate the embolic effect of a single coil as vasospasm associated with the deployment may falsely create the impression of a complete occlusion. Superselective embolization is the method of choice for focal renal arterial bleeding associated with false aneurysm, AV fistulas, trauma, angiodysplasia, or post-biopsy or resection (Fig. 7.7). Superselective embolization may also be considered to reduce tumor bleeding prior or during focal resection or percutaneous ablation [18, 19] (Fig. 7.8).

Clinical Value of Transcatheter Tumor Embolization

To date, embolization is considered in two different situations: preoperative and palliative. The majority of published data on renal tumor embolization is centered around preoperative embolization, approximately 1/3 around palliative embolization.

Preoperative Embolization

Superselective, targeted embolization of small malignant renal tumor prior to minimal invasive nephron sparing surgery or percutaneous ablation may be considered to reduce intraprocedural bleeding in patients with larger lesions or increased bleeding risks [18–20]. The effectiveness of the percutaneous ablation will be enhanced creating larger ablation zones, if performed shortly after the embolization. Published evidence regarding the combination of embolization and ablation is still small but promising.

Renal angioinfarction in locally advanced renal cell carcinoma is discussed controversially in the literature. Protagonists emphasize the benefit of embolization on intraoperative blood loss [21], edema in the resection planes creating a better cleavage plane [22], and earlier control of the renal pedicle due to decompression of vascular structures, thus facilitating radical nephrectomy [4, 23, 24]. It is also believed that embolization may improve control of large tumor thrombus within the venae cavae extending to the liver (grade III) or above the diaphragm (grade IV) by reducing the cephalad extension [25]. Survival benefit has been found in patient cohorts who underwent embolization prior to radical nephrectomy [26]. However, an extensive body of literature refutes the benefit of the embolization procedure which may be associated with a longer hospital stay questioning the need of this procedure even in advanced cases of renal cell carcinoma with vena cava involvement [23, 27–29]. Further discussion

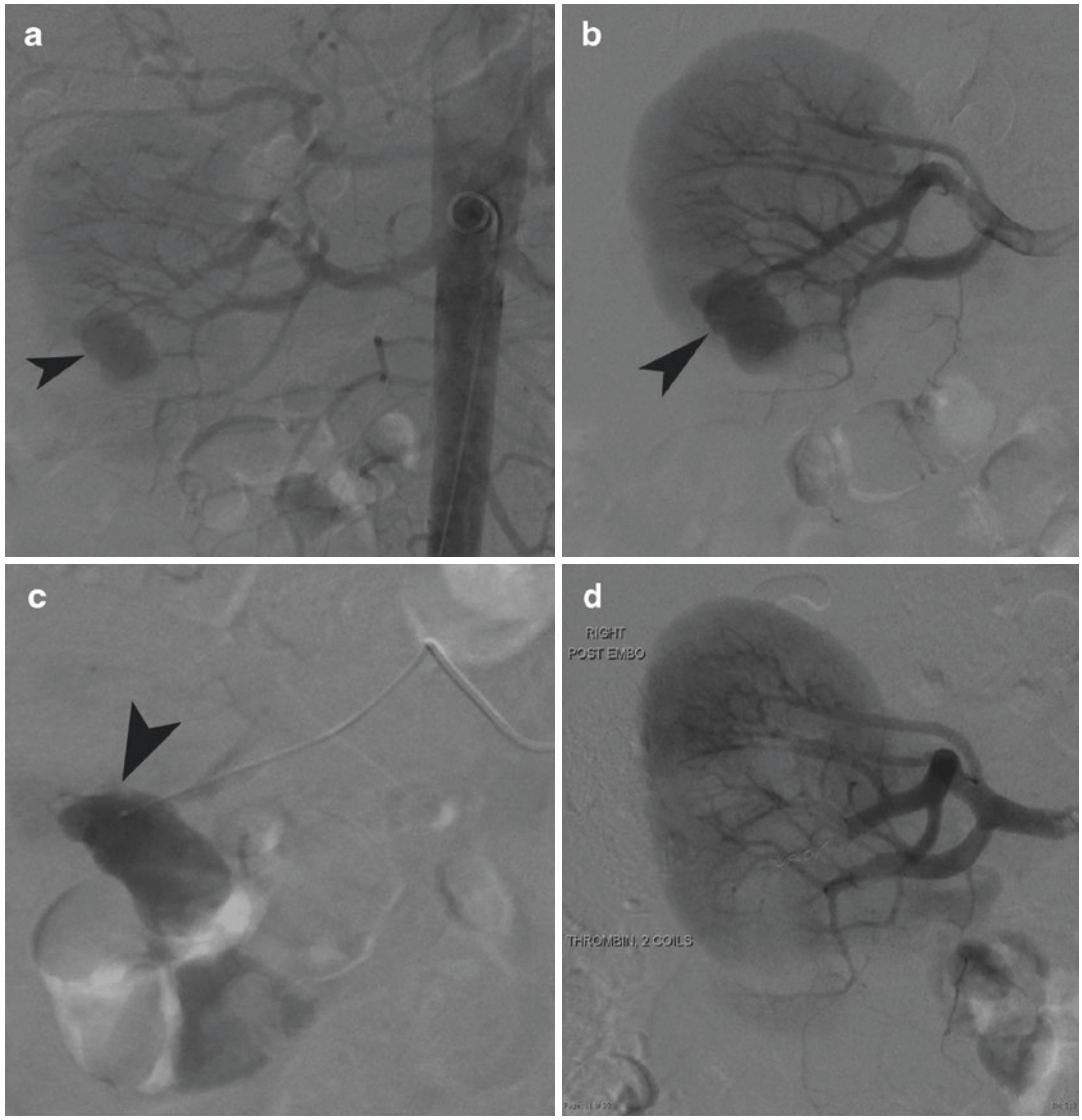

Fig. 7.7 Embolization of a false aneurysm in a 64-year-old male with massive hematuria after left lower pole partial nephrectomy. The initial aortogram shows a large contained contrast extravasation (**a**, arrowhead) near the resection plane of the lower pole. The total extent of the false aneurysm is better appreciated with a selective angiogram (**b**, arrowhead). A microcatheter was advanced into the false aneurysm (**c**, arrowhead), and 1000 units of thrombin was injected before withdrawal of the microcatheter from the false aneurysm and coiling of the feeding artery with two microcoils. The final selection arteriogram shows complete occlusion of the aneurysm with no parenchymal defect

surrounds the optimal time interval between embolization and surgery. Twenty-four hours is favored by many authors, but a longer time interval may allow for tumor shrinkage and encapsulation of the necrotic kidney [25]. At our institution, embolization precedes surgery by more than 20 days (Fig. 7.9).

Despite the fact that more than several thousand cases of embolization have been published, we still do lack clear evidence of the benefits of renal angioinfarction. Randomized controlled trial should be undertaken to compare treatment of locally advanced renal carcinoma with and without embolization. To date,

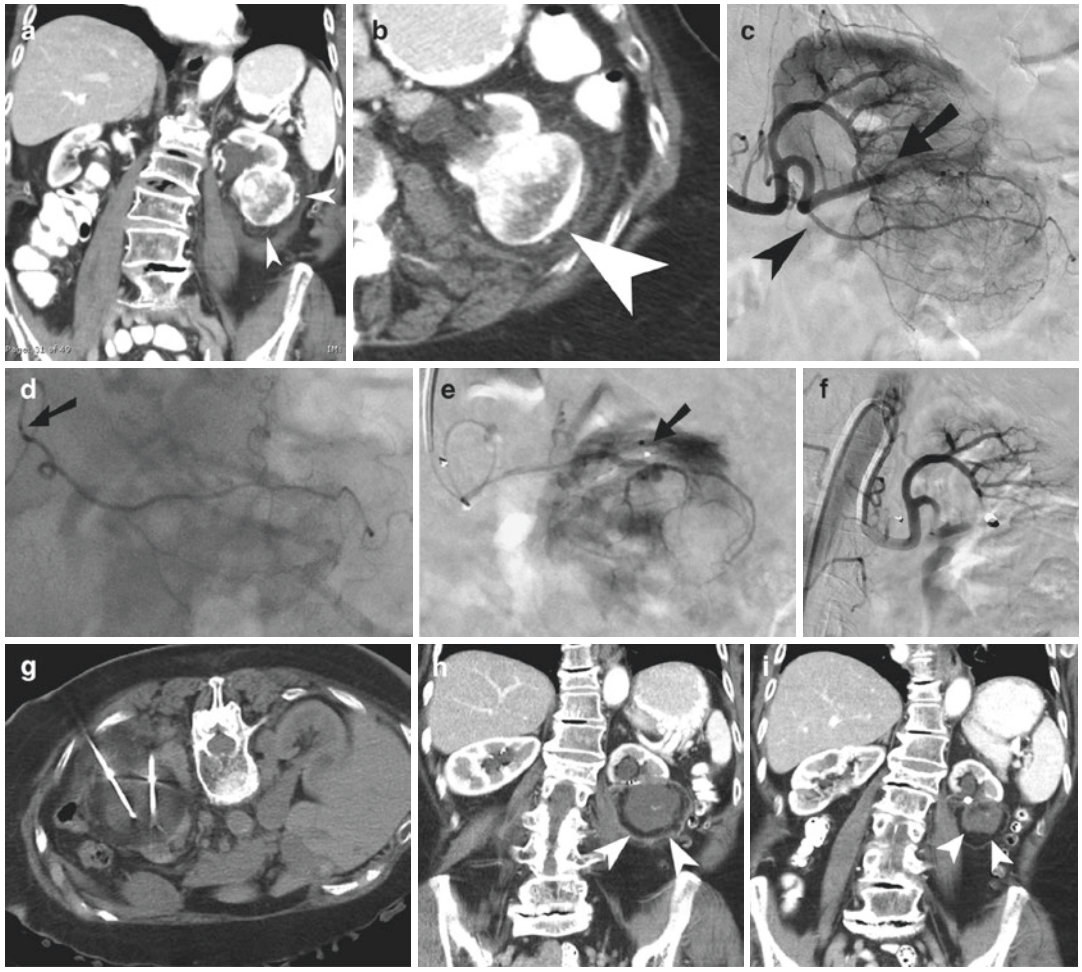

Fig. 7.8 Combined selective embolization and cryoablation of a large lower pole renal mass in a 91-year-old female with multiple comorbidities. A fast growing 5.8 cm in diameter mass of the lower pole of the right kidney (**a**, **b**, arrowheads) was treated on patient' s request. Embolization was performed 24 hours prior to cryoablation of the lesion. A selective angiogram demonstrated the blood supply to the tumor area. Capsular branches (**c**, arrowhead) arising from the adrenal artery and the lower pole artery (arrow) were identified as contributor. A 2.3-French microcatheter was advanced into the capsular artery (**d**, arrow), and small amount of alcohol was injected with the catheter in wedge position. A microcoil was then deployed before withdrawal of the microcatheter. The lower pole artery and tumor were then embolized through a microcatheter (**e**, arrowheads) using concentrated alcohol, 300–500-μm microspheres, and proximal microcoils. The final selective angiogram showed complete devascularization of the tumor with preserved perfusion of the upper pole. Cryoablation (**g**) was performed using 4 cryoablation probes under MAC anesthesia from a dorsal approach. Follow-up CT images in the coronal plane obtained at three (**h**) and 12 months (**i**) after the procedure showed good control of the tumor (arrowheads) without any residual enhancement and slow retraction over time. The upper kidney and collecting system were well preserved

routine angioinfarction of renal cell carcinoma prior to resection is based on weak evidence. However, for a complicated radical nephrectomy and IVC thrombectomy, several nuances exist to the surgical approach, which may require presurgical embolization in selected cases.

Palliative Embolization

Renal Cell Carcinoma

Much less controversy exists regarding the value of embolization in a palliative setting [23, 30]. Palliation of unresectable renal cell carcinoma aims to stop hematuria, paraneoplastic syndromes,

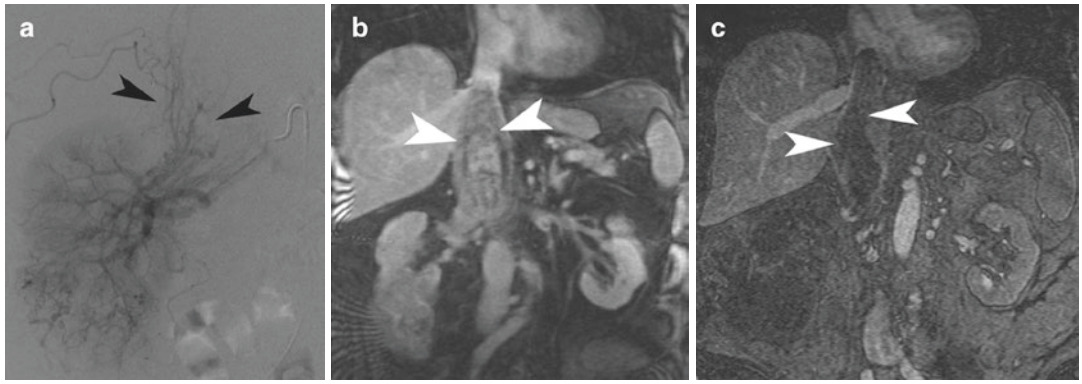

Fig. 7.9 Angiogram prior to angioinfarction of a large renal mass with inferior vena cava involvement in a 74-year-old man. The large mass has infiltrated and replaced the entire lower left kidney. Small arteries (**a**, arrowheads) are seen extending from the renal hilum into the large tumor thrombus within the inferior vena cava. MR images before and after the embolization are displayed in Figure **b** and **c**. 3D-T1-weighted images show the avid enhancement of the tumor and the IVC tumor thrombus extending into the diaphragmatic portion of the IVC after administration of gadolinium containing contrast. A follow-up MR imaging study obtained 4 weeks after angioinfarction shows complete devascularization of the renal mass and IVC thrombus (**c**, arrowhead). The thrombus has not significantly shrunken in cranio-caudal directions but appears less voluminous

or tumor-associated pain. Survival is if at all a secondary target [31]. Success rates of permanent control of hematuria vary significantly in the literature, but this is related, to some extent, to the level of embolization and the material used. Liquid embolic agents usually provide prompt symptomatic improvement of hematuria. The extent of the embolization should be limited to what is necessary to control the symptoms. Angioinfarction of the entire kidney which may result in a notable deterioration of kidney function, increase the risk of infection, and be associated with a post-embolization syndrome is often not necessary.

Angiomyolipoma

Embolization of hypervascular angiomyolipoma is justified in the presence of bleeding, but it is also performed to prevent imminent bleeding. Hypervascular lesion may contain a multitude of vessels with impaired vessel wall function due to a lack of elastic fibers and is thus prone to aneurysm formation (Fig. 7.4). Rupture of this aneurysm creates perirenal bleeding or massive hematuria [32]. Hemorrhagic complications occur more frequently in tumors greater than 4 cm in diameter, in the order of 1 out of 5 per year [33, 34]. This is why prophylactic embolization of renal angiomyolipomas may be considered in hypervascular lesions exceeding 4 cm in diameter. The risk of overtreatment has to be balanced against the possible morbidity associated with the procedure [35]. The goal of the embolization procedure is to devascularized the tumor nodule while preserving as much healthy renal parenchyma as possible. This is especially important in the presence of multiple lesions [34]. Long-term control can be achieved with superselective capillary occlusion of the hypervascular tumor nodules [36–38]. Resorbable material and coil embolization bear a substantial risk of revascularization.

Embolization of the Primary Renal Mass in the Presence of Metastasis

Based on the observation that resection of the primary tumor in the kidney has beneficial effects on lung metastases, embolization of the primary renal mass has been advocated [31]. A survival benefit has been described, but this finding could not be confirmed independently [39].

Embolization of a Nonfunctioning Renal Graft

Embolization of a nonfunctioning renal graft could be considered in poor surgical candidates. This procedure is usually well tolerated if the relative frequent post-embolization syndrome is appropriately managed [40].

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8 Natural History, Role of Biopsy, and Active Surveillance of Renal Masses

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Introduction

Renal cell carcinoma (RCC) is the most common primary malignancy of the kidney, and it is the most lethal of all urologic malignancies. In 2018, the American Cancer Society estimates that more than 63,000 men and women will be diagnosed with RCC and nearly 15,000 will die from the disease [1]. Due to the increased use of cross-sectional abdominal imaging over the past several decades, a stage migration toward low-grade low-stage RCC has been observed in large population-based cohorts [2, 3]. In the decade from 1993 to 2004, the proportion of new RCC cases diagnosed at stage I increased from approximately 43% to 57% [4], and the incidence of tumors less than 3.0 cm in diameter at presentation increased from 32.5% to 43.4% [5] (Fig. 8.1). Today, the vast majority of small renal masses (SRMs) are discovered incidentally [6], are asymptomatic, and have a variable malignant potential. Approximately 15% of SRMs are benign tumors [7], and only an estimated 20–30% of RCC cases are determined by pathologic assessment to have features suggestive for potentially aggressive biology and behavior [8, 9]. Concurrent with the rise in SRM incidence, an "age migration" of RCC has been observed with a peak incidence in persons between 70 and 90 years of age [10]. Paradoxically, although the rates of renal surgery and other interventions have risen as well, the mortality from RCC has not improved significantly over the last decades, suggesting that the absolute number of lethal lesions has not diminished [3]. Many believe this observation indicates that a large proportion of SRMs may be clinically insignificant benign or indolent tumors and that extirpation of all SRMs may represent over-diagnosis and over-treatment.

The concept of over-diagnosis and over-treatment of malignancy is a relatively new concern. The risks and consequences associated with unneeded treatment for low-risk or indolent cancers are potentially the most important and underappreciated harms associated with early cancer detection [11]. While surgical treatment for stage I RCC demonstrates 5-year cancer-specific survival rates in excess of 95% [12], some have begun to question if the driving force behind these favorable outcomes is simply

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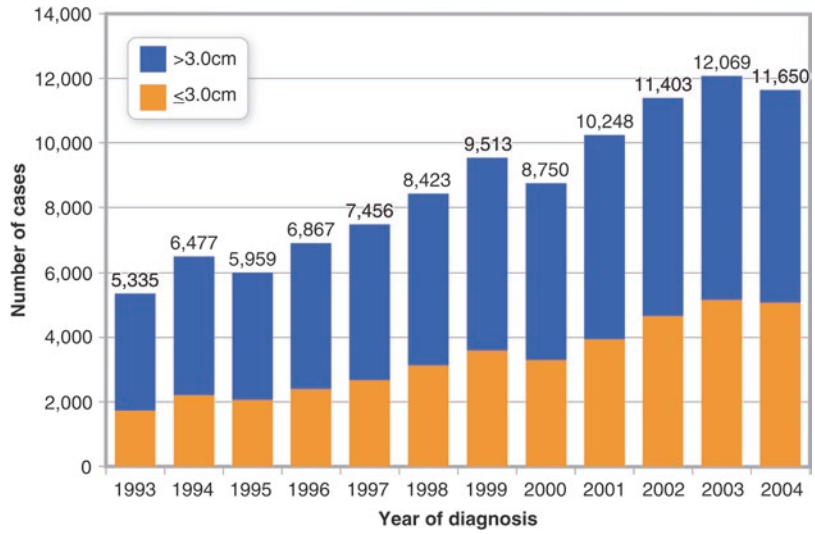

Fig. 8.1 Number of stage I renal cell carcinoma cases by diagnosis year (1993–2004) stratified by tumor size (<3 cm or ≥3 cm). (Modified from Cooperberg et al. [124]; American Urological Association by Elsevier, Inc.)

indolent intrinsic tumor biology rather than treatment effect. Further, there is a growing recognition that the competing risks to survival from medical comorbidities may outweigh the expected benefit of intervention on an SRM in elderly and/or infirmed patients [13].

One clear example of over-diagnosis and over-treatment is reflected in the evolution of the management of prostate cancer. Over the past 25–30 years, the development and aggressive utilization of PSA-based prostate cancer screening in the United States have also resulted in a significant stage migration [14]. The great majority of prostate cancer diagnoses are made in asymptomatic men who are identified to have organ-confined tumors. Though treatment for this stage of prostate cancer can be highly successful, the natural history of the majority of cases of *untreated* low-grade, early-stage prostate cancer is understood to progress along a relatively long and indolent course. Simply put, most men with prostate cancer will likely die from other causes rather than from their disease [15]. The management approach of "watchful waiting," especially for men of advanced age having prostate cancer and substantial concurrent comorbidity, was developed from this concept and carries with it the expectation that definitive treatment of prostate cancer in certain patients provides marginal if any benefit. Recognizing that low-volume, low-grade prostate cancer can behave in an indolent manner for decades, the concept of active surveillance (AS) with serial reassessment and possible delayed intervention has been increasingly applied to younger and healthier men. In the prostate cancer AS paradigm, treatment is considered, but is deferred and offered only in the event that the perceived risk of prostate cancer biology worsens. The practice of AS delays immediate intervention to avoid the potential inherent morbidities of treatment, until evidence of increased clinical risk is identified, at which time curative treatment is justified and can still be applied [16]. Level I evidence now exists showing equivalent cancer-specific and overall survival at 10 years among men with screen-detected prostate cancer who were randomized to undergo treatment versus expectant management [17]. Furthermore, limited long-term retrospective data also support the AS management approach for selected men with prostate cancer [18].

Similarly, AS has been applied in select patients with SRM and significant competing risks. Although limited by small cohorts and retrospective methodology, current data supporting AS for management of the incidental SRM represent perhaps the most comprehensive observational data for any solid organ malignancy to date. In this chapter, we aim to review the natural history and malignant potential of SRMs, discuss the contemporary role of renal mass biopsy, and summarize the existing body of evidence supporting the use of AS for localized SRMs.

Natural History of Untreated Renal Masses

Our knowledge of the natural history of small renal masses has been gleaned predominantly from the experience of centers applying delayed intervention in select patients with SRMs both on and off formal AS protocols. The expected course and behavior of SRMs under observation yield insight into identifying which lesions might be safely observed and which might benefit from routine immediate and definitive intervention. Ideally, an improved understanding of the natural history of SRMs would lead to avoiding treatment for lesions with little to no malignant potential. Historically, surgical excision or other treatment of SRMs has been routinely performed soon after diagnosis precluding any meaningful conclusions regarding the natural history of SRMs. Furthermore, the majority of the initial evidence was comprised of small, retrospective series of selected SRMs monitored with serial abdominal imaging at variable intervals prior to extirpation [19–22] and single institution series investigating outcomes in select patients intentionally managed over the long term with AS alone [23–36]. However, as data from prospectively collected institutional cohorts have matured [37–39], a clearer picture has emerged regarding the threat posed by incidentally detected SRMs.

Benign Versus Malignant SRMs

The published literature examining the rates of benign vs. malignant lesions in patients with SRMs undergoing immediate treatment has been reviewed [7]. The available data included 26 studies published in the past decade and incorporated 27,272 patients from eight countries. The frequency of benign findings in SRM ranged from 7% to 33%, with most studies reporting within a few percentage points of the mean of 14.5% (±5.2%). Histologically, clear cell RCC was identified in the majority of cases, with a mean of 68.3% (±11.9%). Few studies specifically examined the diagnostic accuracy of cross-sectional imaging to distinguish between benign and malignant tumors, but the accuracy of currently available methods was reported as low in identified studies. The association between tumor size and pathological classification (benign vs. malignant) was also evaluated in this review. The authors found an inverse relationship between tumor size and benign pathology in 74% (14/19) studies that examined such a relationship and found a statistically significant increase in the incidence of clear cell RCC with tumor size in 13 (63%) of the 19 studies.

In a separate review assessing outcome of SRM under surveillance, similar results were seen [40] despite the recognized selection bias associated with expectantly managed and untreated masses. Pathologic data were available for 248 patients across 17 studies [19–21, 23–26, 28–36], which confirmed predominantly malignant disease (86.7%) with the majority being low grade (81%). These data highlight that benign renal tumors are common among incidentally detected renal masses (~15% of resected renal tumors) and are more prevalent among small clinical T1a lesions

Factors associated with benign versus malignant pathology have been recently reviewed [41]. Using 20 studies including 12,149 patients, only tumor size (effect size 1.33 increased risk per cm; 95% CI 1.22–1.43) and male sex (effect size 2.71, 95% CI 2.39–3.02) were associated with malignant pathology. Therefore, it appears that current risk models have a limited ability to predict benign versus malignant pathology.

Growth Characteristics of Untreated SRMs

There are several studies using pooled analytic methods to consolidate institutional data and characterize growth trends in SRMs. A pooled analysis of nine single institution retrospective series identified 234 masses followed for a mean duration of 34 months [42]. Initial tumor diameter was 2.6 cm (range 1.73–4.08), mean growth rate was 0.28 cm/year, and pathologic confirmation was available in 46% (92% were RCC or RCC variant) (Table 8.1).

Table 8.1 Meta-analysis of the natural history of observed masses

References	Year	Mean age, years	Number of patients/ number of SRMs	Initial mean tumor diameter, cm (range)	Mean linear growth rate, cm/year (range)	Mean follow-up (months)	# of metastatic events (timing of event)
Fujimoto et al.	1995	59.7 (47–70)	6/6	2.47 (1.7–3.4)	0.47 (0.39–0.74)	29 (9.7–7.1)	0
Bosniak et al.	1995	65.5	40/40	1.73 (all <3.5)	0.36 (0.1–1)	39 (1.8–8.5)	0
Oda et al.	2001	54 (med.) (28–78)	16	2.0 (median) (1.0–4.5)	0.54 (median) (0.1–1.35)	2.1 (median) (12–72)	0
Kassouf et al.	2004	68.3 (29–83)	20/26	3.27 (0.9–1.0)	0.09 (0.13–1.2)	32 (8–86)	0
Volpe et al.	2004	71 (27–84)	29/32	2.48 (0.9–3.4)	0.1	35 (5.3–143)	0
Wehle et al.	2004	70.5 (51–88)	29/29	1.83 (0.4–3.5)	0.12 (n/a)	32 (10–89)	0
Kato et al.	2004	56.5 (37–71)	18/18	1.98 (37–71)	0.42 (0.08–1.6)	27 (12–63)	0
Sowery and Siemens	2004	77 (60–92)	22/22	4.08 (2–8.8)	0.86 (0–6)	26 (1–111)	1 (timing n/a)
Chawla et al.	2006	71 (42–85)	49/61	2.97 (1–12)	0.20 (−1.64–1.8)	36 (12–152)	1 (54 months)
Lamb et al.	2004	76.1 (56–91)	36/36	6 (3.5–20)	n/a	n/a	1 (132 months)
Totals (median)	–		*271/286*	*2.60 (2.48)*	*0.28 (0.28)*	*34 (32)*	*3/271 1.1%*

Adapted from Chawla et al. [38]

Table 8.2 Pooled analysis of small renal masses managed with active surveillance

Study	Year	Median age, years (range)	No. of patient/no of SRMs	Initial mean tumor diameter, cm (range)	Mean linear growth rate, cm/year (range)	Mean follow-up, months (range)	# of metastatic events (timing of event)
Fujimoto et al.	1995	57 (47–40)	6/6	2.47 (1.7–3.4)	0.57 (0.39–0.74)	29 (9.7–71)	0
Bosniak et al.	1995	65.5 (48–84)	37/40	1.73 (0.2–3.5)	0.4 (0–1.1)	43.9 (21–102)	0
Volpe et al.	2004	71 (27–84)	29/32	2.48 (0.9–3.4)	0.1	35.3 (5.3–143)	3
Kato et al.	2004	56.5 (37–71)	18/18	1.98 (0.8–3.4)	0.42 (0.08–1.6)	27 (12–63)	0
Matsuzaki et al.	2007	72 (44–87)	15/15	2.2 (1–3.9)	0.06 (−0.09–0.28)	38 (8–91)	0
Crispen et al.	2009	71 (35–88)	154/173	2.45 (0.4–12)	0.29 (−1.4–2.47)	31 (12–156)	0
Totals (range)		*69 (35–88)*	*259/284*	*2.3 (0.2–12)*	*0.31 (−1.4–2.5)*	*33.5*	*3/259 1.1%*

Adapted from Smaldone et al. [37]
Mean linear growth rate, cm/year (range)

A subsequent comprehensive systematic literature review incorporating 18 studies that included 880 patients with 936 SRMs managed by AS demonstrated consistent findings (Table 8.2) [40]. Summarizing available individual level data from 275 patients (299 SRMs), Smaldone et al. performed a pooled analysis of the six studies that met criteria for inclusion [40]. This analysis revealed a mean age of 66.9 ± 12.3 years (median 69; range 35–88) in 239 patients. The mean maximal tumor diameter and estimated tumor volume at the time of diagnosis were 2.4 ± 1.4 cm (median 2; range 0.2–12) and 17.8 ± 63.9 cm^3 (median 4.3; range 0.004–903.7), respectively. At the conclusion of observation, the mean maximal tumor diameter and estimated tumor volume were 3.2 ± 1.7 cm (median 2.8; range 0.9–15) and 34.3 ± 115.9 cm^3 (median 11.5; range 0.27–1765.1), respectively. Over the duration of observation (mean of 33.5 ± 22.6 months), this represents a change in diameter of 1.2 cm (0.33 cm/yr) and volume of 16.5 cm^3 (7.3 cm^3/yr). The development of metastatic disease was very low as only 18 of the 297 patients (2.1%) developed metastatic disease over a mean period of observation of 40.2 months. This provides evidence that the majority of SRMs managed expectantly grow slowly with a very low rate of disease progression over an intermediate time period following diagnosis.

Recently updated institutional analyses provide further information regarding growth rates of SRMs followed expectantly. McIntosh and colleagues reported median 67-month outcomes for 457 patients (544 tumors) managed with AS [37]. The median initial tumor diameter was 2.1 cm. Overall linear growth rate was 1.9 (IQR 0.3–4.2) mm/year. Five-year cancer-specific mortality was 1.2% (95% CI 0.4–2.8%). Using 271 patients from the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) prospective registry, Uzosike et al. demonstrated similar results at a median follow-up of 1.83 years [38]. Mean linear growth rate was 0.9 mm/year ±15.1 mm/year. The authors noted that both growth rate and variability were greater during initial surveillance (5.4 mm/year ±27.6 mm/year) compared to later surveillance (0.7 mm/year ±5.9 mm/year after 1 year), which may be related to selecting out tumors with rapid growth for intervention. Importantly, no patients had metastatic disease or died from kidney cancer. Finally, Organ and colleagues reported growth kinetics of SRMs on active surveillance in 169 patients from eight institutions in Canada with a median follow-up of 603 months [39]. At diagnosis, the median tumor diameter was 2.15 cm with a median growth rate of 1.2 mm/year.

Radiographic Characteristics of SRMs

While SRMs are identified typically as incidental findings on axial imaging, additional detail regarding their nature or estimated behavior was limited until recently. Historically, few radiographic characteristics existed having validity to inform on the SRM risk that could impact subsequent management. Thus, tumor growth, a relatively crude method to predict disease progression, was used as the most reproducible imaging parameter available on cross-sectional imaging. For example, increase in maximal linear tumor diameter has been shown to correlate with increasing risk of malignant pathology [40, 43, 44], high-grade disease [40, 43, 44], clear cell histology [43, 45], and presence of synchronous metastases [46–48]. In retrospective studies from the Mayo Clinic and Memorial Sloan Kettering Cancer Center encompassing 5445 patients with surgically treated clinically localized renal masses, increasing tumor diameter was associated with greater rates of malignant pathology as well as high-grade nuclear features [43, 44]. Similarly, in a series comparing 168 renal tumors ≤3 cm with 119 renal tumors >3–4 cm, smaller lesions were found to display decreased rates of progression to pT3a disease (19.1 vs. 35.7%, $p < 0.05$), high-grade disease (9.2 vs. 25.5%, $p < 0.05$), and synchronous metastasis (2.4 vs. 8.4%, $p = 0.05$) [9]. Further, these observations have been confirmed using population data investigating the relationship between the tumor size at presentation and histopathological features. From the Surveillance, Epidemiology, and End Results (SEER) dataset, for each 1 cm increase in renal tumor size, the probability of finding a high-grade tumor in 19,932 patients with localized RCC increased by 13% (OR 1.13, $p < 0.001$) [45]. While almost 85% of localized RCCs <4 cm were low grade, the authors found that 70% of organ-confined tumors >7 cm were also low grade; therefore, it is important to note that renal tumors can grow quite large without acquiring the ability to metastasize. Indeed, Mehrazin and colleagues reported favorable short-term outcomes in highly selected patients with cT1b and cT2 renal masses on active surveillance with 14.7% demonstrating no interval growth and none progressing to metastatic disease at a mean follow-up of 38.9 ± 24.0 months [39].

With the knowledge that growth rate may provide some insight into malignant potential, the ability to identify features on the initial axial imaging study that predicted for future rapid growth would be clinically very useful. Unfortunately, despite the ability to measure tumor growth rates accurately, cheaply, and quickly, no discernible CT imaging features have proven sensitive enough to predict for a tumor's future growth rate. Dodelzon et al. examined the relationship between growth rate and MR imaging characteristics in patients on active surveillance [49]. One promising parameter is homogeneity on T2-weighted imaging predicted slower growth rate (defined as doubling time greater than 2 years) on multivariate analysis, suggesting initial MR features may have a role in predicting malignant potential for renal lesions being considered for active surveillance.

Despite data suggesting only a small proportion of renal masses display aggressive biology and metastasize early, distinguishing and identifying these lesions from more indolent tumors remains a clinical challenge. A single institution tumor registry of 110 patients with biopsy-proven synchronous metastatic disease at presentation was compared to 250 controls with clinically localized RCC in a recent study [48]. Larger tumors were more often associated with synchronous metastatic disease compared to smaller lesions (median 8.0 vs. 4.5 cm, $p < 0.001$) with the odds of synchronous metastasis increased by 22% for each 1 cm increase in tumor size ($p < 0.001$) [48]. Metastatic disease was uncommon (<5%) in patients with tumors less than 3 cm, and no patients with tumors 2 cm or smaller presented with metastatic disease. In a larger series by Nguyen et al. evaluating SEER data, the risk for synchronous metastatic disease was clearly related to initial tumor size and occurred infrequently with small tumors [46]. Despite the data presented, no clear tumor size cutoff exists above which one would predict for a high risk of

synchronous metastases. Largely extrapolated from clinical data in patients with von Hippel-Lindau syndrome, the "3 cm rule" has become an acceptable benchmark as a threshold tumor size below which progression to metastases appears unlikely and for which SRM management by AS is of reasonably and acceptably low risk [50]. This concept is supported from experience with non-familial RCC, where SEER data has shown the risk of synchronous metastasis in the setting of SRMs to be extremely low (<5%) in lesions ≤3 cm [46, 47].

Recently, preliminary data using technetium-99 m (^{99m}Tc)–sestamibi single-photon emission computed tomography/x-ray computed tomography (SPECT/CT) for the differentiation of oncocytomas and hybrid oncocytic/chromophobe tumors (HOCTs) from other renal tumor histologies have been reported [51]. Fifty patients with a solid clinical T1 renal mass were imaged. Following resection six tumors were classified as oncocytomas and two as HOCTs. ^{99m}Tc–sestamibi SPECT/CT correctly identified 5/6 oncocytomas and 2/2 HOCTs. Two tumors were falsely positive on ^{99m}Tc–sestamibi SPECT/CT imaging, suggesting it has a specificity of about 95%. Therefore, this imaging modality may be a useful adjunct to guide management and decision-making, particularly useful in patients in whom the risks of intervention are high.

Role of Percutaneous Biopsy and Other Diagnostic Modalities

The diagnosis of RCC is suspected on cross-sectional imaging when renal masses enhance after administration of intravenous contrast [12]. Contemporary management, including patient counseling and treatment planning, is often based solely on suggestive imaging characteristics and in the absence of definitive pathologic confirmation of malignancy. This occurs despite the expectation that approximately 15% of presumed RCC lesions are actually benign and less than 30% of malignant SRMs display high-grade histology and aggressive biologic potential [7, 44]. In contrast to other urologic malignancies where specific pathologic information from biopsy is used to predict risk and tumor behavior and guide intervention, the ability to similarly evaluate an SRM preoperatively and appropriately tailor treatment strategies based on imaging information alone is imperfect [52]. While efforts have been made to use preoperative clinical and radiographic variables to predict malignant potential [53, 54], to date the clinical utility of non-invasive diagnostics and predictive models remains limited [55]. Despite the potential suggested benefits of percutaneous renal mass biopsy, this diagnostic procedure has yet to be accepted as a standard and routine component of the evaluation and management of patients with SRMs. A majority of urologists use percutaneous biopsy in selected cases [56]; however, only a small minority do so regularly [57].

Traditional Role of Renal Mass Biopsy

Historically, there has been a limited perceived benefit from percutaneous needle biopsy and its subsequent impact on the management of SRM. The common standard practice has been to treat all SRMs as RCC, and renal mass biopsy was viewed as lacking sufficient sensitivity or accuracy to adequately confirm the preoperative SRM diagnosis or provide actionable clinical information. However, contemporary biopsy approaches are recognized to have high sensitivity and specificity for cancer and can clarify the histological diagnosis of a renal mass, perhaps affecting clinical decision-making [58]. Traditionally, renal mass biopsy was reserved for the infrequent cases where a renal mass was atypical and suspicious for non-RCC pathology such as lymphoma or infection, or in cases of suspected metastasis from another organ to the kidney [59]. Biopsies have also been performed to confirm the diagnosis of a renal primary tumor in the presence of disseminated metastases or unresectable retroperitoneal masses. Otherwise, biopsy has not generally been advocated due to concerns of inaccuracy as well as about safety and risk for needle tract seeding and tumor spillage.

Modern Biopsy Technique and Results

With historic small-gauge core biopsy needles, renal biopsy exhibited an 81% accuracy rate, with four out of five biopsies correctly diagnosing a tumor's pathology [59]. Since the application of larger 18-gauge core needles for tissue procurement and with improvements in immunohistological techniques, percutaneous renal mass biopsy has demonstrated improved accuracy in differentiating benign from malignant histology (>90%) and is safely performed with minimal procedure related complications [60]. From modern biopsy series, the positive predictive value is reported to be over 95% in cases where a malignancy is detected [59]. In addition, the negative predictive value has been reported to be over 80% in contemporary series with false-negative rates less than 5% [60, 61]. Maturen et al. reported highly accurate sensitivity (97.7%), specificity (100%), positive predictive value (100%), and negative predictive value (100%) for malignancy in a series of 152 biopsies using the 18-gauge core biopsy technique [62]. More recently, Richard and colleagues reported their single institution experience of 529 patients with SRM biopsy [57]. The first biopsy was diagnostic in 90% of cases. Of patients who underwent surgery (n = 171), concordance with biopsy histology (93%) and nuclear grade (94%) were excellent. Only one patient had a complication requiring intervention (angioembolization), and no incidence of needle tract seeding was reported at a median follow-up of 28 (IQR 11–53) months.

Despite these demonstrated improvements in biopsy yield at centers of excellence, a concern remains that biopsy of smaller tumors can often more frequently return a "non-diagnostic" biopsy result. One series reported their differential yield with biopsy of smaller tumors: tissue was insufficient to make a diagnosis in 37% of tumors <3 cm compared to only 9% of tumors ≥3 cm [63]. However, a repeat renal mass biopsy can be performed, which carries with it an equal rate of success as the initial biopsy. An additional recent study that evaluated 345 renal tumors ≤4 cm (mean diameter 2.5 cm) undergoing percutaneous biopsy reported a diagnostic result in 278 cases (81%) and a non-diagnostic result in 67 cases (19%) [64]. Solid appearance on imaging and tumor size were associated with a diagnostic result on multivariate analysis. If the first biopsy was non-diagnostic, then when a repeat biopsy was performed, a diagnosis was subsequently reached in 83% of cases.

While there is increasing evidence demonstrating the high accuracy of renal mass biopsy in determining a tumor's histologic subtype, relatively few data exist on the accuracy of biopsy for tumor grade [59]. Since increasing tumor grade has been shown to be correlated with cancer-specific survival [65], pre-treatment knowledge of this parameter might significantly influence clinical decision-making. In a series of patients on AS undergoing modern renal mass core biopsy, tumor grading was determined in only 63% of patients [66]. Additionally, difficulties exist with the accuracy of assigning nuclear grade on a needle biopsy sample, as an underestimation of nuclear grade has been noted in more than half (55%) of patients, likely due to tumor grade heterogeneity [67].

Although there is great interest in pre-treatment percutaneous renal mass biopsy in the management of the SRM, its indication and role remain controversial [55]. In a survey of practice patterns conducted in the United Kingdom, only 34% of urologists reported always using biopsy in the treatment algorithm of indeterminate SRM, with the remaining respondents reporting either selectively (23%) or never using biopsy (43%) to inform their management decisions [68]. It remains unclear what degree of clinical impact the information from a biopsy has on treatment decisions. Does it justify associated procedural risks and costs? Studies have suggested that biopsy results can significantly impact clinical management in 41–60.5% of cases [62, 69]. Moreover, Richard and colleagues recently reported a significant reduction in benign final pathology following surgery at centers that routinely perform renal mass biopsy compared to those employing a more judicious biopsy approach [70]. Although limited by selection bias, these findings have led some to recommend

an image-guided biopsy of SRMs always be performed before treatment to confirm malignancy, to classify histologic subtype, and to establish tumor grade [71]. While the benefit and use of biopsy have increased and gained traction, it is likely few urologists would currently recommend a routine biopsy in a young or otherwise healthy patient for whom standard surgical treatment is planned. Biopsy continues to be utilized on a selective basis in patients with absolute or relative indications for surgical resection or having specific unusual circumstances such as synchronous bilateral lesions [72].

Complications of Biopsy

Clinically important complications of renal mass biopsy are rare. In a large review of more than 16,000 abdominal fine needle biopsies, mortality following renal biopsy was an extremely unlikely event, with an overall mortality rate of 0.031% [73]. Overall, few major complications have been reported in recent series, and the risk of minor complications (<5%) or tumor seeding (<0.01%) with contemporary co-axial biopsy techniques is also low [58]. Clinically significant bleeding is uncommon and usually self-limiting, with hemorrhage requiring blood transfusions rarely occurring. In the published literature, only eight cases of tumor seeding have been reported [74–81]. Analysis of these cases revealed that needle size did not appear to correlate with the risk of seeding, but the risk may increase with the number of needle passes and with use of non-cutting needles.

The utility of performing renal biopsy for cystic lesions has repeatedly been questioned. While most cysts can be classified as benign on imaging, more complex cystic lesions can be malignant over half of the time [82]. Demonstrating the accuracy of biopsy for complex cystic lesions, Richter et al. used a combination of FNA and core biopsy on 227 Bosniak II/III lesions to obtain histological characterization in 89% [83]. Of 30 benign cysts diagnosed by FNA, the diagnosis was confirmed by pathological evaluation or by negative imaging at up to 8 years in 97% [84]. However, FNA is not recommended in patients with acquired polycystic disease on dialysis or adult polycystic disease because of the risk of misdiagnosing the papillary hyperplasia that frequently occurs in these cysts with RCC [58].

Molecular Biomarkers

Following the sequencing of the human genome and with the evolution of rapid DNA sequencing techniques, medicine continues to move in a "molecular" direction with the goal of providing more individualized diagnostic and therapeutic options. The identification of molecular biomarkers that could be used to accurately predict aggressive RCC phenotypic features from tissue obtained on percutaneous biopsy specimens would be an ideal means of individualizing SRM management strategy to tumor biology [52]. Molecular analysis of biopsy tissue might allow greater clinical benefit beyond that gained from making a histologic diagnosis. Molecular markers of cellular proliferation and apoptosis currently under investigation include Ki-67 (a nuclear antigen that is a marker of active cellular proliferation) [85, 86], p53 (marker of apoptosis) [87, 88], HER-2 (epidermal growth factor) [89], vascular endothelial growth factor (VEGF) [90], bcl-2 (apoptotic inhibitor) [91], cyclin-D1 (cell-cycle regulatory molecule) [92], vimentin (epithelial cell adhesion molecule) [93], C-reactive inflammatory protein [94], and carbonic anhydrase IX (cell surface transmembrane enzyme upregulated by hypoxia-inducible factor in low oxygen environments) [95], among others [96]. Unfortunately only preliminary data currently exist, and while this approach is promising for the future, at present, molecular information is unable to define which patients with SRMs require immediate intervention and which ones can be safely observed [52].

Several studies have investigated biomarker activity in lesions initially managed with a period of radiographic surveillance. Fujimoto et al. analyzed argyrophilic nucleolar organizer regions (AgNORs) and proliferating cell nuclear antigen (PCNA) activity in localized tumors finding

tumor doubling time was significantly inversely correlated with AgNOR expression and PCNA activity [20]. Using the marker Ki-67 and the transferase-mediated dUTP-biotin nick (TUNEL) assay, Kato et al. measured cell proliferation and apoptosis in 18 patients with localized SRMs. A positive TUNEL ratio was associated with tumor growth rate, but not with degree of Ki-67 immunostaining [21]. In an early series investigating growth kinetics of SRMs under observation, Oda et al. observed that the growth rate of incidentally found RCCs varied and that the initial clinical and pathological features did not predict subsequent tumor growth [22]. The authors also examined cell proliferation, apoptosis, and angiogenesis in 16 incidentally found cases of RCC, using the Ki-67 labeling index (KI), apoptotic index (AI), and TUNEL technique. They found that while KI and AI were not associated with each other or tumor growth rates, the KI/AI ratio was strongly correlated with tumor growth rate ($r = 0.71$; $P = 0.01$) [97]. Unfortunately, the role of biomarkers in the selection and management of patients under AS also remains clinically limited [52]. There is an ongoing need to identify both molecular markers that are specific for malignant or metastatic potential and alternative prognostic tools to help stratify risk in patients presenting with incidentally diagnosed SRMs.

Imaging Techniques

Currently, contrast-enhanced axial imaging (CT or MRI) techniques provide the best evaluation of a renal mass. These modalities are adept at distinguishing most renal cystic lesions from solid masses, evaluating enhancement characteristics, assessing bilateral renal flow and function, and obtaining clinical (radiographic) staging data. These studies provide anatomic detail to optimize treatment and surgical planning. Despite these advantages, the vast majority of existing imaging methods remain limited in the ability to accurately distinguish between benign and malignant solid tumors and cannot characterize the histologic subtype or biology of a tumor or predict its potential future behavior. Nuclear medicine modalities such as positron emission tomography (PET) have the potential to characterize biologic processes at the cellular and sub-cellular level non-invasively, in addition to providing the macroscopic anatomic detail when correlated with CT or MRI. The use of 2-deoxy-2-(18F) fluoro-D-glucose (^{18}F-FDG) to functionally image malignancies is based on the anticipated altered glycolytic pathway in malignant cells. When used in combination with standard CT, ^{18}F-FDG PET (PET-CT) provides both functional and anatomic tumor data, thereby improving the diagnostic accuracy and tumor localization for a number of solid malignancies versus either modality alone [98]. Unfortunately the initial enthusiasm for the utilization of ^{18}F-FDG PET to diagnose, stage, or re-stage RCC was tempered by the significant limitations to its clinical application. A review of available PET-CT series (small series ranging from 4 to 66 patients) demonstrated poor diagnostic sensitivity (ranging from 32 to 100%) and limited ability to accurately stage patients (ranging from 47% to 75%) [99]. A majority of these studies were performed prior to combination scanning which may have influenced results; however, the reported false-negative results were as high as 68%, severely limiting the utility of ^{18}F-FDG PET for the initial assessment of primary renal masses.

Molecules involved in cellular pathways such as cellular oxidative metabolism, DNA synthesis, and tumor hypoxia have been recognized as possible targets for alternative novel nuclear imaging techniques and are currently under development and in the early phases of assessment with RCC [100–102]. Other techniques, such as antibody-based molecular imaging, or immuno-PET, may offer a more clinically relevant strategy to improve molecular/biologic imaging in RCC. With the objective of utilizing antibodies having highly selective affinity to cancer-specific antigens as a means to identify radiographically recognizable molecular targets, immuno-PET offers an exciting strategy to image all types of cancers. With a recognized and specific molecular target with RCC, enthusiasm for this imaging technique has grown. One such molecular target is carbonic anhydrase IX (CA IX) having an

associated antibody G250. Expressed on the cell surface of almost all RCCs but not expressed on normal tissues, with the exception of gastric mucosa and larger bile ducts, CA IX is an ideal cancer-specific target for immuno-PET development. In a phase I study imaging 26 patients with renal masses prior to surgery, radiolabeled G250 immuno-PET (^{124}I-G250-PET/CT) was able to discriminate between ccRCC and non-ccRCC with a high sensitivity (94%) and specificity (100%) and no serious drug-related adverse events [103]. This led to considerable enthusiasm regarding the potential for the development of a true molecular imaging test for renal cell carcinoma that can yield histologic data in a non-invasive manner. A subsequent multi-institutional phase III study ("REDECT") was performed and enrolled 202 patients, and results of ^{124}I-G250-PET/CT imaging accurately discriminated ccRCC from non-ccRCC with a much higher sensitivity (86%) and specificity (87%) compared to conventional multiphase CT imaging. The positive predictive value for clear cell RCC for ^{124}I-G250-PET/CT was 95%, and it was well tolerated with no associated serious adverse events [104]. Results from the REDECT trial demonstrate that immuno-PET can be used to provide important preoperative diagnostic information that may help guide clinical decision-making and direct a patient to optimal therapy.

Finally, preliminary data using technetium-99 m (^{99m}Tc)–sestamibi single-photon emission computed tomography/x-ray computed tomography (SPECT/CT) for the differentiation of oncocytomas and hybrid oncocytic/chromophobe tumors (HOCTs) from other renal tumor histologies are promising [51]. Larger studies are needed to confirm these initial results.

Predictive Models and Assessment of SRM Malignant Potential

Several methods of objectively measuring renal mass anatomy have been developed and described, and they are slowly being utilized in regular clinical practice [105–107]. There is increasing evidence to suggest a relationship may exist between renal mass anatomy and underlying pathology. Using a large prospectively maintained institutional cohort, Kutikov et al. evaluated the relationship between anatomical variables stratified by R.E.N.A.L. Nephrometry Score and malignant or high-grade pathologic features at the time of surgical resection [108]. The total Nephrometry Score and all individual anatomic descriptor components significantly differed between tumor histology groups with the exception of the anterior/posterior (A) designation [98]. Papillary and chromophobe tumors had the lowest scores in each attribute indicating that they tended to be small, exophytic tumors with a polar distribution, resulting in low total Nephrometry Scores that are similar to that of benign lesions. Comparatively, clear cell carcinomas and less common but more aggressive histologic subtypes (collecting duct, sarcomatoid) tended to be large, endophytic, interpolar lesions, thereby having higher total Nephrometry Scores. Predictive nomograms integrating anatomic tumor attributes with patient's age and gender were constructed for preoperative prediction of tumor malignant histology (AUC 0.76) and high-grade features (AUC 0.73) [108]. This model, which has been validated, represents the most accurate predictive model to date, with accuracy rates (particularly for tumor grade) that rival the results of contemporary percutaneous core biopsy series [54].

Active Surveillance

The Rationale for AS

From 1983 to 2002, RCC tumors between 2 and 4 cm in diameter increased in incidence from 1.0 to 3.3 per 100,000 [3], and the average size of resected kidney tumors dropped from a maximum diameter of 7.8 cm to 5.3 cm between 1989 and 1998 [109]. Furthermore, the incidental diagnosis of RCC increased from 7% to 13% in the early 1970s to 48% to 66% of kidney cancer cases currently [71]. Incidental tumors are most commonly found in patients older than 65 years [71], a group more prone to the adverse

effects of surgery due to the increased presence of comorbidities. In an examination of a cohort of 26,618 individuals treated surgically for localized kidney cancer, the relative benefit of therapy is notably diminished by competing causes of mortality in older patients, with nearly one-third of patients with RCC aged 70 years and older succumbing to unrelated comorbid disease within 5 years of receiving curative RCC surgery [110]. The current epidemiology of RCC suggests a marked increase in the incidence of cases, and despite a matching increase in therapy for incidentally detected RCC, the overall RCC mortality rates across the population have not decreased. Taken together, these data suggest that many early-stage I RCCs are often clinically indolent and current treatment algorithms may overemphasize the benefits of surgery compared to less aggressive treatment strategies.

One appropriate algorithm for management of the SRM would include consideration of AS in appropriately selected patients with small renal masses and judicious use of renal mass biopsy when histologic information may alter management decisions. The evidence to supporting this protocol includes the following:

1. Not all renal masses are RCC. Review of the literature indicates approximately 15% of SRMs are benign lesions that do not demand or benefit from any intervention.
2. SRMs are frequently detected in elderly patients with comorbidities. The risk of perioperative morbidity and possible mortality is likely higher in these patients and may markedly exceed the anticipated risk of impact from RCC progression or metastasis.
3. The majority of SRMs confirmed as RCC have non-aggressive pathologic features, with histology suggestive of low-grade appearance and anticipated to demonstrate a slow growth rate and a low metastatic potential, early in their natural history. Predictive tools exist to help quantify the likelihood of aggressive vs. indolent disease and to quantify the risk of competing comorbidities on longevity to make informed treatment decisions.
4. A delay in treatment does not appear to lessen the effectiveness of standard surgical intervention. The outcome of RCC therapy may not be compromised if progression is detected early and curative treatment performed. Progression to advanced stage is rare in well-selected patients managed by active surveillance. As techniques to monitor and predict RCC growth and behavior evolve, this risk may be further minimized.

Indications for AS

Paramount to the evaluation of a patient with a newly diagnosed SRM is an assessment of the patient's comorbid conditions with the goal of stratifying risk of treatment prior to choosing a treatment strategy. As with nephron sparing surgery, we tend to categorize the indication for AS into absolute, relative, and elective indication. Patients with severe comorbidities in which surgical treatment would impart an immediate and unacceptable risk of mortality are considered to have an absolute indication for AS. Those with a second and potentially more aggressive malignancy, the potential need for renal replacement therapy, and other significant medical comorbidities that make surgery high risk but not intolerable are considered to have a relative indication for observation. Elective indications include low-risk surgical candidates that choose to pursue AS as an alternative to active treatment [26]. In a review of contemporary AS series, the indications were elective (60.9%), relative (12.5%), and absolute (26.6%) in the eight studies (n = 312 patients) reporting the reason for AS enrollment [40].

Predictive Tools and Use in the Clinical Setting

The primary goal of AS is to balance the risks of treatment versus the risks of disease progression and the development of metastatic disease. A number of post-treatment nomograms have been developed to predict risk of cancer-specific

death or disease recurrence, which are beyond the scope of this review [111]. However, several preoperative predictive models have been developed which one can use to quantify risks based on commonly available preoperative parameters. Initial efforts to predict benign versus malignant disease and indolent versus aggressive tumors using clinical characteristics such as tumor size, age, gender, and smoking history were met with limited success [54].

Subsequent efforts to determine renal grade preoperatively were also unsuccessful with limited predictive accuracy [53]. In contrast, a number of clinical tools have recently been developed to determine tumor malignant potential and risk of death based on pre-treatment characteristics with acceptable predictive accuracy, showing utility for application in the clinical setting. To facilitate their use, we have recently operationalized clinical nomograms with predictive accuracies greater than 70% to expedite their use (www.cancernomograms.com).

In 2011, Kutikov et al. developed a tool (Fig. 8.2) to predict the probabilities of harboring malignant and high-grade pathology based on anatomic variables which was described in more detail earlier in this review [108]. For example, an 80-year-old male with an enhancing renal mass with a Nephrometry Score of 1 + 3 + 1 + a + 2 = 7a has only a 26% chance of malignancy using Kutikov's model. If the mass is malignant, the chance of a high-grade malignancy (Fuhrman grade III or IV) is approximately 30%. Therefore, the probability of harboring high-grade malignancy is 7.8% (0.26 × 0.30 = 0.078). In contrast, the chance of malignancy in an 80-year-old female with a tumor with Nephrometry Score 2 + 2 + 2 + a + 3 h = 9ah is 92% with a 59% chance of high-grade disease should malignancy be present (0.92 × 0.59 = 0.542) or 54.2% chance of a high-grade malignancy. Using readily available clinical information, this validated model has allowed the physician to differentiate between two seemingly similar patients with clear clinical management implications.

Kutikov and colleagues have also developed clinical tools to predict overall mortality, cancer-specific death, and death from other malignancies. Using SEER data, the authors developed a comprehensive nomogram incorporating race, gender, age, and tumor size to calculate competing risks of death and help facilitate clinical trade off decisions (Fig. 8.3) [13]. Whereas the initial effort was criticized for lack of comorbidity information, the authors recently updated this tool incorporating the Charlson comorbidity index (CCI) based on claims available in linked SEER-Medicare data. Using this nomogram, an 80-year-old African American male with a history of a myocardial infarction, moderate renal insufficiency (CCI of 3), and a 4-cm renal mass is expected to have a 5-year mortality of 5% from RCC versus 48% from non-RCC causes. Meanwhile, a 75-year-old Caucasian female with no significant comorbidities (CCI of 0) and a 7-cm renal mass is predicted to have a 5-year mortality of 13% from RCC and 7.5% from other causes [112]. Although these tools are limited by use of only treated patients for model development, with further refinement, these and other predictive models show significant potential for education and counseling of patients newly diagnosed with SRMs, particularly elderly individuals with significant competing risks.

These predicted probabilities can then be objectively incorporated into treatment planning accounting for risks of comorbid medical conditions and the morbidity of treatment itself. As part of the initial workup, each physician must attempt to quantify life expectancy, assess the patient's performance status and operative risk, and compare these factors against the potential for morbidity and mortality of an untreated SRM after calculating the probability that an aggressive RCC is present. This optimally would be a multidisciplinary approach that includes the urologist, primary care provider, cardiac, pulmonary, and nephrology specialists, and an anesthesiologist. In patients that are elderly and/or have diabetes, hypertension, and other systemic diseases that predispose to chronic kidney disease (CKD), the potential need for postoperative dialysis must be taken into consideration. It is well known that end-stage renal disease carries significant adverse morbidity and mortality [113]. Furthermore, increased risks of death, cardiovascular events,

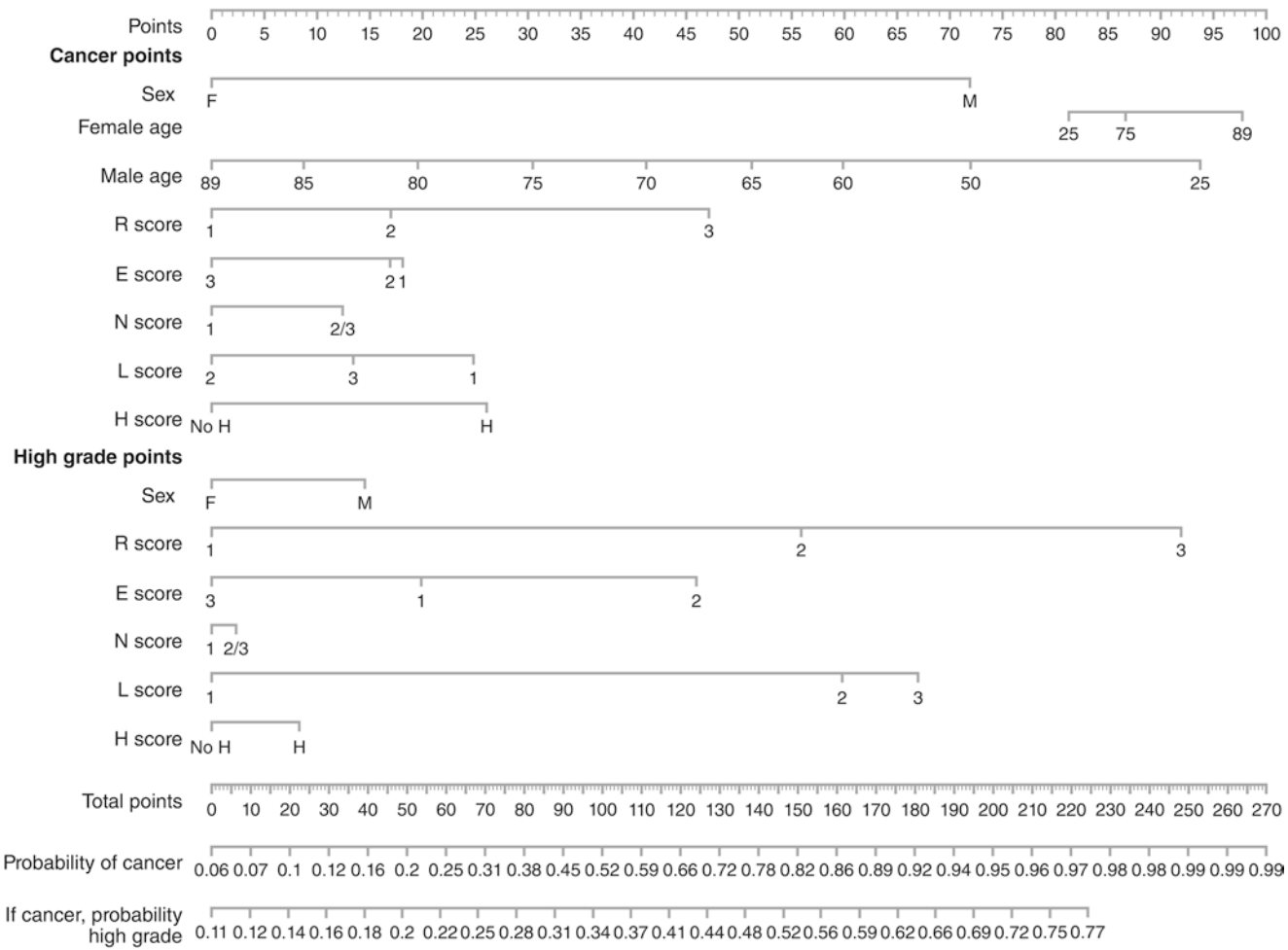

Fig. 8.2 Nomogram evaluating risks of an enhancing renal mass being malignant and high grade. Total point values are independently calculated for the cancer and the high-grade models and then applied to the corresponding probability scale at the bottom of the figure. (Modified from Kutikov et al. [108]; European Association of Urology by Elsevier, Inc.)

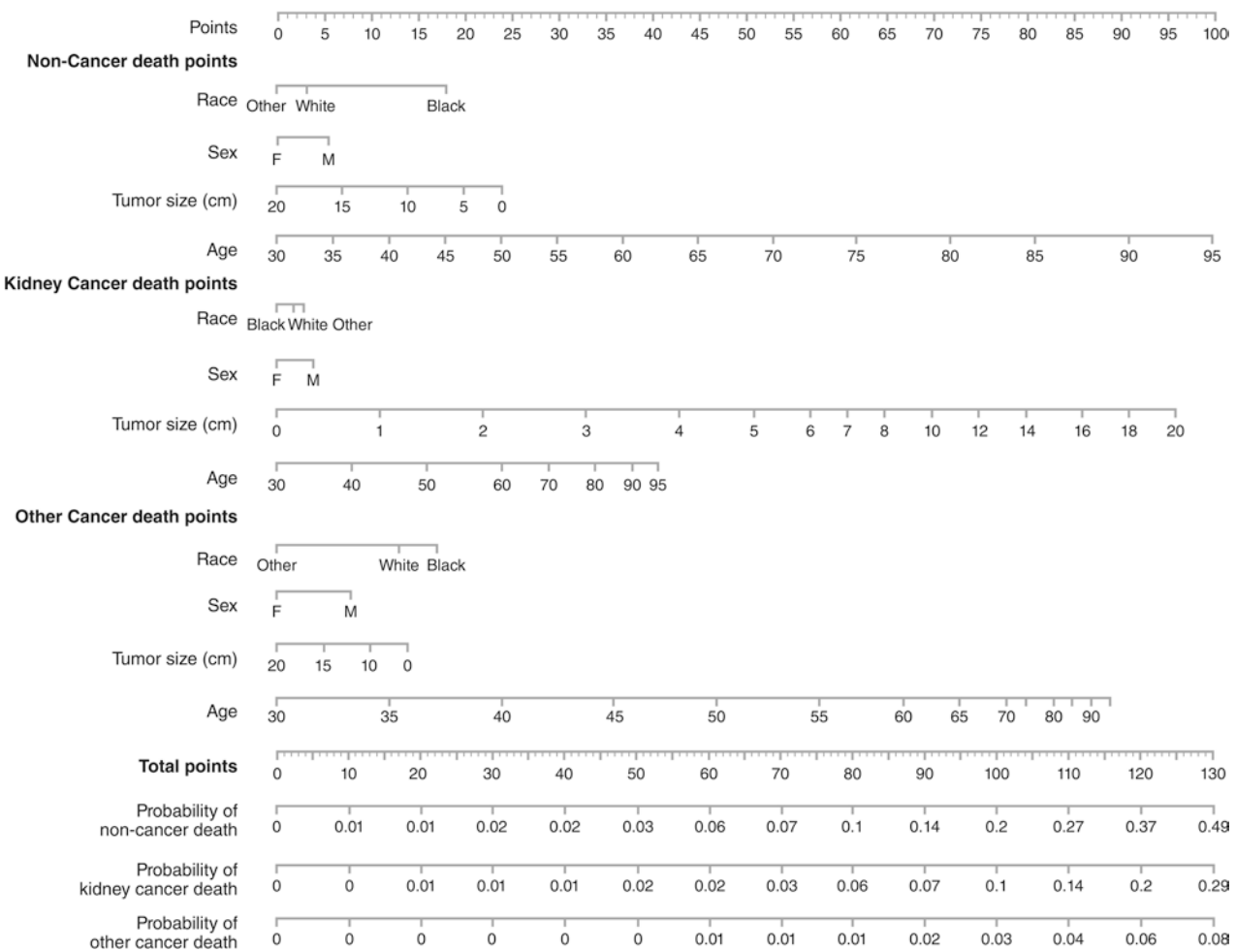

Fig. 8.3 Nomogram evaluating 5-year competing risks of death in patients with localized renal cell carcinoma. Total point values are independently calculated for each cause of death and then applied to the corresponding probability scale at the bottom of the figure. (Modified from Kutikov et al. [13]; American Society of Clinical Oncology by Elsevier, Inc.)

and hospitalization have been demonstrated in patients with mild renal insufficiency in recent large population-based cohort data [114]. At our intuition, all consultations for SRMs include a determination of the creatinine clearance and GFR allowing for stratification into CKD stages. Patients with CKD stage IV or V are typically referred to nephrology for further evaluation of functional risk preoperatively. In all situations where patients choose AS over active treatment, in-depth counseling as to the limitations of radiologic surveillance and growth kinetics and the possibility of disease progression including metastases and death is critical. Patients must understand and accept the estimated risk of different outcomes due to the occasionally unpredictable behavior of RCC, prior to proceeding with AS.

AS Protocols

Currently, there are no data to support any specific AS protocol, in regard to the frequency and type of radiographic follow-up. Unfortunately, no randomized trials exist comparing the effectiveness of active surveillance/delayed intervention with traditional surgical therapies or ablative techniques. Performing such trials poses tremendous logistical challenges under current practice patterns/incentives. In addition, a high degree of patient adherence is required to participate in such trials due to the implicit risk involved with AS. Studies must also examine the costs of possible morbidity and mortality secondary to surgery in these cohorts. To minimize the risks of undetected disease progression, current recommendations call for repeat imaging utilizing a consistent modality at defined intervals (initially 3–6 months) [12]. The interval to repeat imaging should be based on clinical risk factors specific to the renal mass and the patient's overall health status. We typically obtain initial repeat imaging at 3 to 6 months following initiation of AS with the goal of establishing baseline growth kinetics (Fig. 8.4). Once these are established, the timing of further imaging studies is determined. Tumor size comparisons should be performed using the same lesion characteristics (e.g., maximum tumor diameter or estimated tumor volume) obtained from consistent imaging modalities, measured at the same tumor level [26]. Most importantly, in the event that a tumor exhibits a rapid growth rate, a new lesion appears, or the onset of clinical symptoms occurs, patients must be appropriately counseled regarding the risks of continued AS versus immediate treatment.

Radiographic Predictors of Tumor Growth Rate and Malignant Potential

The majority of localized renal tumors exhibit slow radiographic growth with low metastatic potential while under an initial period of observation, as shown from pooled published observations [40, 115]. Definitive radiographic characteristics predictive for rapid growth or aggressive malignant potential have yet to be identified. There has been no correlation documented between tumor growth and patient age [26, 28], initial MTD [23, 24, 28, 34, 55], tumor size >4 cm [25, 33], development of clinical symptoms vs. incidental detection [33], multifocality [116], or solid/cystic appearance [33, 34]. Initial assumptions that larger renal masses demonstrated faster growth rates have been proven incorrect. In fact, smaller tumors have been shown to grow at proportionally faster rates than larger tumors based on annual percent change in tumor size and volume [26]. The theory behind this observation is that a tumor's growth rate is initially exponential and then decreases with increasing size (Gompertzian theory of growth kinetics) [117]. Some series have reported on applying AS with larger tumors (clinical T1b and T2) in select patients with significant medical comorbidity signifying that the indications for non-treatment may be expanding [118]. However, the biology of these lesions must be distinguished from the infrequent case of a localized SRM with aggressive malignant potential whose disease progresses during a period of AS.

Efforts to predict the malignant potential/growth rate of SRMs have yielded conflicting results and often lack complete pathologic assessment. Studies examining Fuhrman grade

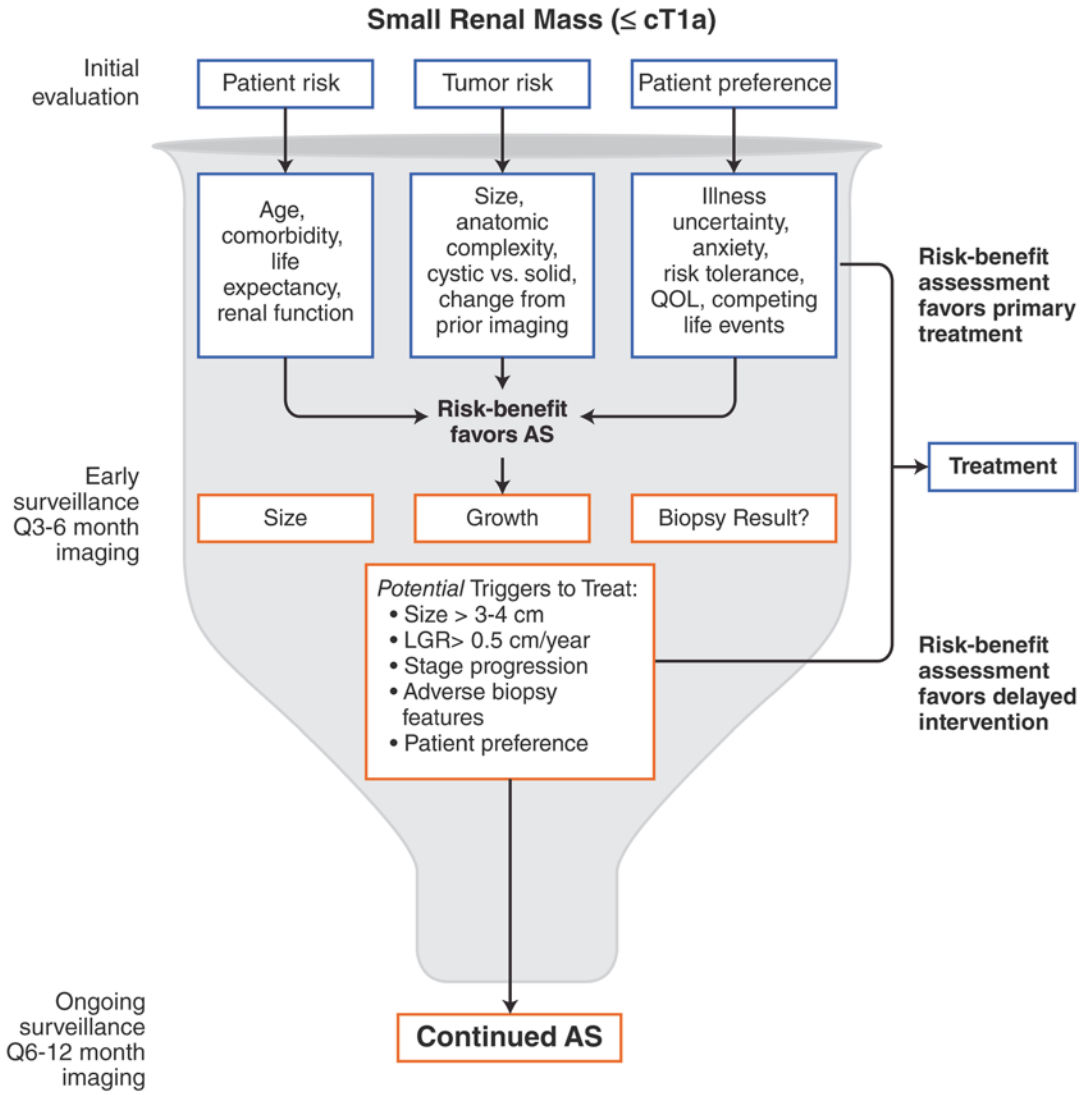

Fig. 8.4 Shared decision-making model for patients with SRMs on active surveillance. QOL quality of life, AS active surveillance, LGR linear growth rate. (Modified from Ristau et al. [125])

on final pathology and growth rate during surveillance showed grade 3 lesions grew faster than grade 2 lesions (0.93 vs. 0.28 cm/yr.; $p = 0.01$); however, these findings are limited by small sample size ($n = 18$). In addition, grade 1 lesions grew faster than grade 2 lesions (0.37 vs. 0.28 cm/yr) although this trend was not statistically significant ($p = 0.47$) [21]. Others have retrospectively compared patients with proven RCC ($n = 10$) vs. oncocytoma ($n = 6$), reporting no statistical differences in tumor growth rate between groups (0.71 vs. 0.52 cm/yr) [32]. Data from one of the largest single institution experiences to date (154 patients, 173 SRMs followed for a minimum of 12 months) [26] showed no differences in growth rates when stratified by Fuhrman grade or presence of benign histology. Chawla et al. reported no difference between initial MTD (2.0 vs. 2.2 cm; $p = 0.59$) and mean growth rate (0.1 vs. 0.4 cm/yr.; $p = 0.15$) in oncocytomas vs. RCC [42]. This finding is supported by the observation from two studies that

percutaneously biopsied oncocytomas have displayed positive growth rates with observation suggesting that a positive growth rate is not always indicative of malignant histology [119, 120]. Kawaguchi et al. observed a yearly linear growth rate of 0.2 cm, which is similar to the growth rates of SRMs of variable histology reported in other series [120]. However, only eight of the 45 oncocytomas diagnosed by biopsy underwent resection, and subsequently one of the eight tumors was identified to actually harbor chromophobe RCC. These data highlight the need for the identification of characteristics that better predict aggressive malignant potential.

Small Renal Masses Exhibiting "Zero Net Growth" While Under Surveillance

The range of linear growth rates of SRMs on surveillance in contemporary series is between 0.06 and 0.86 cm/yr. [19–35]. Two publications summarizing the available data report mean linear growth rates range from 0.28 [42] to 0.31 [40] cm/year. However, within these reported series of SRMs on AS are a subset of SRMs that demonstrated no interval growth on serial imaging. When comparing radiographic characteristics of zero net growth lesions ($n = 35$) and those exhibiting growth ($n = 70$), no differences were seen with respect to patient age ($p = 0.96$), initial MTD ($p = 0.41$), solid/cystic appearance ($p = 1.0$), or incidental detection rate ($p = 0.38$) [115]. As expected, lesions demonstrating positive growth rates underwent higher rates of active treatment (51 vs. 17%, $p = 0.001$) yet revealed similar malignancy rates (83 vs. 89%, $p = 0.56$). This observation has been confirmed in other small series [19, 35]. Among the studies with available data [19–21, 24, 26–30, 32, 34–36], 22.9% of SRMs exhibited zero net growth over time and no difference in initial MTD (2.3 ± 1.3 cm vs. 2.5 cm ± 1.3; $p = 0.21$) or pathologic malignancy rate (88.2% vs. 92.3%, $p = 1.0$) was observed between lesions exhibiting positive and zero growth when the available data were pooled [40]. While the lack of growth under surveillance did not correlate with benign histology, all of these zero net growth lesions remained localized radiographically with no patients developing measurable metastatic disease.

Observed SRMs Progressing to Metastases

Fortunately, progression to metastatic disease in patients with SRMs under AS is rare. Of 880 patients with SRMs under AS (2.1%) identified in a systematic review, only 18 patients progressed to metastatic disease [40]. Indications were absolute in 61.5% and elective in 38.5%, for the 13 patients with indications for AS documented. Patterns of progression were distant visceral or bony disease with or without positive lymphadenopathy (8 patients; 73%) versus only lymph node involvement (3 patients; 27%) as described in the patients with available information. Histology was predominantly clear cell (66.7%) [23, 26, 29, 32, 36, 121] and papillary (22.2%) [23, 31] with one lesion exhibiting mixed clear cell and papillary features (11.1%.) [26]. Moreover, the mean time to detection of metastasis, on average, occurred late in the course of AS (mean of 40.2; range 12–132 months) lending credence to the relative safety of an initial period of active surveillance to determine growth kinetics.

Comparing patients with metastatic disease to those that remained on AS (Table 8.3), there were significant differences in mean patient age (75.1 vs. 66.6 years; $p = 0.03$), but the duration of observation was similar between groups (40.2 vs. 33.3 months; $p = 0.47$). Larger tumor size (4.1 vs. 2.3 cm; $p < 0.0001$) and estimated tumor volume (66.4 vs. 15.1 cm^3; $p < 0.0001$) at diagnosis as well as mean linear (0.80 vs. 0.30 cm/year; $p = 0.0001$) and volumetric growth rate (27.1 vs. 6.2 cm^3/year; $p < 0.0001$) were greater in patients that progressed to metastasis [40]. Lesions progressing were predominantly high grade at the time of histologic confirmation. Tumors that progressed were more common in elderly patients with absolute indications for surveillance and having higher-risk tumors. This group included

Table 8.3 Comparison of clinical and cross-sectional imaging characteristics in patients who did not progress to metastasis (pooled cohort series data) and patients who demonstrated evidence of progression (case series data) during periods of observation

		Nonprogressors		Progressors	
Characteristic	No.	Mean ± SD: Median (range)	No.	Mean ± SD: Median (range)	*P*
Age, year	230	66. ± 12.3: 69 (35–88)	9	75.1 ± 9.1: 78.0 (54. 0–84.0)	0.03
Initial MTD, cm	281	2.3 ± 1.3: 2.0 (0.2–12.0)	16	4.3 ± 2.1: 3.1 (2.0–8.8)	<0.001
Initial ETV, cm^3	281	15.1 ± 60.3: 4.3 (0.004–903.7)	16	66.3 ± 100.0: 15.2 (4.3–363.0)	<0.001
Final MTD, cm	249	3.0 ± 1.6: 2.7 (0.9–15.0)	14	5.9 ± 2.1: 5.9 (3.1–10.7)	<0.001
Final ETV, cm^3	281	29.0 ± 109.8: 10.3 (0.3–1765.1)	14	132.1 ± 170.9: 87.9 (13.4–653.0)	<0.001
Linear growth rate, cm/year	249	0.4 ± 0.3: 0.25 (−1.4–2.47)	13	0.80 ± 0.7: 0.65 (0.1–2.72)	<0.001
Volumetric growth rate, cm^3/year	281	6.2 ± 27.5: 1.6 (−20.0–430.7)	14	27.1 ± 24.9: 19.1 (4.8–84.4)	<0.001
Time under AS, mo	281	33.3 ± 22.6: 27.0 (5.3–156.0)	17	40.2 ± 31.2: 29.0 (9.0–132.0)	0.47

Reproduced with permission from Smaldone et al. [40], American Cancer Society by Wiley, Inc.
AS active surveillance, *ETV* estimated tumor volume, *MTD* maximum linear tumor dimension, *SD* standard deviation

some individuals who were lost to follow up, and it is conceivable that some of these patients would have undergone definitive treatment before developing distant disease, if more closely followed.

AS remains an underutilized and evolving management strategy, and the interpretation of these data involve significant limitations including the level of evidence (all ≤ level III) and the lack of centralized pathologic review. These studies may contain significant selection bias, and therefore, it is especially important to exclude rapidly growing (if serial imaging available at presentation) and clinically high-risk lesions. *Despite the limitations inherent to AS, the available data demonstrate that (1) metastasis tends to occur late in the course of AS (>3 years following diagnosis), (2) almost all lesions that progress to metastasis are >3 cm and demonstrated positive growth rates at the time of metastatic presentation, and (3) no lesion exhibiting zero net growth while under surveillance has developed metastases while under observation* [40]. The most accurate available predictor of potential for disease progression among readily available metrics signaling the need for definitive intervention appears to be positive growth rate. Only one case (2.4-cm renal mass) progressing to bony metastases (after 5 months) with no change in tumor size has been reported [121]. Although this tumor may have been systemic at its initial diagnosis, this one case reinforces the need for careful patient selection for management with AS. Therefore, based on the best available data, lesions demonstrating zero net growth almost never metastasize and appear the best candidates for prolonged AS.

Cost-Effectiveness of AS Versus Active Treatment

With the increasing total costs of healthcare, cost-effectiveness relative to other treatment modalities has become an increasingly significant component in clinical decision-making. This may be especially true in clinical scenarios where the intervention has questionable effect on disease biology, such as the treatment of low-risk early-stage cancers. Using decision analytical modeling, a means to assess evidence from multiple sources and evaluate the impact of uncertainty on clinical outcomes, several recently published studies have estimated the cost-effectiveness of various approaches for management of SRMs. Measuring the costs associated with making a diagnosis, Heilbrun et al. performed a cost-effectiveness analysis of percutaneous biopsy and AS vs. active treatment in a hypothetical cohort of 2-cm renal masses in 60-year-old healthy men [122]. Immediate

treatment was the highest cost, but was the "most effective" diagnostic strategy and provided the longest overall survival of 18.53 life-years. AS was the lowest cost, "least effective" management strategy. On cost-effectiveness analysis using a societal willingness to pay threshold of $50,000, active surveillance was the preferred choice at a $75,000 willingness to pay threshold while biopsy and treatment were acceptable ($56,644 and $70,149 per life-year, respectively). When analysis was adjusted for quality of life, biopsy was superior to immediate treatment as the most cost-effective strategy at $33,840 per quality-adjusted life-year gained. Using the base hypothetical case of an SRM in a healthy 65-year-old male, to evaluate the cost-effectiveness of various nephron sparing treatment approaches, Chang et al. found that observation was the least costly approach but that immediate laparoscopic partial nephrectomy was the most cost-effective approach among the strategies that treated the tumor, with an incremental cost-effectiveness ratio of $36,645 per quality-adjusted life-year gained [123]. It should be noted that laparoscopic partial nephrectomy has largely been supplanted by the more expensive robotic-assisted approach.

Inherent to all decision analytic models, these studies are limited by the validity of the data used to develop them. The data on observation and even ablation strategies are limited to short- and intermediate-term follow-up, making the development of lifetime models incorporating these treatment options difficult. Furthermore, the model cannot answer the question of which patients are best observed. Future advancements to improve the identification of clinically significant tumors using novel markers or imaging will be important developments for optimizing the cost-effectiveness and decision-making regarding the treatment of SRMs.

Conclusion

Due in part to increased utilization of cross-sectional imaging, we have witnessed a substantial rise in incidentally detected, small, clinically localized renal masses <4 cm (SRMs). The gold standard for the management of enhancing renal lesions remains surgical excision. However, cancer-specific mortality remains unchanged despite a concurrent increase in treatment. This implies that a proportion of SRMs are indolent tumors that may not require or benefit from definitive intervention. With intermediate-term (up to 5 years) follow-up, recent data suggest that the vast majority of SRMs demonstrate slow growth kinetics with a very low rate of progression to metastatic disease. Moreover, a significant percentage (20–30%) of SRMs exhibit zero net growth under observation. While malignancy rates appear to be equivalent in zero growth lesions when compared to lesions demonstrating positive growth, progression to metastatic disease in lesions with zero net growth remains a case reportable event. Lesions that are more likely to progress to metastases under observation are larger at diagnosis (>3 cm) with a high nuclear grade and more rapid growth kinetics. In addition, metastatic progression in these patients appears to be a late event. Therefore, a period of initial active surveillance to determine growth kinetics appears to be a safe strategy in well-selected patients.

Despite these observations, improved methods of recognizing lesions with more aggressive biologic potential at the time of presentation are needed. Until such metrics are available, our clinical decision-making will be dependent on tumor linear growth rate. For SRMs that demonstrate rapid growth kinetics, one should strongly consider definitive intervention. Lesions exhibiting zero or minimal growth appear to be safe for continued AS. As the experience with AS progresses, we anticipate that improved imaging techniques, utilization of percutaneous biopsy, and predictive biomarker discovery will allow physicians to more confidently match appropriate treatment to individual tumor biology. Until then, use of preoperative nomograms to stratify SRM malignant potential and account for competing medical risks will remain invaluable in treatment planning.

AS for localized solid renal masses is a reasonable initial management strategy for many patients. When discussing observation of the

incidentally diagnosed SRM, patients and clinicians must calculate and accept the risks of surveillance. These risks must be weighed against the risk of intervention in a shared decision-making model when deciding upon the optimal management for patients with SRMs.

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Rationale for Partial Nephrectomy, Current Practice Patterns

9

Nicholas M. Donin and William C. Huang

Abbreviations

AS	Active surveillance
ASCO	American Society for Clinical Oncology
AUA	American Urological Association
CKD	Chronic kidney disease
EAU	European Association of Urology
EORTC-GU	European Organization for Research and Treatment of Cancer Genito-Urinary Group
ESRD	End-stage renal disease
LPN	Laparoscopic partial nephrectomy
LRN	Laparoscopic radical nephrectomy
MDRD	Modification of Diet in Renal Disease
MSKCC	Memorial Sloan-Kettering Cancer Center
NCCN	National Comprehensive Cancer Network
NSS	Nephron-sparing surgery
OPN	Open partial nephrectomy
ORN	Open radical nephrectomy
PN	Partial nephrectomy
QOL	Quality of life
RCTs	Renal cortical tumors
RMS	Renal mass sampling (RMS)
RN	Radical nephrectomy
RPN	Robotic partial nephrectomy
SEER	Surveillance epidemiology and end results
SRMs	Small renal masses

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Introduction

The oncologic and medical rationale for PN has evolved over the past two decades, and is built upon the convergence of epidemiologic, histologic, oncologic, and renal functional data, all of which point to PN as an ideal strategy for maximizing oncologic control of malignant RCTs, while preserving renal function and minimizing the long-term risks associated with a decreased number of nephrons. Historically, localized solid renal masses were treated with RN, stemming from the recognition that systemic medical therapy is rarely curative for kidney cancer. PN, while described as early as 1887, was traditionally limited to patients with a solitary kidney, bilateral tumors, or patients with underlying chronic kidney disease (CKD), because of its surgical complexity, increased rate of complications, and a lack of recognition of the potential morbidity associated with removal of a significant amount of functioning, nonneoplastic

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nephrons. This paradigm began to shift in the early 1990s, driven by a host of new radiologic, pathologic, oncologic, and cardiovascular developments and discoveries. The increasing use of cross-sectional imaging meant greater numbers of small, asymptomatic lesions were being diagnosed incidentally, resulting in an overall downward stage migration in kidney cancer. Evolving surgical techniques and experience allowed for increasing numbers of urologists to safely perform partial nephrectomy. There was increasing recognition that a nontrivial proportion of these small, asymptomatic solid renal lesions were in fact benign, meaning that a nontrivial proportion of patients were undergoing RN for these lesions and were thus losing significant portions of their renal function in the treatment of lesions with no metastatic potential or mortality threat. Concurrent with these observations was newly available long-term follow-up data of a large series of patients undergoing PN for small renal lesions that demonstrated oncologic equivalency between PN and RN. Finally, retrospective studies of large cohorts of patients with modestly decreased renal function from a variety of causes demonstrated these patients to be at an increased risk of cardiovascular disease and death. The convergence of these considerations led PN to become increasingly recognized, in the United States and abroad, as an optimal strategy for the treatment of SRMs, both maximizing oncologic control and minimizing morbidity. However, despite the strong retrospective data in favor of PN, the single prospective randomized trial evaluating PN versus RN failed to demonstrate an overall survival benefit in those undergoing PN compared with RN. Various possible explanations have been posited to explain this finding, with some arguing that the decreased renal function resulting from loss of nephrons during renal surgery may carry fewer long-term risks than decreased renal function from medicorenal renal disease, thus diminishing the theoretical potential benefit of PN in certain patients. Despite this result, PN remains the preferred treatment for SRMs and is reflected in the 2017 American Urological Association Guideline for Renal Mass and Localized Renal Cancer. This chapter will outline the evidence and rationale for PN as a treatment for renal cortical tumors.

Epidemiology of Renal Masses

Kidney cancer accounts for almost 4% of all adult malignant neoplasms and is the third most commonly diagnosed genitourinary malignancy. In 2018, there are predicted to be 65,340 incident cases and 14,970 deaths from kidney cancer in the United States, with an approximately 3:2 male-to-female predominance [1]. The annual incidence of kidney cancer has increased at a rate of approximately 3–4% annually over the past three decades. The vast majority of this increase is represented by clinically localized disease. Simard et al. demonstrated the annual rate of localized disease increased from 7.6 per 100,000 in 1999 to 12.2 per 100,000 in 2008 [2]. Furthermore, several population-based studies have demonstrated that the majority of this increase in localized disease can be accounted for by an increase in diagnosis of clinical stage T1a lesions (<4 cm diameter [2–4]), often referred to as small renal masses (SRMs) (see Fig. 9.1).

Today, the majority of newly diagnosed renal tumors are SRMs, and SRMs account for the majority, if not all, of the increasing incidence of renal tumors [5–7]. The gradual increase in the number and proportion of SRMs has been met with a parallel increase in the number of renal surgeries, meaning that an increasing number of patients now undergo surgery for small, asymptomatic RCTs [8].

The increasing incidence of small renal lesions in the past three decades has been attributed at least partially to the advent and growing clinical use of modern imaging procedures such as computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US). Beginning in the 1970s, these new technologies revolutionized the diagnosis of kidney cancer. The classically taught triad of flank pain, hematuria, and abdominal mass is rarely encountered in modern clinical practice and has given way to the asymptomatic mass found incidentally on imaging performed for a variety of signs and symptoms, most often unrelated to the

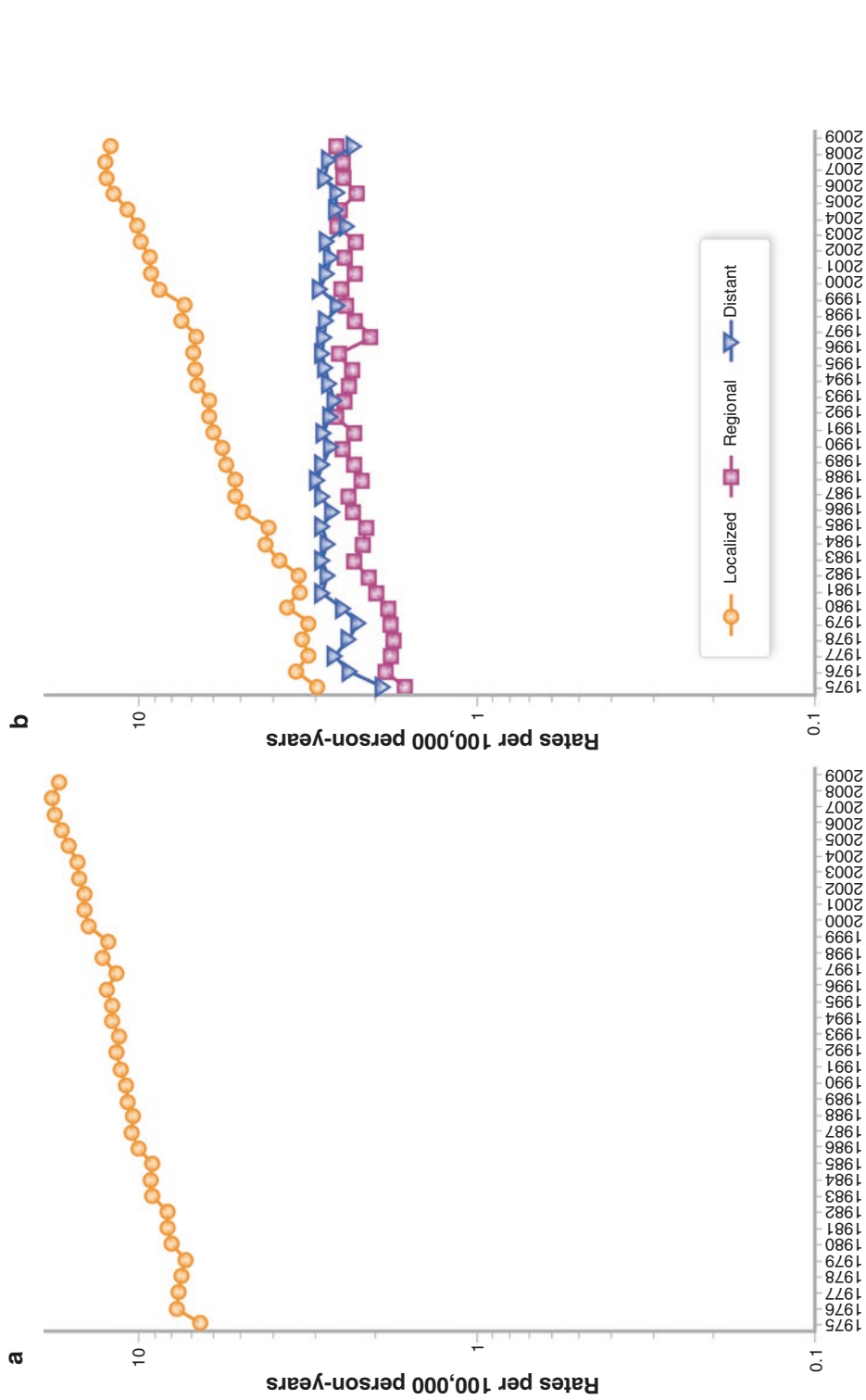


Fig. 9.1 Overall age-adjusted incidence rates of kidney cancer (**a**) and stratified according to disease stage (**b**), Surveillance, Epidemiology, and End Results (SEER), 1975–2009. (Adapted from Gandaglia et al. [6])

renal lesion itself. Indeed, it has been estimated that at least 48–66% of RCC diagnoses in the modern era occur as a result of cross-sectional imaging in an otherwise asymptomatic patient [9]. Consistent with this trend is the observation that the number of renal masses, both benign and malignant, discovered at autopsy has been observed to be declining, possibly due to an increased detection and treatment before death [10].

Given that smaller renal masses are associated with a decreased risk of malignancy, as well as increased survival rates, one would expect mortality from kidney cancer to decrease as greater proportions of renal masses are diagnosed at <4 cm. This phenomenon, however, has not been clearly demonstrated in the epidemiological data. A 2006 study by Hollingsworth et al. of Surveillance Epidemiology and End Results (SEER) cancer registry data demonstrated that from 1983 to 2002, despite the increasing proportions of renal masses that were <4 cm and detected incidentally on cross-sectional imaging, overall mortality for patients with kidney cancer rose to 155% [8]. This effect persisted despite a virtually identical increase in renal tumor surgery to match the observed increase in renal tumors, suggesting that the trend of increased mortality could not be attributed to inadequate numbers of surgeries being performed to treat these masses. Additionally, when investigators stratified the lesions by tumor size, the proportional increase in overall mortality rate for lesions 2–4 cm (from 0.2 to 1.5 deaths per 100,000) was in fact slightly greater than for lesions >7 cm in size (0.4–2.2 deaths per 100,000). These findings, which utilize a data set spanning 1983–2002, suggested that early detection of renal tumors and treatment at a lower stage did not provide an overall survival benefit during this era. The most recent data from the SEER program, however, does suggest that mortality from kidney cancer has been decreasing – at a rate of approximately 0.7% per year from 2006 to 2015 [11]. Despite these modest gains in the more recent data, it is unknown why the observed downward stage migration of kidney cancer and seemingly appropriate increase in treatment of small renal lesions has not resulted in greater decreases in mortality from kidney cancer.

Heterogeneity of Renal Cortical Tumors

RCTs represent a diverse group of biological entities with varying cytogenetic defects, histologies, and biological aggressiveness. While any RCT, benign, indolent, or malignant, can display growth over time, any given lesion's metastatic potential is intrinsically related to the lesion's histological subtype. Several large series have demonstrated the prognostic relevance of histologic type in univariate analysis models, with papillary and chromophobe subtypes thought to display favorable biological behavior, and clear cell, collecting duct, and unclassified subtypes thought to display more aggressive behavior [12, 13]. As such, knowing the histology of the lesion may help to determine which patients with small, localized RCTs are at risk for metastatic disease. This scenario, however, presents a clinical problem because at present, reliable methods for determining the histologic identity of a renal lesion prior to surgical excision are limited. Researchers have investigated the sensitivity and specificity of percutaneous biopsy, or renal mass sampling (RMS), and while diagnostic yields are improving with time at several specialized centers, robust clinical utility of RMS is limited at this time [14, 15]. Determining the malignant potential of RCTs, particularly small RCTs, from cross-sectional imaging is also limited due to the significant overlap in imaging characteristics of benign and malignant lesions on traditional cross-sectional imaging. Work is ongoing to develop functional imaging modalities able to better differentiate benign from malignant lesions [16, 17], but the majority of these assays are still under investigation and not available for widespread use. As a result of these limitations, a considerable number of patients with RCTs undergo nephrectomy for masses ultimately found to be benign. Contemporary series of patients undergoing nephrectomy for RCTs have demonstrated that 10–20% of lesions are in fact benign [18–20]. Clearly, techniques that could reliably determine a lesion's histologic identity prior to surgery could significantly alter the management of SRMs.

History of Partial Nephrectomy

The modern era of renal surgery began on August 2, 1869, in Heidelberg, Germany, when Gustav Simon performed a planned RN on a 46-year-old female with persistent urinary fistula [21]. The procedure was performed in front of 50 observers and took 40 min, with an estimated blood loss of 50 cc. The patient survived her procedure and was cured of her disease. Eighteen years later, in 1887, Vincenz Czerny performed the first PN to remove an angiosarcoma in a 30-year-old gardener, who also recovered from his procedure. Since these initial descriptions, renal surgery has evolved substantially, with modifications and improvements in surgical approach, antisepsis measures, and mortality rates. In 1969, Robson published the results from his landmark series of 88 patients with solid renal masses who underwent RN, a new and more aggressive approach to surgery for solid renal masses that included removal of perinephric fat, the ipsilateral adrenal, overlying peritoneum, and regional lymph nodes. In this series, he demonstrated improved rates of survival over historical standards and a 3% mortality rate [22]. His radical procedure would become the surgical gold-standard treatment for localized and locally advanced renal tumors for the next 40 years. The next major milestone in renal surgery occurred in 1991 when Clayman published the initial case report of a laparoscopic RN (LRN) [23]. From the early 1990s onward, there was progressive adoption of both LRN and open PN (OPN) as literature grew revealing equivalent intermediate and longer-term oncologic outcomes between these modalities and the gold standard of open RN (ORN) for renal masses up to 7 cm.

Despite early descriptions of PN, along with clinical and experimental evidence of its technical feasibility as early as the 1800s, its use during the first half of the twentieth century remained limited, likely due to its increased technical demands and surgeon reticence for fear of complications. Textbooks published between 1937 and 1970, almost 100 years after the first PN was successfully performed, rarely mention the procedure [21]. PN was utilized during this time period, albeit infrequently, in cases of a tumor in a solitary kidney, bilateral tumors, or in patients with significant underlying medicorenal disease or renal insufficiency. Several surgeons who had successfully performed PN for renal masses advocated the procedure in cases of modest-sized tumors limited to the poles of the kidney [24].

By the mid-twentieth century, the limited role of PN began to yield to a greater interest in performing the procedure in broader groups of patients, including those with normal contralateral kidneys. Vermooten was the first to suggest that PN may be undertaken in certain appropriately selected patients with normal contralateral kidneys [25]. Herr and Licht are credited as the first to publish follow-up data on a large series of patients with suspected malignant renal masses undergoing PN. In 1976 Herr began performing planned PN on patients with normal contralateral kidneys and in 1994 published a landmark case series of 230 patients, 41 of whom underwent PN, in which he reported no complications and 95% freedom from disease [21]. Moreover, while Herr conceded in his publication "the best available data indicate no functional advantage to PN when the opposite kidney is normal," he concluded that the sacrifice of uninvolved renal parenchyma might be unnecessary if local tumor control can be achieved by a partial excision.

Since these initial cohorts, interest in PN for the treatment of SRMs grew, driven by a variety of factors. The aforementioned downward size and stage migration of newly diagnosed renal cortical tumors meant increasing numbers of patients were presenting with small masses that were technically amenable to PN. Technical concerns about tumor multifocality, endophytic location, and nearness to the collecting system and major vessels could be routinely overcome by a variety of techniques developed over subsequent decades. Intraoperative ultrasound allowed for determination of tumor multifocality, depth of invasion, and location respective to critical structures. Nearness to vessels and the collecting system were managed with suture repair, adjunct hemostatic agents, and modern renorrhaphy techniques, which are effective in achieving hemostasis and maintaining the integrity of the collecting

system [26]. Complication rates for PN are now comparable with RN and can usually be managed conservatively [27]. Previously, desire for 1-cm surgical margin, deemed necessary for adequate oncologic control, meant many tumors with a central or hilar location were not considered candidates for PN. However, it has since been demonstrated that gross tumor resection with only a microscopically negative margin is adequate for effective oncologic control [28, 29]. As such, greater numbers of tumors are now considered technically and oncologically amenable to PN. Minimally invasive PN is now effectively performed both laparoscopically and robotically, with oncologic results equivalent to OPN and with low complication rates.

Oncologic Outcomes in Partial Nephrectomy

Oncologic outcomes following surgery for localized RCC are dependent on several clinicopathologic factors, including stage, tumor size, nuclear grade, and histologic subtype, with pathologic stage being the single most important factor. Data from one randomized prospective trial, as well as multiple large institution and population-based studies, have consistently demonstrated that PN provides equivalent oncologic outcomes to RN for the treatment of cT1a and cT1b tumors, with 5-year cancer-specific survival rates following surgery for clinically localized disease exceeding 90% [30–36]. Lee et al. published follow-up results of a retrospective analysis of 262 nephrectomies, 30% of which were PN, performed for pT1a RCC [30]. In this study, with an overall median follow-up of 40 months, there was no difference in disease-specific, disease-free, or overall survival between patients who underwent PN versus RN. While patients undergoing PN were slightly younger (mean 61 vs. 64) and the tumors excised by PN were slightly smaller (mean 2.5 vs. 3.0), there were no differences in tumor histologic type or pathologic stage. At approximately the same time, Lau et al. published a matched comparison of RN versus PN in 164 pairs of patients matched for tumor grade, pathologic stage, tumor diameter, age, gender, and year of surgery [31]. At 15-year follow-up, they found no significant difference in overall survival, cancer-specific survival, metastasis-free survival, or local-recurrence free survival. Results of these studies, both of which utilize data from specialized tertiary-care centers, have been corroborated in population-based cohorts, from which results may be more generalizable [32].

Additional studies have shown similar results for stage pT1b masses. A collaborative study between the Mayo Clinic and Memorial Sloan-Kettering Cancer Center of 1159 patients who underwent surgery for sporadic spontaneous unilateral renal masses 4.1–7 cm demonstrated no difference in overall survival or cancer-specific survival when comparing patients undergoing PN versus RN [33]. While the risk of death from RCC was increased for patients undergoing RN compared with PN, the results did not achieve significance – HR 1.97 (0.92–4.20) – and patients undergoing RN were on average older and were more likely to have larger tumors with perinephric or renal sinus fat invasion than patients treated with PN. The oncologic equivalency between PN and RN for pT1b masses has been demonstrated by other investigators in multiple patient cohorts, both in American and European centers [33–36]. Finally, in 2011 the European Organization for Research and Treatment of Cancer Genito-Urinary Group (EORTC-GU) published results of a randomized phase 3 clinical trial comparing RN to PN for the treatment of a solitary renal mass ≤5 cm. This trial, designed as a noninferiority trial, found nearly equivalent 10-year CSS rates of 75.2% for PN versus 79.4% for RN ($p = 0.07$) [37]. This is the only prospective randomized study comparing PN to RN and helps to confirm results of the various retrospective studies with regard to CSS.

A central tenet of PN is the goal of complete excision of the mass with a margin that is devoid of tumor. The precise amount of normal parenchyma that needs to be excised along with the tumor to achieve adequate cancer control is not fully agreed upon. For experienced surgeons, a positive margin during PN is relatively rare, with published rates of approximately 2.4–5.5% [38, 39]. The effect of a positive surgical margin on oncologic outcome has been examined, and at present the best available evidence demonstrates

that a microscopic-positive surgical margin does not adversely affect cancer-specific or overall survival. In a bi-institutional retrospective study, Yossepowitch et al. examined the effect of a positive margin on survival and recurrence in 77 patients who had positive surgical margins following PN [38]. With a median follow-up of 3.4 years, including 5-year follow-up in 33% of the cohort, and 10-year follow-up in 10% of the cohort, there was no difference between the 5- and 10-year freedom from local disease recurrence or metastatic progression when comparing patients with positive and negative surgical margins. In a multivariable analysis, positive margin status did not predict the likelihood of local recurrence or development of metastatic disease. In a retrospective study of multiple European centers, 111 patients with positive surgical margins following PN were compared with a cohort matched for tumor size, indication for PN (imperative vs. elective), and age [40]. They found that while rates of recurrence were greater for patients with a positive surgical margin (10.9% vs. 2.9%, $p = 0.03$), rates of cancer-specific survival and overall survival were the same among patients with positive and negative surgical margins. Multivariable modeling showed that positive surgical margin did not predict recurrence. Similar results have been found in other studies [41]. Despite these findings, the risk of recurrence likely remains greater in instances where residual tumor tissue is left behind in the resection bed. Some have suggested that what are read to be positive margins on pathology may in fact be the result of a tissue-processing artifact, which distorts the tumor and causes margins which are in fact negative to appear positive on pathology, thus making the true positive margin rate lower [42]. These false positives could theoretically wash out what may in fact be increased risk of recurrence and progression in patients with positive margins. Persistence of these uncertainties means that a negative surgical margin remains a key goal during PN.

As elective PN is increasingly being performed for clinically localized T1 disease, there exists a concern that PN may be inadvertently performed for more aggressive pathologic T3a disease that traditionally mandated RN. Several investigators have examined the outcomes of PN for clinical T1a lesions that were ultimately found to be pT3a (venous involvement) on final pathology [43]. Investigators from Columbia University Medical Center revealed no evidence of disease recurrence in their cohort of patients with incidental pT3a disease following NSS, with good preservation of kidney function [44]. While venous invasion on pathologic analysis portends worse prognosis, these studies indicate that it is still unclear whether or not performing NSS for incidental pathologic T3a disease compromises oncologic outcomes [45].

Renal Functional Outcomes in Partial Nephrectomy

The central concept driving contemporary interest in nephron-sparing approaches for the treatment of RCTs is the appreciation of the potentially deleterious long-term effects that radical extirpative renal surgery has on non-oncologic morbidity and mortality in the population of patients with RCTs. Historically, it was believed that RN, although likely to cause a detectable and permanent rise in serum creatinine because of the sacrifice of normal renal parenchyma not involved by tumor, would not contribute to serious long-term morbidity unless the patient were to develop renal replacement therapy such as dialysis or transplantation. This assumption was rooted in clinical outcomes data from renal transplant literature, in which patients undergoing donor nephrectomy were not reported to have higher rates of kidney failure requiring dialysis or resulting in death [46, 47]. However, key differences between the population of patients undergoing donor nephrectomy and the population of patients with renal masses make these assumptions invalid. Kidney donors tend to be younger (<40 years), carefully selected, and screened for medical comorbidities. In contrast, patients with spontaneous renal tumors are older (mean age 61) and often have systemic comorbidities known to affect renal function (e.g., hypertension, diabetes, vascular disease, metabolic syndrome). The known and predictable decline in renal function over time, as nephrons atrophy and glomerular filtration rate (GFR) falls, means that

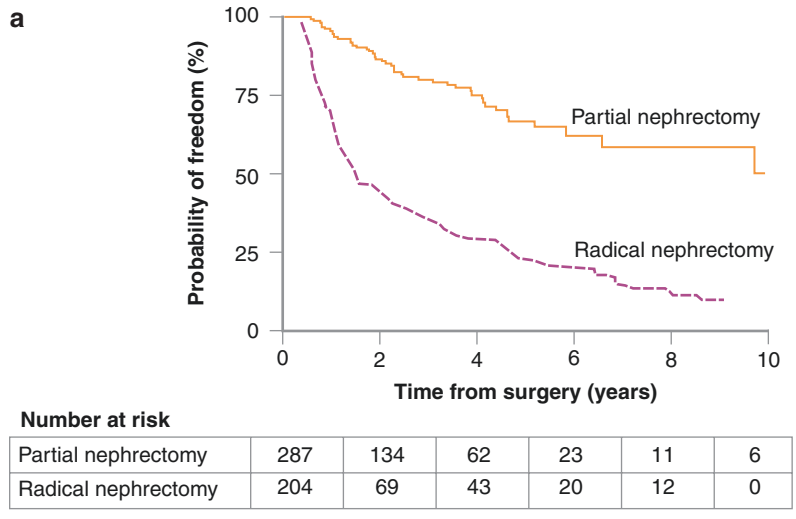
patients with RCTs, by mere fact of their age alone, are likely to harbor significantly depressed baseline renal function in the nonneoplastic parenchyma of their kidneys. Indeed, both clinical and pathologic studies have demonstrated that a substantial proportion of patients undergoing surgery for small RCTs have significant baseline underlying chronic kidney disease (CKD). Huang et al. found a 26% rate of Stage 3 CKD in a cohort of 662 patients with a solitary RCT <4 cm and a serum creatinine in the normal range [48]. A pathologic study from Harvard Medical School evaluated nonneoplastic normal tissue adjacent to the tumor in nephrectomy specimens from patients who underwent PN or RN [49]. These investigators found that only 10% of patients who underwent surgery had completely normal adjacent renal tissue. Twenty-eight percent were found to have histologic evidence of vascular sclerotic changes, and the remaining 62% demonstrated evidence of significant intrinsic renal abnormalities, including diabetic nephropathy, glomerular hypertrophy, mesangial expansion, and diffuse glomerulosclerosis. These studies provide clinical and pathologic evidence to suggest that a significant proportion of patients who undergo surgical treatment for RCTs have underlying, and potentially unrecognized, renal disease.

A substantial body of retrospective evidence from numerous large institution and population-based studies has demonstrated that renal volume loss during RN adversely affects long-term renal function and is a risk factor for the development and progression of CKD. In 1995, Butler et al. published results from a series of 88 patients undergoing RN or PN for pT1a unilateral RCC [50]. At a mean follow-up of 48 months, they found no significant difference between preoperative and postoperative creatinine in the PN group (1.3 ± 0.4 vs. 1.3 ± 0.6 mg/dl) but a significant increase in postoperative creatinine in the RN group (1.1 ± 0.3 vs. 1.5 ± 0.4 mg/dl, $p < 0.001$). This initial report was followed several years later by studies from the Mayo Clinic in 2000 and Memorial Sloan-Kettering Cancer Center (MSKCC) in 2002, both of which demonstrated a detrimental effect of RN on renal function. In the Mayo Clinic study, Lau et al. retrospectively compared matched cohorts of patients who underwent RN or PN for a single sporadic unilateral RCC with a normal contralateral kidney and serum cr <1.5 mg/dl [31]. Patients were matched for age at surgery, sex, tumor size, pathologic T stage and grade, and year of surgery. While median preoperative serum creatinine was 1.1 in both the PN and RN groups, at a median follow-up of 3.8 years, the cumulative incidence of chronic renal insufficiency (arbitrarily defined in this study as creatinine >2.0 mg/dl) was 22.4% in the RN group versus 11.6% in the PN group (risk ratio 3.7; 95% CI, 1.2–11.2; $p < 0.01$). These investigators also looked at a subset of patients for whom 10-year follow-up data was available and found the cumulative 10-year incidence in chronic renal insufficiency was almost twice as high in RN versus PN (20.2 vs. 10.5, RR; 5.5, 95% CI 1.2–25.0). In the study from MSKCC, McKiernan et al. retrospectively identified 290 patients with normal preoperative serum creatinine and normal contralateral kidney undergoing PN or RN for a single spontaneous unilateral pT1a renal mass [51]. With a mean follow-up of 26 months, they demonstrated a significantly higher postoperative creatinine in the RN group versus PN group (1.5 mg/dl vs. 1.0 mg/dl) despite having no difference between groups in preoperative creatinine. Nine percent of the patients in the RN group achieved a creatinine level >2.0, versus none in the PN group, and Kaplan-Meier analysis demonstrated the chance of developing a creatinine >2.0 was significantly higher in the RN group ($p = 0.008$).

These early reports were corroborated in 2006 in a landmark study in Lancet Oncology in which Huang et al. clearly demonstrated the measurable detrimental effect RN can have on long-term postoperative renal function in patients undergoing surgery for RCTs [48]. This study from MSKCC included 662 patients who underwent RN or PN for a unilateral RCT <4 cm and who had a normal preoperative serum creatinine concentration and a normal contralateral kidney on imaging. Rather than using serum creatinine concentration as an estimate of renal function, this study utilized the Modification of Diet in Renal Disease (MDRD) equation to calculate estimated glomerular filtration rate (eGFR). This equation, which estimates GFR

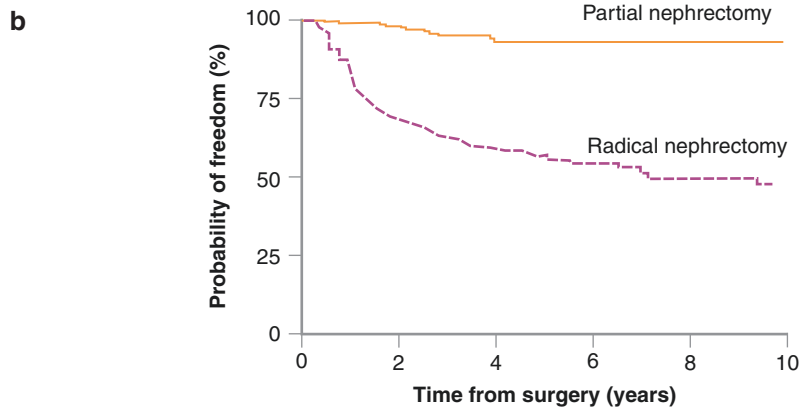
using serum creatinine, age, race, and gender, was developed in a group of over 1500 patients and has since been validated in larger, diverse groups of patients and has proved to be a more accurate estimate of kidney function than measured serum creatinine [52–54]. Using this equation, Huang et al. made several novel observations. First, as mentioned previously, in this group of 662 patients with normal preoperative serum creatinine levels, the use of the MDRD equation revealed a 26% rate of Stage 3 CKD (eGFR < 60 ml/min/1.73 m^2), demonstrating a high level of baseline renal insufficiency in this population of patients with normal serum creatinine and normal contralateral kidneys. Additionally, after surgery, the 3-year probability of freedom from new onset of eGFR lower than 60 ml/min/1.73 m^2 was 80% (95% CI 73–85) after PN and only 35% (28–43; $p < 0.0001$) after RN; corresponding values for GFRs lower than 45 ml/min/1.73 m^2 were 95% and 64% ($p < 0.0001$), respectively (see Fig. 9.2).

Multivariable analysis showed that RN remained an independent risk factor for patients developing new onset of eGFR lower than 60 ml/min/1.73 m^2 (hazard ratio 3.82 [95% CI 2.75–5.32]) and 45 ml/min/1.73 m^2 (11.8 [95% CI 6.24–22.4]; both $p < 0.0001$). These trends were similarly demonstrated in a cohort of 510 patients with cT1b renal masses from the



Number at risk

Partial nephrectomy	287	134	62	23	11	6
Radical nephrectomy	204	69	43	20	12	0



Number at risk

Partial nephrectomy	385	187	84	33	13	6
Radical nephrectomy	262	130	86	56	33	21

Fig. 9.2 Probability of freedom from new-onset GFR lower than 60 ml/min/1.72 m^2 (panel **a**) and 45 ml/min/1.72 m^2 (panel **b**), by operation type. (Adapted from Huang et al. [48])

Cleveland Clinic [55] as well as a US population-based cohort from the SEER program [11]. At present, all available data have clearly demonstrated that the loss of normal, functioning nephrons during RN has a measurable detrimental effect on postoperative renal function and puts patients at risk for new-onset CKD when compared with PN.

Chronic Kidney Disease, Morbidity, and Mortality

Chronic Kidney Disease is a significant public health concern in the United States. Currently, it is estimated that CKD affects over 30 million Americans or approximately 14.8% of the US adult population [56, 57] (see Fig. 9.3).

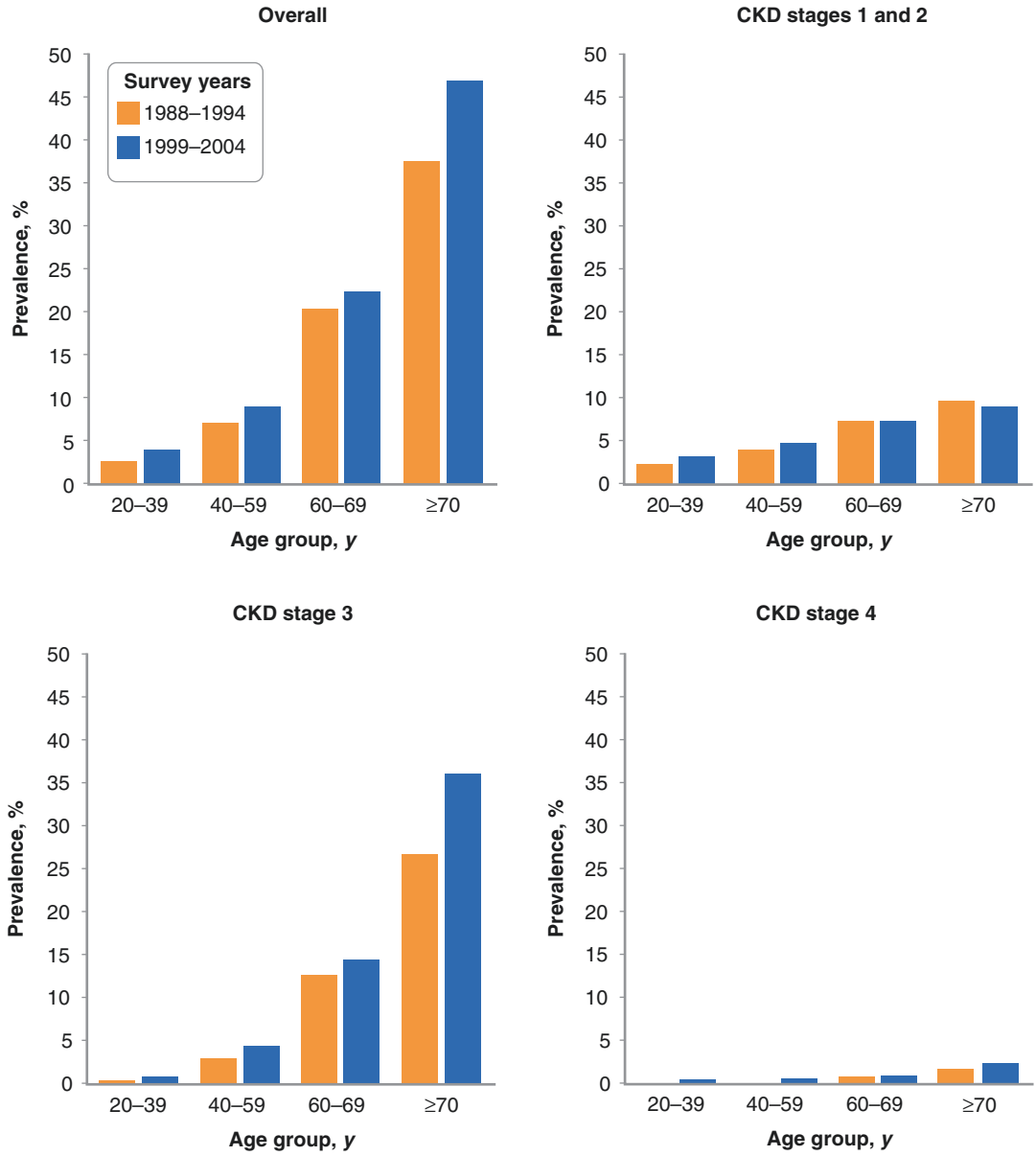


Fig. 9.3 Prevalence of chronic kidney disease (CKD) stages by age group in NHANES 1988–1994 and 1999–2004. (Adapted from Coresh et al. [56])

The prevalence and incidence of CKD rose progressively during the end of the twentieth century, but in the last decade, more advanced stages of the disease appear to be leveling off [58]. Despite this, a person today is over five times more likely to be diagnosed with CKD than they were 20 years ago. Because of the effects of aging on renal function, the disease disproportionately affects older persons, and it is estimated that 47% of persons over the age of 70 have early stages of the disease [59]. The human and financial toll of this disease is tremendous. Once hemodialysis is initiated, the expected remaining life span is 8 years for patients aged 40–44 and 4.5 years for those 60–64 years of age. Treatment costs for patients with CKD are more than double than those without CKD and can reach up to $23,000 per person annually [57]. The high prevalence of conditions that contribute to CKD, such as diabetes, obesity, and hypertension, mean that CKD will continue to be a significant US public health issue.

Beginning in 1999, the National Kidney Foundation began to recognize that a significant number of patients in the United States had underlying, undiagnosed early stages of kidney disease, and that, if detected early, could be treated and potentially prevented from progressing to more severe stages of renal dysfunction. In response, they launched the Kidney Disease Outcomes Quality Initiative (KDOQI), which aimed to increase the detection of early stages of CKD, improve the treatment of kidney disease in these patients, and hopefully slow the progression of their kidney disease and prevent progression to ESRD. The most recent Kidney Disease Improving Global Outcomes (KDIGO) guidelines define CKD as abnormalities of kidney structure or function, present for >3 months, with implications for health, and is classified into one of four risk groups based on etiology of CKD, eGFR category, and albuminuria category [60]. The eGFR is calculated using one of several Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations which use gender, age, race, and either serum creatinine or serum cystatin C to estimate the GFR. These equations have been evaluated in large numbers of patients and various clinical settings and have proven an effective method for determining eGFR, especially in patients without preexisting CKD [61, 62]. The risk groups (e.g., low, moderate, high, and very high) are aimed at predicting the risk of concurrent and future complications from CKD.

It has been known since the 1970s that risk of adverse cardiovascular events is dramatically increased in patients who are on renal replacement therapy [63]. Mortality rates for patients requiring maintenance hemodialysis approach 20%, with more than 50% of deaths attributable to cardiovascular disease. However, until relatively recently, little was known about the risk of death among patients living with more modest levels of CKD. In 2004, Go et al. published their seminal work in the New England Journal of Medicine demonstrating the association between CKD and the risk of cardiovascular events, hospitalization, and death [64]. These investigators estimated the longitudinal GFR among 1,120,295 adults within a large, healthcare delivery system in whom serum creatinine had been measured between 1996 and 2000 and who had not undergone dialysis or kidney transplantation. In this population, with a median age of 52, the risk of death increased progressively as the GFR decreased below 60 ml/min/1.73 m^2. The adjusted hazard ratio for cardiovascular events also increased inversely in a dose-dependent fashion, as did the risk of hospitalization (see Fig. 9.4).

This study was groundbreaking because it was the first to demonstrate significantly increased risk of death in patients whose eGFR was only moderately decreased (<60 ml/min/1.73 m^2), and that risk increased in a graded response inversely proportional to eGFR. These original findings have since been corroborated in subsequent large, longitudinal cohort studies, again demonstrating that CKD is a significant risk factor for poor cardiovascular outcomes and cardiovascular death [65–68]. Other researchers have found an eGFR <60 ml/min/1.73 m^2 to be a risk factor for morbidity and death from other noncardiovascular causes in elderly populations [69].

The connection between renal dysfunction and cardiovascular disease has been an active

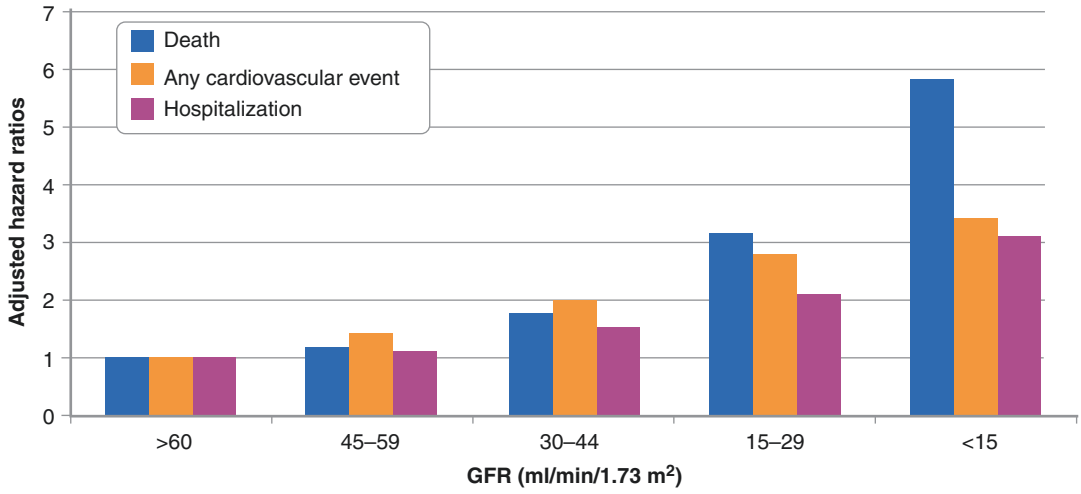


Fig. 9.4 Adjusted hazard ratio for death from any cause, cardiovascular events, and hospitalization among 1,120,295 ambulatory adults, according to estimated GFR. (Adapted from Go et al. [64])

area of research since it was first observed over 30 years ago, and while the mechanisms behind the association are incompletely characterized at present, some associations have been established. Increased rates of atherogenesis in patients with CKD have been observed and are thought to be one of the major contributors to increased cardiovascular morbidity and mortality among patients with CKD [70]. Evidence for this phenomenon was noted in a retrospective case-control study evaluating pre- and post-nephrectomy aortic calcium volume scores (ACS) [71]. In this study, 739 patients who underwent RN were compared with an age and gender-matched control cohort. Investigators found that patients who underwent nephrectomy had greater postoperative ACS compared with controls and that age, postoperative GFR, and time since nephrectomy was an independent predictor of ACS on multivariate regression. As a cause or consequence of this atherogenesis, evidence of oxidative stress and a state of micro-inflammation is usually found in patients with CKD. In addition, other well-established risk factors for cardiovascular disease, such as hypertension and left ventricular dysfunction, have been demonstrated to be increased in patients with intrinsic renal disease, even in patients with a normal GFR [72]. Both experimental and clinical studies have demonstrated increased sympathetic output in patients with even minor degrees of CKD, possibly due to activation of intrarenal chemoreceptors and baroreceptors that send activating signals to the hypothalamus, where catecholamine turnover is increased [73, 74]. Other serum abnormalities such as altered apolipoprotein patterns with increased Lp(a) have been found in patients with renal disease even when inulin clearance was still normal [75]. The pathophysiologic connections behind decreased GFR and cardiovascular disease continue to be an active area of research, and fully elucidating the mechanisms behind the connection between CKD and cardiovascular disease may shed light on potential therapeutic targets for intervention.

Renal Surgery, Morbidity, and Mortality

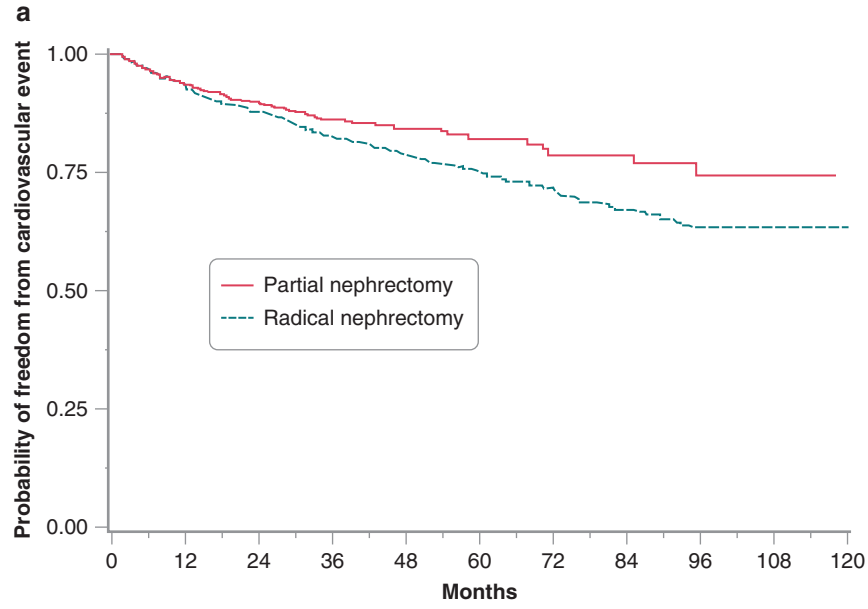
Increasing awareness of the association between CKD and cardiovascular disease and mortality as well as the recognition of the deleterious effects that nephron loss during kidney surgery can have on postoperative renal function has prompted interest in examining the impact of renal surgery on cardiovascular outcomes, as well as overall

mortality. While the previously cited studies demonstrate an association between RN and an increased risk of new-onset CKD, there exists some uncertainty over whether the CKD resulting from surgically induced loss of nephrons leads to increased risk of adverse cardiovascular events and death.

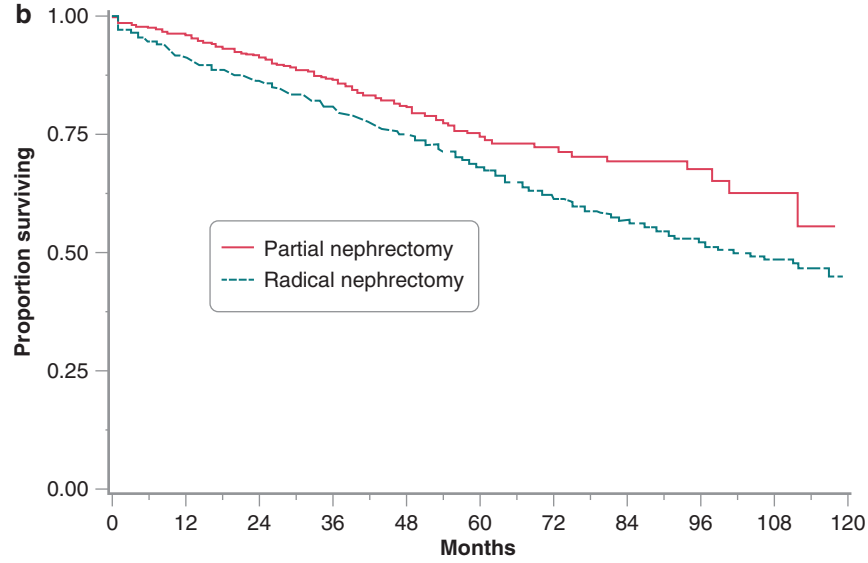
A number of retrospective studies have examined the relationship between surgery and nononcologic morbidity and mortality and have demonstrated that RN is a risk factor for adverse cardiovascular events and worsened overall survival. The first of such papers was published using data from 648 patients who underwent either RN or PN at the Mayo Clinic between 1989 and 2003 [76]. When analyzed as a whole, investigators found no significant association between the type of surgery (RN vs. PN) and overall mortality. However, during multivariate analysis, they found a significant interaction between age and mortality, leading them to stratify their cohort by the median age of 65. In doing so, they found that in patients <65 years old, RN was associated with an increased risk of death from any cause when compared with PN (RR 2.16, 95% CI 1.12–4.19, $p = 0.022$). This initial report was followed soon thereafter by researchers analyzing data from the SEER cancer registry linked to Medicare claims, who demonstrated an association between RN, overall mortality, and postoperative adverse cardiovascular events [77]. In this study, 2991 patients older than 66 years were identified who were treated with RN or PN for renal tumors 4 cm or less between 1995 and 2002. Multivariate and Kaplan-Meier analysis demonstrated that RN was associated with an increased risk of overall mortality (HR 1.38, $p < 0.01$) and a 1.4 times greater number of cardiovascular events after surgery ($p < 0.05$) (see Fig. 9.5).

Several subsequent studies have demonstrated similar findings. Using SEER data from 1998 to 2004 for T1a lesions, Zini et al. reported that RN was significantly associated with increased overall mortality (RR 1.23, $p = 0.001$) as well as noncancer-related mortality as compared with PN for cT1a masses [78]. Research published in JAMA using SEER-Medicare data as recent as 2007 demonstrated that for cT1a lesions, PN resulted in a predicted survival increase of 5.6 (95% CI, 1.9–9.3), 11.8 (95% CI, 3.9–19.7), and 15.5 (95% CI, 5.0–26.0) percentage points at 2, 5, and 8 years posttreatment ($p < 0.001$) when compared with RN [79]. This finding corresponded to a number-needed-to-treat of 7 at the 8-year time point. In other words, treating 7 patients with PN rather than RN would result in one life saved during 8 years of follow-up. Investigators have demonstrated published similar trends in patients with tumors greater than cT1a. In a study of data from 1004 patients who underwent surgery at the Cleveland Clinic for cT1b renal masses, Weight et al. demonstrated that RN resulted in greater averaged decrease in postoperative eGFR (23.5% vs. 16.6%) when compared to PN and that postoperative eGFR was associated with overall survival and cardiovascular survival in an independent and graded fashion [55, 80]. The paradigm suggested by these studies – that PN saves nephrons and that greater numbers of nephrons and higher eGFR (irrespective of absolute level of eGFR and irrespective of baseline underlying renal disease) translates into lower cardiovascular disease and death – was widely adopted by the urologic community and prompted some to promote partial nephrectomy virtually "at all costs" when technically feasible.

However, this paradigm, which was widely accepted and promoted by the urologic community based on the retrospective studies, was called into question in 2011 when the EORTC-GU published the results of the only randomized prospective clinical trial comparing RN with PN for the treatment of a solitary renal mass. The study compared RN with PN for patients with a solitary renal mass ≤5 cm and a normal contralateral kidney [37]. The study was initially designed as a noninferiority trial intended to detect a 10% difference in overall survival. However, after 5 years, the decision was made to redesign the trial to detect a more modest 3% difference, and the trial would ultimately close early due to poor accrual after randomizing 541 patients. The two groups were well-balanced with regard to preoperative characteristics. The primary outcome of the study was overall survival, and in the



At risk partial nephrectomy	556	505	454	275	168	89	66	47	27	10	0
At risk radical nephrectomy	2435	2110	1874	1348	930	573	398	262	155	73	0



At risk partial nephrectomy	556	534	492	324	198	106	78	56	33	12	0
At risk radical nephrectomy	2435	2217	2077	1544	1099	711	522	363	233	105	0

Fig. 9.5 Probability of freedom from cardiovascular events (panel **a**) and freedom from death (panel **b**) by surgery type. (Adapted from Huang et al. [77])

intention-to-treat analysis, investigators found, unexpectedly, that RN had a slightly higher 10-year overall survival rate when compared with PN 81.1% versus 75.7%. With a hazard ratio of 1.50 (95% CI 1.03–2.16), the statistical test of noninferiority for OS was not significant ($p = 0.77$), while the test for superiority was significant ($p = 0.03$). When considering only the clinically and pathologically eligible

patients, the hazard ratios were more modest, and the findings were no longer significant, but the results trended similarly – there was no overall survival benefit to PN. There were only 12 deaths from RCC, with no difference between treatment groups, and there was no difference in progression rates. Interestingly, rates of cardiovascular deaths were higher in the PN group compared with the RN group (9.3% vs. 7.3%), and the authors were at a loss to explain this observation. This study is, at present, the only prospective randomized trial comparing PN with RN, and also the only study to find an overall survival benefit for RN, and has caused some to reevaluate the previously accepted paradigm which holds that PN should produce a survival benefit compared with RN. This will be discussed below.

The findings of the EORTC randomized trial have been questioned by some. The questioning is not only because its findings are inconsistent with the large body of retrospective data but also because of concerns about the study design and methodology. First, the study was closed prematurely because of poor accrual and was thus statistically underpowered to detect small differences. Second, while designed as a noninferiority trial, the finding of an overall survival benefit in the intention-to-treat analysis for RN over PN was based on a test of superiority. Additionally, there was no standardization of surgical technique (surgeries were carried out at over 60 centers), and there was unequal crossover between arms. The authors themselves acknowledge that their findings are perplexing, inconsistent with the existing observational data, and continue to recommend PN when feasible.

However, more recently, a reappraisal of retrospective data has led to newfound perspective on the surgical effect of nephrectomy on renal functional outcomes and its downstream effects and allows for a reconciliation of the prospective and retrospective data. The paradigm in which PN produces overall survival benefits over RN owing to its improved postoperative renal functional outcomes relies on several assumptions which have more recently been called into question. These assumptions and the data suggesting they may not be appropriately applied to patients undergoing surgery for renal masses are described below.

Flawed Assumption #1 – The entirety of the increase in cardiovascular and mortality risk conferred by CKD can be determined by the eGFR. This assumption was largely adopted by the urologic community during the emergence of PN and formed the backbone of the foundation of the support for the potential benefits of PN over RN in improving overall survival. However, this assumption has never been consistent with the nephrologic literature, which has long recognized that, in addition to eGFR, both the cause of the CKD and the degree of albuminuria have a significant impact with regard to the prognosis and potential future complications from CKD. This entity is a recognized component of the KDIGO clinical practice guidelines, which classify CKD, not only by eGFR but also by the cause of the CKD and albuminuria category. The significance of proteinuria in the calculation of risk of adverse events from CKD has largely been ignored by the urologic community, which has relied almost entirely on eGFR in calculations of risk. In fact, albumin-to-creatinine ratio is known to be an independent predictor of both all-cause and cardiovascular mortality, suggesting that intrinsic renal disease, in addition to a decrease in the number of functioning, is a critical determinant in the evaluation of risk attributable to CKD.

Causes of CKD include renal volume loss (cystic kidney disease, trauma, *kidney cancer surgery*), intrinsic renal disease (glomerulonephritis), and systemic diseases affecting the kidney (DM, HTN). The differing etiologies of chronic kidney disease produce different clinical outcomes, and as such the cause of the CKD has clear implications on clinical outcome from the disease. This idea is also a recognized concept in nephrologic literature and reflected in KDIGO guidelines, which advocating classifying CKD by its cause (renal volume loss vs. intrinsic renal disease vs. medical diseases affecting the kidney). Consistent with this have been recent observations that CKD from renal volume loss, as can occur following nephrectomy, appears to have a lower risk of progressive loss in GFR and lower risk of mortality when compared with CKD caused by systemic or intrinsic renal disease. Lane et al. investigated this consideration in a very large cohort of >4000 patients undergoing

nephrectomy for renal masses from the Cleveland Clinic [81]. They compared the patients who had decreased preoperative eGFR (CKD from intrinsic renal diseases or medical diseases affecting the kidney) versus those who had normal renal function preoperatively but developed an eGFR <60 following surgery (CKD from renal volume loss). They found that a low preoperative eGFR (from medicorenal disease) was a strong predictor of overall survival when compared with those with a normal preoperative eGFR. However, interestingly, they found that neither surgically induced chronic kidney disease (CKD from renal volume loss) nor postoperative glomerular filtration rate was a significant predictor of survival in patients without preexisting CKD. This scenario suggests that patients with CKD attributable entirely to renal volume loss from surgery may not be at greater mortality risk. They also found that annual renal functional decline was 4.7% and 0.7% for patients with CKD from medicorenal disease and CKD from renal volume loss, respectively, suggesting that CKD from renal volume loss may not result in a further progressive loss of eGFR over time. The same group of researchers published a second study using the same cohort of patients in which they compared patients with postoperative eGFR >60 (no CKD), patients with normal preoperative eGFR but postoperative eGFR <60 (CKD from renal volume loss), and those with both pre- and postoperative eGFR <60 (CKD from both medicorenal disease and renal volume loss) [82]. They made several interesting observations. First, they found no difference in the rate of progressive renal decline or the need for dialysis between those with no postoperative CKD and those with CKD from renal volume loss. This scenario again suggests that CKD attributable solely to loss of nephrons during surgery may not result in further declines in eGFR after surgery. Second, they found all-cause and nonrenal-cancer-cause mortality was highest in those with CKD from both medicorenal disease and renal volume loss, followed by those with CKD from renal volume loss and then those with no CKD. This finding was again consistent with their first study and suggested that those with decreased eGFR exclusively from surgery may not be at increased mortality risk. Finally, they found that the probability of various adverse outcomes including 50% drop in eGFR, need for dialysis, and 5-year all-cause mortality did not begin to increase until the postoperative eGFR reached a level of approximately 45 ml/min/1.73 m^2 (see Fig. 9.6).

This observation was interesting and suggested that the commonly used cutoff of <60 ml/min/1.73 m^2 – widely discussed in urologic literature – for determining who may be at risk of the consequences of postoperative CKD may have

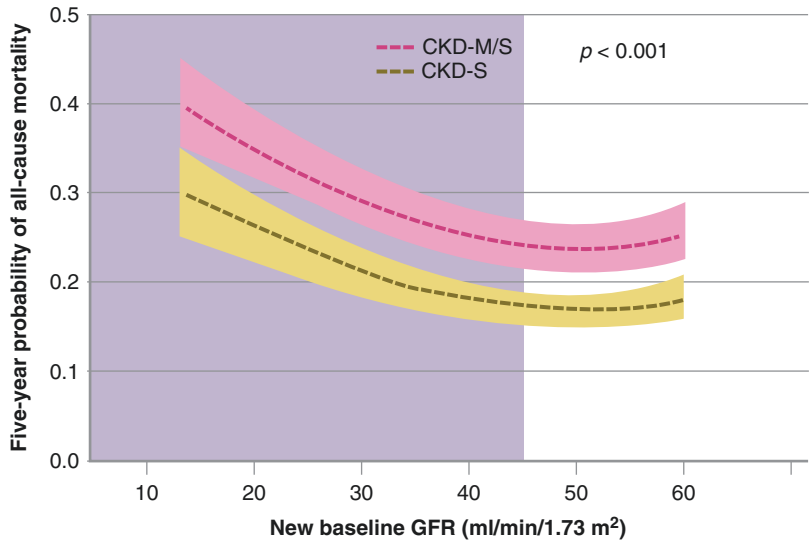


Fig. 9.6 The 5-year probability of all-cause mortality according to new baseline GFR (CKD-M/S = chronic kidney disease attributable to medicorenal disease and loss of nephrons from surgery, CKD-S = chronic kidney disease attributable to loss of nephrons from surgery). (Adapted from Lane et al. [82])

been too stringent, and in fact, the risk of cardiovascular disease and death may not begin to rise until a much lower level of eGFR – 45 ml/min/1.73 m^2 – is reached. These observations led the authors to conclude that CKD from renal volume loss is associated with better renal functional outcomes and overall survival than CKD from medicorenal disease and that the probability of adverse events does not truly begin to rise until the postoperative eGFR falls below 45 ml/min/1.73 m^2. This scenario led the authors to further conclude that in patients without preexisting CKD, and in whom the postoperative eGFR is expected to be >45, RN is an appropriate choice, particularly in cT1b and cT2 tumors, and in those in whom PN could be technically challenging.

Flawed Assumption #2 – Inverse linear relationship exists between eGFR and cardiovascular mortality risk at all levels of eGFR. As described above, data from the Cleveland Clinic cohort suggests that the increase in cardiovascular risk may not begin at an eGFR <60 ml/min/m^2, but rather at lower levels of eGFR, perhaps <45 ml/min/m^2 (see Fig. 9.6). Interestingly, a similar finding is present in the seminal work of Go et al. They found that while rates of death, cardiovascular events, and hospitalization all began to increase at an eGFR of <60 ml/min/m^2, the increases in risk at this level of eGFR are relatively minimal. However, these risks increase in a much more dramatic fashion at an eGFR <45 ml/min/m^2 (see Fig. 9.4). This observation has not been widely adopted by the urologic community, in which the majority of publications use an eGFR cutoff of 60 ml/min/m^2 as the meaningful cutoff for determining CKD. And interestingly, it is this point which may help explain why PN did not produce overall survival benefits in the EORTC randomized trial. In a manuscript by Scosyrev et al., the EORTC investigators reported the renal functional outcomes of the two trial groups [83]. With a median follow-up of 6.7 years, they reported that, as expected, modest postoperative renal dysfunction (eGFR <60 ml/min/1.73 m^2) was significantly more common in the RN group versus the PN group (85.7% vs. 64.7%, $p < 0.001$). However, more advanced renal dysfunction (eGFR <30 ml/min/1.73 m^2) was similar between the two groups (10.0% vs. 6.3%, nonsignificant), and very advanced renal dysfunction (eGFR <15 ml/min/1.73 m^2) was almost identical between the two groups (1.5% vs. 1.6%, nonsignificant). Given the appreciation that the increased risks of cardiovascular events, hospitalization, and death may not truly begin to increase until eGFR falls below 45 ml/min/1.73 m^2 and that the rates of these levels of more severe renal dysfunction were relatively similar between the two treatment arms in the EORTC trial, it is not surprising that PN failed to improve overall survival compared to RN. This result is further supported when considering that the postoperative renal dysfunction in this cohort is largely attributable to CKD from renal volume loss (preoperative eGFR was similar between the treatment arms) and that, as the studies from the Cleveland Clinic suggest, this form of CKD tends not to result in progressive renal decline and does not carry with it the same risk of cardiovascular disease or death as medicorenal disease.

While RN may not put patients at the increased risk of cardiovascular benefits originally believed, there is some evidence that RN may be a risk factor for other adverse outcomes including increased rates of osteoporosis and poor postoperative quality of life metrics when compared with PN. A retrospective analysis of 905 patients undergoing either RN or PN with a mean follow-up of 6.4 years evaluated the primary outcomes of development of osteoporosis and non-pathologic fractures. While the two groups were comparative preoperatively with respect to prevalence of osteoporosis and fractures, postoperatively a significantly greater proportion of patients in the RN group had developed osteoporosis (22.6% vs. 12.5%, $p < 0.001$) and postoperative fractures (9.8% vs. 4.4%, $p = 0.007$). Several studies have attempted to evaluate the impact that surgical approach for localized renal masses has on overall postoperative quality of life. Poulakis et al. utilized quality of life (QOL) questionnaires to retrospectively evaluate 416 patients and prospectively evaluate 51 patients, all of whom underwent RN or PN for localized RCTs [84]. Using three validated QOL questionnaires along with two sets of questions designed

to address fear of recurrence and attitudes associated with having less than two functional kidneys, they found that at the 12-month postoperative mark, patients after elective NSS showed significantly better scores on physical functioning, role functioning, fatigue, and bodily pain than those who underwent RN ($p < 0.05$). There was no statistically significant difference in the fear of recurrence between patients who underwent PN versus RN. Similar results were found by Novaro et al., who prospectively evaluated 129 patients undergoing RN or PN and demonstrated that patients undergoing elective PN had significantly higher chances of returning to baseline physical functioning scores 6 months after surgery and significantly higher probability of returning to baseline social function scores 12 months after surgery compared with those undergoing mandatory NSS [85]. One possible explanation for this finding is that patients who underwent mandatory NSS, presumably for either bilateral tumors, a tumor in solitary kidney, or CKD, may have a heightened awareness and sensitivity to the potential deleterious effects kidney surgery may have on their overall kidney functioning. This hypothesis is supported by findings by Clark et al. who demonstrated that a patient's self-reported perception of the amount of remaining kidney tissue after their surgery was directly and highly correlated with the overall physical quality of life [86]. Clark also found that patients with more remaining parenchyma were less apt to worry about cancer recurrence or to believe that renal cancer had negatively impacted their overall health.

Complications of Partial Nephrectomy

PN is an inherently technically demanding procedure. Control of segmental blood vessels, repair of the collecting system, excision of the tumor with an adequate margin, and performing satisfactory renorrhaphy all contribute to the difficulty of the operation. Despite these challenges, the majority of procedures are completed without complications, and when they do arise, complications are generally minor. Reported rates of complication in the literature vary somewhat widely, from 10% to 36% [87, 88], likely based in part on inconsistent criteria and reporting. Contemporary series using more standardized grading criteria demonstrate complication rates of approximately 20%, with equivalency between open and laparoscopic approaches. In two large studies of complications graded using a standardized 5-tiered scale, investigators from the Cleveland Clinic and MSKCC found overall rates of complications for PN were less than 20% and that over 70% of these complications were relatively minor and could be successfully managed conservatively [26, 27]. When interventional procedures were necessary, the vast majority were either endoscopic (placement of a ureteral stent) or percutaneous (drainage of urinoma or angioembolization). The most common complications are hemorrhage and urine leak, with both reported to occur in approximately 2–5% of patients in most contemporary series from high-volume centers [26, 27, 88]. Hemorrhage is generally managed expectantly with observation, bedrest, and transfusion as needed. Bleeding that cannot be controlled with these modalities prompts angioembolization or rarely, reexploration. Urine leak is treated with percutaneous image-guided drainage and ureteral stent placement, as indicated. Prolonged fistula is rare and requires long-term percutaneous drainage. Death was extremely uncommon, occurring in only 0.2% of cases. In the study from MSKCC, there was no significant difference in overall complication rates between PN and RN; however, PN did result in higher rates of procedural complications (9% vs. 3%) and need for intervention (2.5% vs. 0.6%) [27].

Investigators have evaluated the factors associated with complications following PN. Patient age, tumor stage, operative time, and surgery on a solitary kidney have been shown to be independent predictors of postoperative complication following PN. Some of these variables, such as tumor size, operative time, and tumor in a solitary kidney may function as surrogates for the technical difficulty of the procedure, in which case higher rates of complication might be inferred. An early study comparing complication rates in

1800 laparoscopic PN (LPN) and open PN (OPN) demonstrated that LPN was independently predictive of greater rates of postoperative complications, hemorrhage, and need for reintervention [89]. A follow-up study from the same group, however, demonstrated that that complication rates for LPN have decreased over time and that contemporary rates for LPN are equivalent to OPN [26]. This improvement is presumably due to technical improvements and increased surgical experience. More recently, investigators have shown that on average, complication rates after PN are lower at high-volume centers when compared with centers that perform fewer PNs, again suggesting that experience and volume contribute to lower rates of complications [90].

One potential way to improve surgical complications and outcomes after LPN is through the utilization of robot-assisted LPN or robotic PN (RPN). LPN is technically challenging, thus limiting its use to few experienced laparoscopic surgeons. With articulating, wristed arms, magnified visualization, and more precise control, RPN may allow for more facile tumor excision and renorrhaphy than LPN and thus broaden potential utilization of minimally invasive NSS to a larger urologic community. In contrast to the estimated learning curve of over 100 cases to master LPN, studies have suggested that the learning curve for RPN is on the order of two-dozen cases [91]. Literature examining the initial experience with RPN reveals similar complication rates as LPN. In a large multi-institutional review of RPN versus LPN, Benway et al. demonstrated that morbidity after RPN was equivalent to LPN [92].

Utilization of Partial Nephrectomy

The growing awareness of the potential functional benefits of PN, the diffusion of technology allowing for more rapid and widespread adoption of PN, growing surgical experience, and publication of guidelines for the management of renal masses has resulted in a progressive decrease in the number of RNs being performed in the United States, in favor of NSS. This finding is particularly true for the small renal mass. The trend away from RN and toward PN has been ongoing for decades. Multiple investigators have reported slowly increasing annual rates of PN over the last two decades. Based on SEER data abstracted between 1988 and 2001, Miller et al. demonstrated that the use of PN progressively increased for all tumors less than 7 cm in size, and a patient diagnosed in 2001 was nearly five times more likely to undergo PN than those diagnosed in 1988 [93]. Follow-up studies capturing data through 2008 demonstrated a 49% increase in the PN as a proportion of all renal surgeries [94, 95]. By 2009, the number of patients who underwent a nephron-sparing procedure as treatment for SRM in United States eclipsed those who underwent radical nephrectomy [96]. Despite this, there is evidence that PN may remain underutilized in the management of surgically amenable RCTs [97]. While in high-volume tertiary-care centers, approximately 90% of pT1a lesions are treated with PN [98, 99], population-based studies suggest PN is likely utilized less frequently outside these centers [93, 100]. The reasons for the underutilization of PN are unknown, but a number of factors have been identified that appear to predict the likelihood of a patient receiving PN. Size has been clearly demonstrated to be associated with probability of receiving PN, with larger tumors treated less frequently with PN than smaller ones [93, 100]. This finding may be unsurprising given that size may serve as a surrogate for increased perceived technical difficulty in performing PN on the part of the surgeon. Along these lines, nephrometry score, a standardized scoring system developed to capture a tumor's complexity based on size, location, and endophytic or exophytic position, has also been found in single-institution studies to predict the likelihood of receiving PN [18, 101].

Older age has been found in multiple studies of both US and European populations to predict a decreased likelihood of undergoing PN [99, 100]. One speculative explanation for this age-bias toward RN is the result of surgeon preference, as RN is believed to carry fewer perioperative complications than PN. Another possible explanation is surgeon perception of a decreased benefit of preserved renal function in older patients.

However, given the age-dependent decrease in GFR, older patients may be the most likely to benefit from aggressive preservation of renal parenchyma and renal function [102, 103]. Female gender has also been demonstrated to be significantly associated with a decreased likelihood of receiving PN [99, 100]. One postulated explanation for this phenomenon includes physician underestimation of the risk of CKD in women due to lower preoperative serum creatinine values as a result of lesser muscle mass in females, rather than improved renal function. This phenomenon is especially troubling given that women are more likely to have a benign renal mass [104]. The presence of comorbidities has been shown to be associated with a decreased risk of being treated with PN [94]. Again, the reasons for this assumption are unknown, but one potential explanation is surgeon preference to perform the less-complex RN in patients in whom perioperative complications may be poorly tolerated. This logic, however, fails to appreciate that patients with multiple comorbidities, and preoperative intrinsic renal disease may be those at the highest risk for the potential morbidity and mortality that may result from post-RN renal dysfunction. As a result, patients with multiple comorbidities may be those who stand to benefit most from aggressive pursuit of a nephron-sparing approach. Several additional risk factors for being treated with a non-nephron-sparing approach have been identified, including rural hospital setting, nonacademic institution, and lower nephrectomy surgical volume [93, 94, 100]. Whether these trends are truly the result of underutilization of PN at low-volume centers or the tendency for low-volume centers to refer patients to higher-volume nephrectomy centers is unknown. Some have postulated that the increasing use of laparoscopy and specifically LRN has contributed to an underuse of PN. This hypothesis is based on the premise that PN, particularly LPN, is an inherently more complex procedure with higher rates of perioperative complications. Thus, surgeons faced with a choice between LRN and PN (open or lap) may be preferentially performing LRN, for which they have an increased level of experience and comfort. While evidence for this phenomenon has been observed in one population-based study, data supporting this conjecture remains limited [97, 105].

Candidate Selection

The absolute indications for PN, many of which have been recognized as early as the 1800s [24], include tumor in a solitary kidney, bilateral tumors, or patients with preexisting renal disease for whom RN would likely result in the need for hemodialysis. In addition, multifocal tumors, frequently associated with genetic syndromes, should also be strongly considered for excision by PN, given that these patients are at high risk for developing subsequent ipsilateral and contralateral tumors, requiring additional surgeries and further loss of renal parenchyma and function. Relative indications for PN include preexisting medicorenal disease or conditions that predispose to CKD such as hypertension, diabetes, or atherosclerotic vascular disease in whom RN would potentially lead to significant acceleration or worsening of kidney function. As mentioned previously, while there appears to be a tendency for surgeons to preferentially perform RN in more elderly patients or in patients with greater burdens of comorbidity, careful consideration should be taken in these instances because these patients may be at highest risk for postoperative CKD and its associated morbidity and mortality, particularly if their postoperative eGFR is anticipated to be <45 ml/min/1.73 m^2.

For patients without absolute indications, tumor stage is paramount when considering PN. At present, given the strong evidence for the oncologic efficacy, safety, and superior renal functional outcomes provided by PN for cT1 lesions, only the location of the tumor and complexity of the resection should be considered contraindications to the procedure. However, it must be remembered that PN is first and foremost a procedure performed for a suspected malignancy, and as such any procedure must be undertaken with the goal of complete excision of the tumor with a pathologically negative surgical margin. Surgeons should be familiar with anatomic

complexity scoring systems such as the RENAL score and should plan procedures with the aim of complete tumor resection as the primary goal, with preservation of functional parenchyma as secondary. While surgical excision is the mainstay in the treatment of any enhancing renal mass suspected to be malignant, the potentially indolent nature of a significant portion of SRMs must be appreciated. In elderly or significantly comorbid patients with competing mortality risks from other disease processes, AS may be an appropriate management alternative in this patient population, despite the poorly characterized natural history of enhancing renal masses at this time.

The oncologic efficacy and safety of PN in the treatment of clinical T2, T3, and locally advanced tumors remains largely unproven at this time. There is some limited data, however, to suggest that PN may be oncologically equivalent to RN in these larger tumors. Breau et al. compared the outcomes of 69 patients who underwent PN for pT2, pT3a, and pT3b spontaneous unilateral renal tumors with a matched cohort of 207 patients who had undergone RN [106]. They found no significant difference in recurrence, metastasis, or cancer-specific survival at a mean follow-up of 3.2 years. In a single-institution retrospective study of 213 patients undergoing nephrectomy for cT1 who were upstaged to pT2 disease or greater, PN demonstrated at least equivalent cancer control and overall survival outcomes when compared with RN, a finding that held when tumors were stratified stage for stage [107]. On multivariate analysis, the type of nephrectomy did not predict overall survival. A single-institution study of eight patients in whom PN was performed for tumors presumed preoperative to be cT1a, but who were ultimately pathologically upstaged to pT3b (renal vein involvement) demonstrated high rates of negative surgical margins and no recurrences at a median of 20 months [44]. It must be remembered that the aforementioned findings were in cohorts of patients who were cT1 and then subsequently upstaged intraoperatively or on final pathology. As a result, these results may not be generalizable to patients who present with >cT1 disease. While these promising oncologic findings suggest that PN may ultimately be proven to be a viable option for the treatment of renal masses >cT1, researchers have noted higher rates of complications in these larger masses, likely due to more difficult resection and more complicated reconstruction. As a result, the potential benefits of preserved parenchyma afforded by PN will ultimately have to be weighed against the technical difficulties and potential higher rates of complications associated with PN for larger renal masses.

Small Renal Masses and Partial Nephrectomy in Clinical Practice Guidelines

The American Urological Association (AUA) [108], American Society for Clinical Oncology (ASCO) [109], European Association of Urology (EAU) [110], and the National Comprehensive Cancer Network (NCCN) [111] all have published and widely available guidelines which provide recommendations and guidance in the management of renal tumors. The majority of recommendations provided across these multiple guidelines are congruent, with some notable, albeit subtle, differences. It should be noted that these guidelines are limited by a paucity of level 1 evidence in the field, particularly with regard to active surveillance and ablative treatment of masses. The retrospective design of most studies makes them subject to selection bias and heterogeneous practice patterns. All guidelines emphasize that management recommendations be based on a comprehensive evaluation of both disease (tumor size, location, multifocality) and host (age, comorbid status, baseline renal function, life expectancy) characteristics. Active surveillance is an option in the elderly and comorbid with small masses in all guidelines, despite no prospective comparative data evaluating its effectiveness versus active treatment. AUA guidelines are somewhat unique in specifying a particular size (<2 cm) in which active surveillance is a particular option for patients with both solid and cystic masses. All guidelines list PN as the preferred treatment of choice in patients in whom

intervention is indicated for a cT1a renal mass, in whom PN is technically feasible, and all guidelines recommend radical nephrectomy when partial is not feasible based on tumor characteristics (central location, complexity). AUA guidelines, however, go further in specifying that RN is preferred when tumor is complex AND no preexisting CKD AND postop eGFR expected to be >45 ml/min/1.73 m^2, perhaps reflecting the increasing appreciation that modestly decreased eGFR resultant from surgery may not be a significant risk factor for mortality or cardiovascular disease.

Conclusion

The widespread use of cross-sectional abdominal imaging means that significant numbers of patients in the United States and abroad are diagnosed with asymptomatic, early-stage renal cancers. At present, given the limitations in determining the biological identity and aggressiveness of a lesion preoperatively, as well as a paucity of data regarding the natural history of kidney tumors, surgery remains the reference standard for curative treatment of these lesions. While RN has traditionally been the procedure of choice for renal tumors, data has consistently demonstrated that PN provides oncologically equivalent control to RN, with comparative rates of complication when performed by experienced surgeons. There is a substantial body of evidence demonstrating that RN may put patients at an increased risk for CKD and its attendant morbidity when compared with PN. However, the single prospective study aimed at evaluating this question found no difference in overall survival between those receiving RN and PN, calling this paradigm into question. Closer evaluation of retrospective data suggests that the potential benefits may apply only to those with a significantly diminished postoperative eGFR. Despite this, PN has become increasingly recognized, in the United States and abroad, as the ideal strategy for the treatment of small RCTs, both maximizing oncologic control and minimizing morbidity and mortality.

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10 Objectifying Complexity of Kidney Cancers: Relationship of Tumor Anatomy and Outcomes

Serge Ginzburg, Alexander Kutikov, Robert G. Uzzo, and Stephen B. Schloss

Kidney cancer is an aggressive disease with incidence on the rise. In 2012, in the United States, 64,770 new kidney cancers were detected, and 13,570 patients died from this malignancy [1]. The highest rise in incidence is noted for localized tumors and is widely believed to be due to the ubiquitous utilization of cross-sectional imaging [2–4]. Management options for localized kidney cancer continue to evolve and move away from the former gold-standard, open radical nephrectomy [5, 6]. Open and minimally invasive nephron-sparing approaches are being applied as alternatives to complete renal unit removal and have been endorsed by the American Urologic Association and the European Association of Urology [7, 8]. Despite being on the rise at high volume tertiary care centers, diffusion of nephron-sparing approaches nationally remains limited [9]. While ablative techniques have gained significant clinical traction over the years, tumor resection in appropriate surgical candidates remains the gold standard [10]. Evidence demonstrating oncologic non-inferiority of nephron-sparing approaches relative to radical nephrectomy continues to accumulate. Thus, given a plethora of treatment options, clinical treatment decisions for a localized renal mass are increasingly complex [4, 11]. Despite the rise in incidence of small renal masses, resulting in a rise in interventions, the proportional impact on mortality has yet to be documented, suggesting that ideal target populations for intervention remain imperfectly defined [12, 13]. The incidence of benign tumors may range between 15% and 30% in the localized renal mass population, depending on size. Meanwhile, a majority of histologically malignant tumors are low grade and/or potentially destined for a more indolent course [14, 15]. Even patients with localized disease and high-grade pathology may exhibit a protracted clinical course [16]. In fact, active surveillance is beginning to emerge as a viable option for a select population with localized kidney cancer, recognizing issues of overtreatment and appreciating competing death risks [17].

With ablation, active surveillance, or a number of surgical approaches being available to the

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patient or the physician, appropriate patient selection is paramount. While the choice of which intervention to pursue is multifactorial, unfortunately these treatment decisions are rarely objectified by the physician [18, 19]. A patient's clinicodemographic characteristics and medical/surgical comorbid risks have an obvious impact on treatment choice; intangibles such as physician biases stemming from training, ability, and available technology may also affect critical clinical decision-making [18, 19]. Furthermore, anatomic attributes and tumor location play a critical role in the selection of treatment choice for patients with small renal masses. Yet, until recently, anatomic attributes of a renal tumor which reflect its surgical complexity, and thereby risk, have neither been quantified nor compared. This lack of a standardized objectification system has made published treatment outcomes difficult to interpret [20]. In recent years, a flurry of manuscripts describing and validating a common language to communicate renal tumor anatomy and location has emerged.

Basis of Anatomic Classification System Development

In the general surgery literature, the Couinaud classification, adopted by the hepatobiliary surgeons and radiologists, for decades has allowed for standardized reporting of the location of liver lesions and for a more meaningful comparison of surgical outcomes [21, 22]. The urologic literature is replete with large case series and multi-institutional studies, reporting surgery on renal masses of variable and often unreported anatomic complexity, yielding surgical outcomes that are difficult to interpret or compare.

Tumor size, location, and depth have classically been described as the anatomic features that play a role in surgical decision-making [23]. As such, these attributes largely form the basis for modern renal tumor anatomic classification strategies.

Tumor Size

It was recognized early that tumor size is an important prognosticator both of surgical and oncologic outcomes. While the early staging systems by Kadesky and Robson underappreciated tumor size as a prognostic factor, the TNM staging system was thought to be a major improvement [5, 24–27]. Not only did size correlate with oncologic prognosis, but it was also suggestive of the likelihood of complications and postoperative renal function [24, 28, 29]. Campbell et al. were able to correlate tumor size with the likelihood of postoperative urinary leak and acute renal failure [30]. Although tumor size may correlate with residual renal function, it has been shown that it is the preoperative renal function and the volume of the residual parenchyma that may have a higher impact on functional outcomes [31, 32].

Tumor Location

Tumor location is defined in relation to the renal topography and vascular system. Anterior versus posterior location may be important in preoperative planning when minimally invasive transperitoneal or retroperitoneoscopic approaches are being considered, as additional kidney mobilization may be required [33, 34]. Tumor polarity, upper versus middle (mesonephric) versus lower pole location, adds additional complexity as lesions at the tips of upper and lower poles may be easier to excise [35]. The "hilar" designation has been inconsistently defined and used in the literature, sometimes interchangeably with a description of a central location, and other times describing a spectrum of lesions, from those that abut the hilar vessels to lesions >5 mm from the hilum [36, 37]. Some authors have suggested that hilar location is the most influential factor in deciding between an open and minimally invasive approach for nephron-sparing surgery (NSS) [38].

Tumor Depth

Tumor depth is defined as the tumor's relation to structures such as renal sinus or collecting system as well as the relative degree of the exophytic component. Tumor depth relative to the renal capsule can determine the need for hilar clamping during a nephron-sparing surgery (NSS), impacts the complexity and feasibility of NSS, and has been correlated with surgical complications [35, 39]. The depth of a renal tumor can range from nearly completely exophytic to entirely intrarenal. Earlier literature inconsistently attempted to characterize lesions as central, peripheral, cortical, exophytic, endophytic, or mesophytic [35]. It is often difficult to localize and map to the surface of the kidney an entirely endophytic lesion, which may present significant barriers to using some minimally invasive surgical techniques.

Contemporary Classification Systems for Renal Masses

Lack of standardization in description and in means of comparison of renal lesions persisted until recently, when several scoring and classification systems emerged. The first such system, the RENAL nephrometry score (NS), was developed in 2008 by the team at the Fox Chase Cancer Center [23, 40]. The proposed objective scoring system was designed to standardize reporting and facilitate decision-making in a simple, reproducible manner. It is based on the five most surgically relevant, commonly available, and radiographically measurable anatomic features of renal masses. It requires only the availability of cross-sectional imaging. In developing the system, the investigators hoped to design not only a reproducible but also a simple means of objectifying salient anatomic attributes of renal tumors. The components that follow the acronym RENAL include *(R)adius – size (albeit measured by tumor's maximum diameter), (E) endophytic/exophytic characteristics, (N)earness to the collecting system or renal sinus, and (L)ocation relative to the polar lines, with each component scored on a 1–3 point scale. Qualitative descriptors correspond to the designator (A) and include (a)nterior, (p)osterior, or (x) indeterminable location descriptor with relationship to the renal axis* (Fig. 10.1). *An additional suffix (h) captures hilar location of tumors and is reserved for tumors that abut the main artery or vein*, thereby potentially making hilar dissection more complex. Following the TNM staging size cutoffs, tumor size (R) is given one point for lesions <4 cm, two points for tumors 4–7 cm, and three points for masses >7 cm. The exophycity attribute (E) is assigned one point if the tumor is >50% exophytic, two points for those tumors with >50% of their diameter surrounded by normal renal parenchyma, and three points for entirely endophytic masses. The nearness (N) descriptor of the RENAL nephrometry score designates proximity of the mass to the sinus or the collecting system. (N) is assigned one point if the closest portion of the mass is >7 mm from the renal sinus or the collecting system, two points if 4–7 mm, and three points if <4 mm. Albeit the 4 and 7 mm cutoff distances are arbitrary, the values were chosen for simplicity to parallel the values in the R component of the score. Polar lines have been developed to define three relative zones – the upper pole, the interpolar region, and the lower pole – each separated by a polar line. Each renal unit has two polar lines which border the interpolar region. Polar lines are defined by the axial cuts on cross-sectional imaging as the transition where the concentric rim of parenchyma is interrupted by the renal sinus/vessels (Fig. 10.1). Polar (L)ocation score assignments relate the tumor's position relative to the polar lines. Several authors have criticized the RENAL NS for necessitating coronal reconstructions [20, 41]; however, while polar assignment can be made on coronal imaging, it is *best to do so on the axial images* as the mass is often out of plane with the polar line on coronal views. As such,

	1 pt	2 pts	3 pts
(R)adius (maximal diameter in cm)	≤4	>4 but <7	≥7
(E)xophytic/endophytic properties	≥ 50%	<50%	Entirely endophytic
(N)earness of the tumor to the collecting system or sinus (mm)	≥7	>4 but <7	≤4
(A)nterior/Posterior	No points given. Mass assigned a descriptor of a, p, or x		
(L)ocation relative to the polar lines* * suffix "h" assigned if the tumor touches the main renal artery or vein	Entirely above the upper or below the lower polar line	Lesion crosses polar line	>50% of mass is across polar line (a) or mass crosses the axial renal midline (b) or mass is entirely between the polar lines (c)

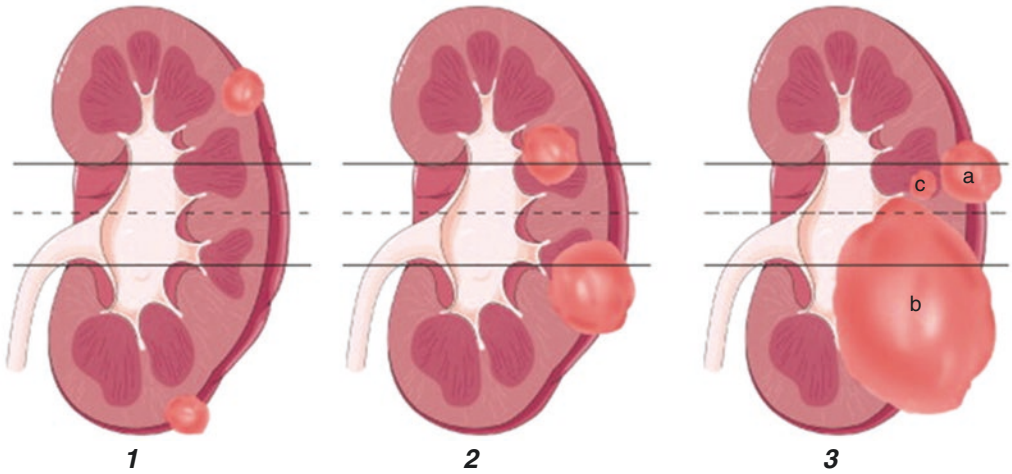


Fig. 10.1 RENAL nephrometry score with scoring of (L) ocation component. Polar lines (*solid lines*) and axial renal midline (*broken line*) are depicted on each sagittal view of kidney. Numbers 1–3 represent points attributed to each category of tumor [23]

lesions that are entirely above or below a given polar line are assigned one point. Two points are given if <50% of a tumor crosses into the interpolar region. Tumors with >50% of volume crossing the polar line or large tumors that cross the renal interpolar axis are assigned three points (Fig. 10.1). The interpolar axis is the plane halfway between the polar lines.

The nephrometry sum is the combination of individual RENAL nephrometry components and may be used for broad comparisons, with sums between 4 and 6 (inclusive) considered as low complexity, 7–9 as moderate, and greater than 9 as high complexity renal masses (Fig. 10.2). Qualitative descriptors *a*, *p*, *x*, and *h* provide additional information. Nevertheless, reporting of the nephrometry sum alone without individual components is of less value, since masses with different individual nephrometry components may vary significantly in complexity but are associated with the same nephrometry sum. The RENAL NS system has been opera-

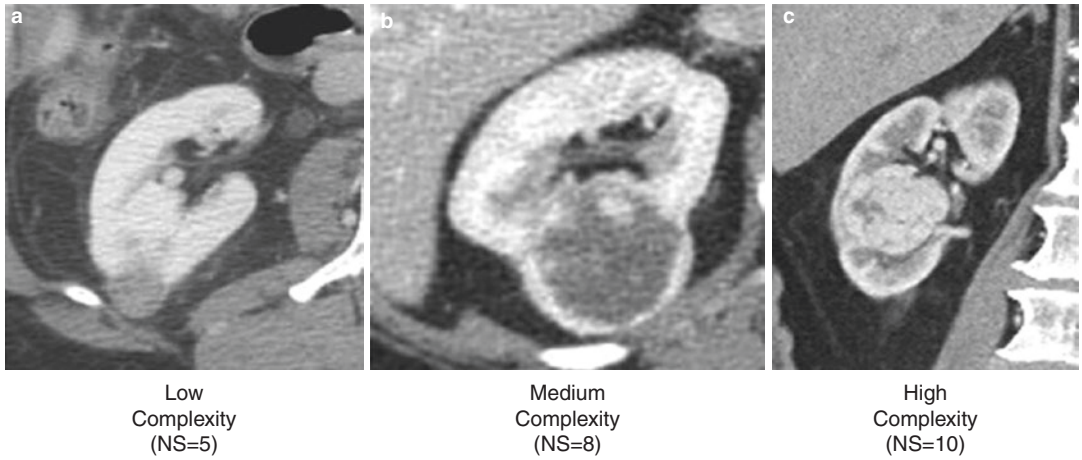


Fig. 10.2 Examples of tumor complexity based on RENAL nephrometry score [23]. (**a**) Low complexity mass, treated with robotic-assisted partial nephrectomy; (**b**) medium complexity mass, treated with robotic-assisted partial nephrectomy; (**c**) high complexity mass, treated with open partial nephrectomy

tionalized and can be accessed via a web-based tool at www.nephrometry.com [42].

Another classification system, developed after the RENAL NS, was the preoperative aspects and dimensions used for an anatomical (PADUA) classification of renal tumors. PADUA is very similar to nephrometry, although in its initial report, the stated intention was to predict overall perioperative complication risk of open nephron sparing surgery [41]. This system assigned a score based on the following anatomic characteristics: longitudinal location (polarity), rim location (lateral vs. medial), relations to renal sinus and collecting system, percentage of tumor that is endophytic, and maximum diameter. Similar to the RENAL NS, anterior/posterior qualifier was used. Points were assigned for each characteristic. One point is given for upper/lower and two for interpolar location. Depth is scored by assigning one point if tumor is >50% exophytic, two if <50%, and three if entirely endophytic. Lateral tumor location incurred one point, whereas medial location was given two points. Involvement of the renal sinus and urinary collecting system were assigned two points each, whereas one point was given to each if invasion was absent. Tumor size was scored similar to the RENAL NS system. Complexity was categorized into low, moderate, and high, corresponding to PADUA scores of 6–7, 8–9, and >10, respectively. The major differences between the PADUA classification and the RENAL NS include the radiologic, definition of renal sinus and polar locations, as well as the PADUA's more detailed assessment of tumor involvement with the sinus and the collecting system, possibly at the expense of ease of use and reproducibility. The focus of PADUA's classification on collecting system invasion may warrant merit, as the prognostic value of collecting system invasion has been documented before [43]. RENAL NS and PADUA are compared in Table 10.1 [44].

A third classification system, known as the Centrality (C) Index, also emerged recently, focusing on tumor location relative to renal central sinus [45]. Using the Pythagorean theorem, the distance between the tumor center and the renal sinus center is calculated and divided *by* the tumor radius, yielding a C-Index value. C-Index of 0 corresponds to a tumor concentric with the renal center, and C-Index of 1 corresponds to a tumor which abuts the renal center (Fig. 10.3). This system was initially reported in the context of a laparoscopic NSS cohort, focusing on its ability to predict intraoperative outcomes and perioperative complications.

Table 10.1 RENAL nephrometry and PADUA classification scoring systems

	1 pt	2 pts	3 pts
RENAL nephrometry score [23]			
(R)adius (maximal diameter in cm)	≤4	>4 but <7	≥7
(E)xophytic/endophytic properties	≥50%	<50%	Entirely endophytic
(N)earness of the tumor to the collecting system or sinus (mm)	≥7	>4 but <7	≤4
(A)nterior/posterior[a]	No points given. Mass assigned a descriptor of a, p, or x		
(L)ocation relative to the polar lines[b]	Entirely above the upper or below the lower pole line	Lesion crosses polar line	>50% of mass is across polar line or mass crosses the axial renal midline or mass is entirely between the polar lines
Preoperative aspects and dimensions used for an anatomic (PADUA) classification [41]			
Longitudinal (polar) location	Superior/inferior	Middle	–
Exophytic rate	≥50%	<50%	Endophytic
Renal rim	Lateral	Medial	–
Renal sinus	Not involved	Involved	–
Urinary collecting system	Not involved	Dislocated/ infiltrated	–
Tumor size (cm)	≤4	>4 but ≤7	>7

Adapted from [44]

[a]Anterior or posterior face can be indicated with a letter ("a" or "p") following the score

[b]Suffix "h" assigned if the tumor touches the main renal artery or vein

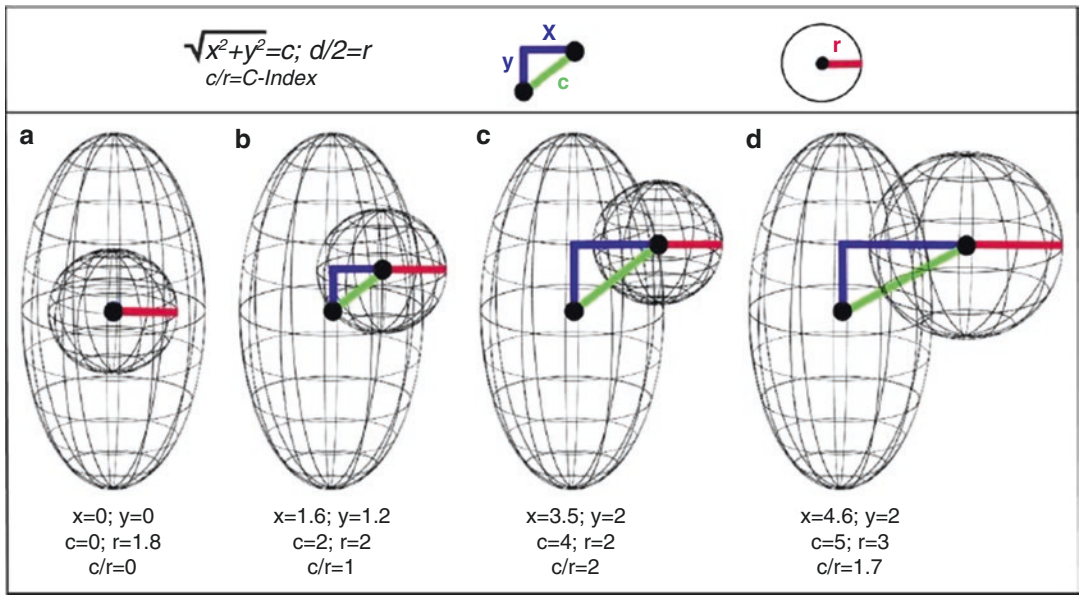


Fig. 10.3 (**a**–**d**), in C-Index model *c* (*green lines*) is hypotenuse of triangle formed by sides *x* and *y* (*blue lines*). C-Index is calculated by dividing *c* by *r* (*red lines*) [45]

Validation of Current Classification Systems

The clinical applications of these anatomic classification systems depend on their validity, reliability, and reproducibility. In recent years, multiple publications have focused on external validation of the existing classification systems. Interobserver reliability, a necessary characteristic of any robust classification system, has been assessed in numerous studies and demonstrated excellence for all three classification systems after a relatively short learning curve [46–49]. Inter-reviewer agreement has been demonstrated to be high for RENAL NS across a spectrum of training levels and specialties; however, scoring of large tumors may be less reproducible [50]. Kolla et al. found the RENAL NS to have substantial to almost perfect interobserver reliability for all components, with the (L)ocation component being least reliable with a 54% frequency of concordance (Kappa 0.73) [47]. This phenomenon is somewhat surprising as appropriate scoring of the L component is objective and requires identification of the polar line (the axial cut where the parenchyma opens) and quantification of the number of cuts on which the tumor appears above and below this polar line. Validation of the PADUA system has also been described, with some reporting that it is the involvement of and the proximity to the urinary system that were more difficult to reproduce [46, 51].

Surrogate metrics to assess tumor complexity, such as perioperative outcomes and complications, are often used in these analyses. Despite the controversy on the importance of warm ischemia time, it continues to be used as an indirect metric of anatomic tumor complexity [32, 52]. Early in 2009, Lifshitz et al. published a nomogram to predict warm ischemia time of >30 min, based on tumor size, location (central vs. peripheral), and patient's BMI [39]. Later, in a multivariable analysis, RENAL NS >9 and PADUA >10 were shown to be independent predictors of relative total ischemia time and perioperative complications, with RENAL NS predicting the need for any ischemia [46, 51]. Ficarra et al. demonstrated the ability of the PADUA to predict longer warm ischemia time and overall complication rates in a robotic-assisted nephron-sparing surgical cohort, even when controlling for tumor size, and others have shown similar results using the RENAL NS and C-Index [53–55]. Samplaski et al. correlated C-Index with short-term postoperative renal function, estimated by GER via MDRD formula, demonstrating >30% decrease in GFR for lesions with C-Index of 2.5 or less [55].

Application of Standardized Classifications

Since their inception, the classification systems have been actively applied for standardized comparisons, prognostication of perioperative outcomes, surgical complications, and beyond [18, 53, 54, 56–58]. For example, according to a large multi-institutional series, without stratification, a patient undergoing a minimally invasive partial nephrectomy may be informed of a 19% risk of incurring a complication [59]. When stratified by RENAL NS, patient counseling, including major, minor, overall, and organ-specific complications, can be individualized [57]. RENAL NS has been shown to risk-stratify for specific urologic complications, such as a urine leak, which in itself can be as high as 20% for complex lesions [57, 60, 61].

Studies suggest that RENAL NS also has predictive value with respect to long-term survival, metastatic potential, and cancer-specific survival, independent of tumor size [50]. Additionally, based on a large retrospective cohort, Kutikov et al. developed a nomogram to establish a relation between RENAL NS and tumor pathology, benign versus malignant, histology, and grade (high vs. low) [56]. This concept was further confirmed and externally validated in Australian and Chinese cohorts [62, 63]. Nephrometry scores were correlated with surgical treatment preferences, where higher complexity tumors were preferentially addressed via radical nephrectomy or open approaches [18, 64].

Limitations of Current Classification Systems

Current classification systems are not without limitations. As described, none account for multifocality of renal masses which can dramatically alter treatment decisions. Also, the complexity of renal vasculature with respect to the tumor is not reflected. While anterior and posterior location qualifiers in the RENAL NS and PADUA scoring systems are used, currently no score is assigned to this descriptor, yet anterior (a) versus posterior (p) locations can potentially affect or complicate treatment choices. For example, posterior lesions may require near-complete mobilization of the kidney with additional dissection of adjacent organs, including the liver, adrenal gland, spleen, or pancreas. For larger tumors, anatomy may be distorted, making it difficult to estimate individual E and N components of the RENAL NS [50].

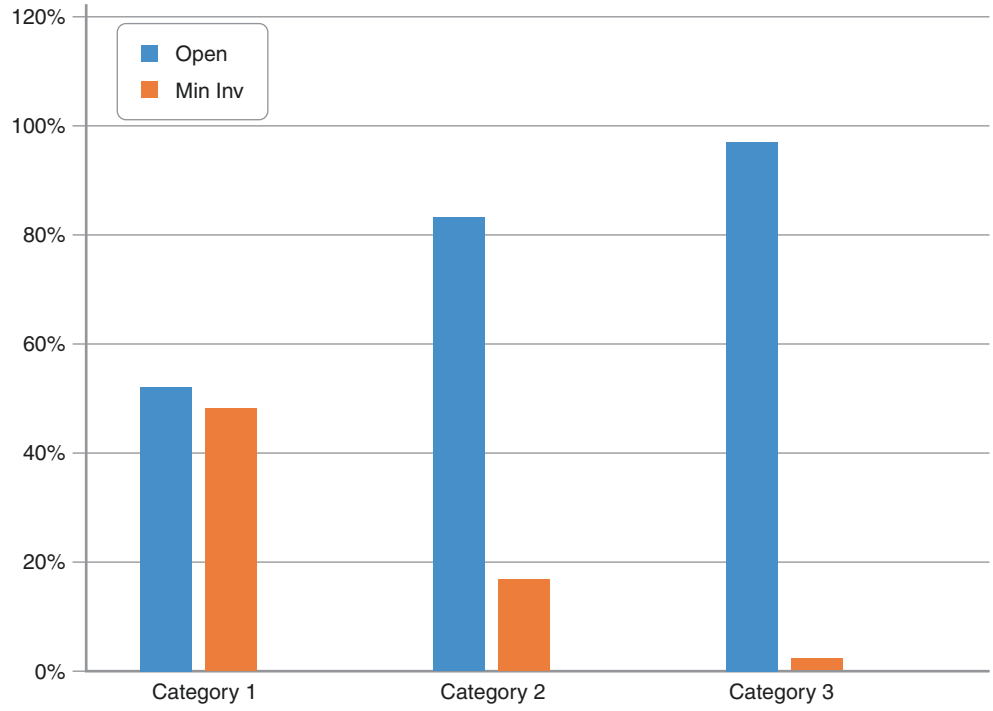
The Role of Nephrometry Score in Partial Nephrectomy: Lahey Experience

As has been pointed out earlier in this chapter, there are a multitude of treatment options available for the management of localized renal tumors. Clinical treatment decisions are increasingly complex and multifactorial. The complexity of the lesion, the preoperative renal function, and the general medical condition of the patient are but to name a few. The proportional impact on mortality and renal function has not been completely elucidated, suggesting that the ideal procedure for various lesions and their clinical settings is not clearly defined. As we have come to appreciate the choice for intervention is multifactorial and the treatment decisions are rarely objectified by physicians who are biased by their surgical skill set. One can imagine that a patient who has a complex lesion, with a high nephrometry score, and marginal renal function might have a radical nephrectomy rather than a partial nephrectomy because of the surgeon's skill set or lack thereof. Clearly, the nephrometry score can help objectify this decision-making process, knowing that 60% of radical nephrectomy specimens have evidence of histologic medical renal disease in addition to the renal tumor for which the kidney was removed (Chap. 24).

With this in mind, we reviewed a large series of patients who underwent partial nephrectomy at the Lahey Clinic Medical Center [65]. It was our aim to evaluate the role of nephrometry scores in directing the surgical approach for partial nephrectomy open versus minimally invasive. Nephrometry scores and the surgical approaches' impact on the ultimate postoperative renal function (see Chap. 24) formed the basis for this analysis of unpublished data and the type of partial nephrectomy chosen, open versus minimally invasive.

A retrospective analysis of perioperative outcomes was performed on a prospectively collected database of 838 patients who underwent laparoscopic, robotic, or open partial nephrectomy from 2003 to 2012 at a single institution. Various preoperative, intraoperative, and postoperative characteristics and outcomes were compared between the OPN and MIPN groups. These characteristics and outcomes included preoperative Charlson comorbidity indices and postoperative complications as categorized by the Clavien–Dindo classification of surgical complications. The nephrometry scoring system was used to stratify patients into low (4–6), moderate (7–9), and high (10–12) tumor complexity groups (Fig. 10.4).

Five-hundred patients were included for the analysis; 376 (75%) underwent OPN and 124 (25%) underwent MIPN, which included laparoscopic and robotic techniques. Moreover, 153 patients (52% OPN) were stratified in the low tumor complexity group, 275 patients (83% OPN) in the moderately complex group, and 68 patients (97% OPN) in the highly complex group. An overall comparison showed no difference in age, gender, BMI, tumor stage, margin positivity, recurrence, or death. There was a statistically significant difference in OPN cases with higher preoperative Charlson comorbidity scores (2.0 vs. 1.2) and larger tumor size (3.5 vs.



Nephrometry score	(4,5,6)	(7,8,9)	(10,11,12)
N=	153 pts	275 pts	68 pts

Fig. 10.4 Surgical approach by nephrometry score

2.5 cm) than MIPN cases. Overall and in every nephrometry complexity subgroup, the MIPN cohort had significantly less blood loss (211 vs. 696 cc), shorter lengths of hospital stay (3.2 vs. 5.6 days), and fewer Clavien I complications (17% vs. 37%). Incidences of Clavien II–V complications and blood transfusion requirement did not differ between OPN and MIPN in any of the tumor complexity strata. The open cohort had shorter operative times (216 vs. 247 min) and used the non-clamping technique, which accounts for the greater blood loss and better preservation of renal function. Statistical analysis was not performed in the high tumor complexity strata due to limited number of cases by MIPN.

Our observations based on nephrometry score demonstrated that minimally invasive partial nephrectomy shows similar perioperative outcomes with the advantage of decreased blood loss, shorter length of hospital stay, and fewer minor complications in patients with smaller and less complex tumors. Among patients with higher complexity lesions and multiple comorbidities, there was a propensity to use the open approach, indicating the recognized advantage of the open, non-clamping, nonischemic approach in more complex, azotemic patients with larger tumors and increased incidence of medical comorbidities [65].

Conclusion

Standardized anatomic classification of renal lesions offers the potential to objectify clinical decision-making by quantifying previously qualitative variables that influence clinical treatments of patients with localized renal tumors. Using these systems may help standardize patient selection, individualize risk, and objectify quality of care outcomes.

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History of Renal Surgery for Cancer

11

Brendan M. Browne and Karim Joseph Hamawy

The understanding of renal anatomy and physiology goes back to antiquity, based on observations by individuals including Hippocrates (460 BCE–373 BCE), Aristotle (384 BCE–322 BCE), and Galen (130 CE–210 CE), and further progress by Vesalius (1514–1564) (Fig. 11.1). The current understanding of renal function with solute transfer and collecting ducts was first described by Lorenzo Bellini (1643–1704). Despite careful depiction of renal form and function, surgical procedures on the kidney were long avoided. Early procedures on the urinary system dealt primarily with lower tract urolithiasis, and lithotomy for bladder stones is described as far back as ancient Egypt and Mesopotamia. Conversely, surgery for stones in the upper tracts was advised against, and the first recorded operation did not occur until 1550 when Cardan of Milan opened a lumbar abscess and removed renal stones. While stone disease and its surgical management has been documented for centuries, renal surgery for cancer was not performed until the modern era.

Following the development of anesthesia in the 1840s and antiseptic technique by Lister in 1876, the capacity for abdominal surgery greatly expanded. The first reported nephrectomy occurred in Milwaukee in 1861 when Wolcott accidentally removed a kidney during an operation for liver cysts. Similar accidental nephrectomies occurred in the subsequent years, reported by Otto Spielgelberg in 1867 and Wells and Peaslee in 1868. All of these patients died either during or shortly following the operation, but from causes other than renal failure. Previous experiments in the eighteenth century had shown that dogs could survive with a single kidney, but this fact had not been replicated in humans. These "successful"

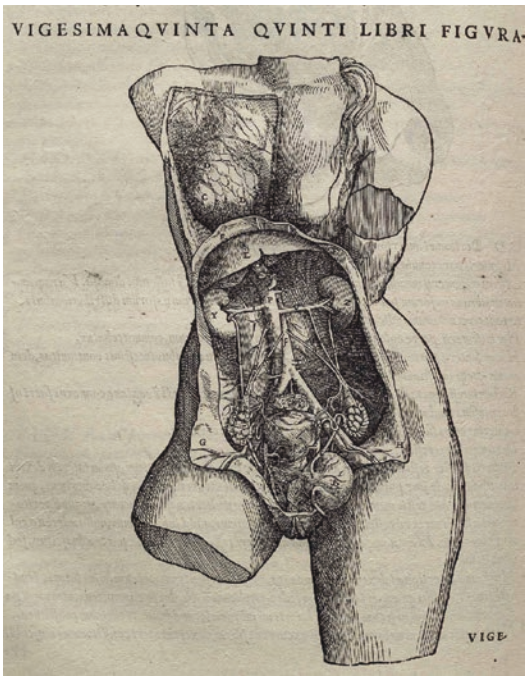

Fig. 11.1 Retroperitoneal anatomy, Andreas Vesalius, 1543. (Source: Andreas Vesalius' De humani corporis fabrica (1543), page 378)

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Fig. 11.2 Gustav Simon (1824–1876), German surgeon who performed the first planned nephrectomy in 1869. (Source: Garrison [38])

accidental nephrectomies opened the possibility of planned nephrectomy for a variety of known renal pathologies. In 1868, William Hingston attempted a planned nephrectomy in Hotel Dieu in Montreal, but the patient expired on the operating table following removal of the kidney [1].

Shortly thereafter, Gustav Simon (1824–1876) (Fig. 11.2), a professor of surgery at Heidelberg, undertook the first successful planned nephrectomy on August 2, 1869. His patient was a woman who developed a ureterovaginal fistula following ureteral injury during hysterectomy and oophorectomy for ovarian cyst. After practicing the operation on 30 dogs and multiple cadavers, Simon performed the operation through a lumbar incision. The patient survived the operation, and, despite a postoperative wound infection and pneumonia, she was discharged home 1 month postoperatively [2].

The success of this operation opened the door for nephrectomy as a viable treatment option for an array of renal pathologies including recurrent pyelonephritis, stones, and tuberculosis. The second successful, planned nephrectomy, and first in the United States, was performed by Gilmore in Mobile, Alabama, in 1870, undertaken for persistent pyelonephritis in a woman who was 5 months pregnant [3]. The first planned nephrectomy for renal malignancy was performed by Carl Joahn Langenbuch (1846–1901) in 1877 in Berlin [4].

Utilization quickly expanded across Europe and the United States. In the 15 years after Simon first performed the procedure, 233 nephrectomies were reported, of which 49 were for malignant growths [5]. The smaller fraction of operations for malignancy likely results from the limitations of diagnosis, which relied almost entirely on symptoms and physical examination, at which point renal malignancies have higher chance of tumor invading adjacent structures, thus increasing the difficulty of excision.

While anesthesia and antiseptic surgery were instrumental for safe and successful surgery, the improvement of diagnostic capacity further expanded the potential of surgery for renal malignancies. In 1895, Wilhelm Röntgen produced the first X-ray, which revolutionized medicine. By the early 1900s, this technology was rapidly integrated into diagnosis and operative planning. The first retrograde pyelogram was captured by Voelcker and von Lichtenberg on accident in 1905, and then purposefully in 1906 [6]. Intravenous pyelography followed in 1923, reported by Rowntree from the Mayo Clinic [7]. Arteriography [8] and retroperitoneal air insufflation [9] were two additional techniques for evaluation of renal symptoms, used to differentiate malignant from benign renal lesions [10]. The ability to diagnose renal tumors earlier with imaging allowed surgeons to undertake nephrectomy earlier, before significant local invasion.

The Golden Era of Radical Nephrectomy

After nephrectomy was proven to be technically feasible – and more importantly, survivable – the next step was to perfect the procedure. Emil Kocher (1841–1917) performed the first transperitoneal nephrectomy in 1878 [11], and Atle Berg utilized a lateral midline incision in 1913. The approach via a lumbar incision as used by Simon gathered support as it reported better survival, with perioperative mortality 37% ($N = 111$) via lumbar

approach compared with 51% (N = 120) for abdominal approach [5]. The high rate of perioperative mortality reflected the dangers of early surgery where operative speed was prized as antisepsis and anesthesia were still in their infancy. Complications included tears in the inferior vena cava and hemodynamic collapse after clamping the renal vein, likely reflecting embolization of an unrecognized tumor thrombus.

Not until 1949 did Chute describe the thoracoabdominal approach for nephrectomy [12]. This exposure provides excellent exposure to the renal hilum as well as adjacent structures with the potential for tumor invasion. Shortly thereafter, Vernon Dick from Lahey Clinic reported a series of 280 nephrectomies using this technique over a period of 20 years.

Drawing from the techniques of wide excision shown to be effective with Halstead's radical mastectomy procedure, Stevens first suggested the resection to all perirenal fat and fascia as well as local lymph nodes [13], but the precise surgical technique was not described until Foley in the 1950s [14]. Additionally, isolated metastases identified during nephrectomy or other surgeries were successfully removed. Extension of a renal neoplasm into the inferior vena cava was frequently seen in the early years of nephrectomy due to late-stage presentation. Ligation of the IVC was reported back as far as the 1920s in cases of significant obstruction of venous flow or in the case of accidental injury. Intentional opening of the vena cava for removal of the malignant thrombus was first reported in 1932 [15].

With the increasing sophistication and experience with the procedure, the survival rates steadily rose. Nearly 100 years after Simon performed the first nephrectomy, Robson reported overall survival of 61% at 3 years and 49% at 10 years, a significant improvement over earlier series [16]. One primary limiting factor for survival remained stage at diagnosis, as evidenced by the fact that in this series only 38% were organ-confined tumors and 45% had vascular or metastatic spread. Nevertheless, radical nephrectomy utilization continued to expand and readily became the gold standard for treatment of renal cancer.

History of Histology

Kidney specimens from autopsy and anatomical dissection established the histologic basis for renal cancers. Reports of renal malignancy date as far back as the seventeenth century, but were often contested. The first consensus diagnosis of renal carcinoma was reported by Miriel in 1810 [17]. Although the histologic characteristics were agreed upon, a long-standing debate arose over the cellular origin of these tumors. In the mid-nineteenth century, French pathologist Robin proposed that solid renal tumors originated from renal tubular cells [18]. However, 20 years later, Grawitz described subcapsular tumors appearing similar to adrenal tissue and thus proposed an adrenal origin for renal tumors [19]. The adrenal etiology gained significant support, which led to renal tumors being termed "hypernephromas" for decades. However, there were many who disagreed with this theory, most preeminent being Hugh Hampton Young, who argued for the abandonment of this term [20]. The controversy persisted until 1960 when ultrastructural features of renal tumors gave convincing evidence of a renal tubule origin [21].

Koenig put forward the first classification system using macroscopic morphology in 1826 [22], and in the following decades, multiple classification systems were proposed for renal tumors, some of which were too rudimentary and others were overly intricate. Deming and Harvard developed a comprehensive classification system based on all-known cellular subtypes, but this included 11 categories and nearly 70 subtypes, making it too cumbersome for clinical use. In 1980, Glenn simplified the classification system renal tumors to seven categories including benign lesions, tumors of renal pelvis, pararenal tumors, embryonic tumors, nephrocarcinoma, and other malignancies. It was not until 1997 with the Heidelberg–Rochester Consensus Classifications that concise and agreed-upon system emerged [23, 24]. This system served as the basis for the histologic and genetic classifications including clear cell carcinoma, papillary carcinoma, oncocytoma, and others upon which the current WHO classification system was built [25].

Rise of Partial Nephrectomy

> Few procedures provide the urologist with more satisfaction than those that preserve renal function
> Abeshouse, 1950

The desire to preserve renal parenchyma existed even as the technical feasibility of radical nephrectomy was being established. The year after performing the first nephrectomy, Gustav Simon performed the first partial nephrectomy for hydronephrosis [2]. Later, Wells reported an accidental partial nephrectomy when resecting a perirenal fibrolipoma [26]. German surgeon Vincenz Czerny (1842–1916) performed the first partial nephrectomy for cancer in 1887 [27] to treat an angiosarcoma (Fig. 11.3).

The early experience with partial nephrectomy had very poor outcomes due to immediate or delayed hemorrhage or urine leak, and many patients died due to sepsis, uremia, and shock. Patient selection and tumor characteristics were not always heavily weighed against the quest to maintain maximum renal parenchyma.

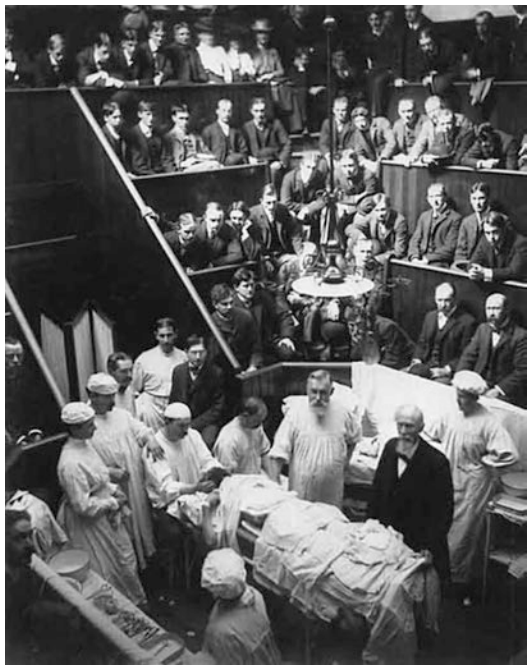

Fig. 11.3 Vincenz Czerny at surgery. (Source: http://www.uni-heidelberg.de/presse/ruca/ruca04-02/gelehrt.html)

Furthermore, patient survival after nephrectomy had confirmed the idea that humans can live with a solitary kidney. Consequently, partial nephrectomy remained a novelty with clear preference for radical nephrectomy.

The goal of maximal oncological control logically pointed to radical nephrectomy as superior. However, as early as 1938, Bell reported the different metastasis patterns of clear cell renal cell carcinoma, noting that tumors less than 3 cm in diameter rarely metastasize [28]. Further pathologic studies showed a well-defined capsule around renal cell carcinomas, a principle that was embraced by Vincent Vermooten (1897–1969) who advocated for partial nephrectomy in small renal tumors [29]. The concept still did not gain rapid acceptance by urologists, and partial nephrectomy was reserved for patients with a renal mass for whom radical nephrectomy would render them anatomically or functionally anephric. To that point, Zinman and Dowd published a series of partial nephrectomies in patients with solitary kidneys, but they still strongly advised for radical nephrectomy with excision of the adipose capsule and perihilar lymphatics in the setting of a normal contralateral kidney [30].

In the later part of the twentieth century, the experience with partial nephrectomy steadily expanded, with several centers publishing large case series. Most of these procedures were done with the kidney in situ, but other surgeons drew on the experience of renal transplant and would remove the kidney, resect the tumor on the back bench, and then reimplant into the native fossa. Also drawing on renal transplant experience, the principle of renal ischemia was included with clamping the renal artery to achieve a bloodless field. Rossi first studied human kidneys during ischemia, noting proximal tubule degradation at 20–30 minutes of warm ischemia, which still serves as a benchmark in contemporary practice. The addition of surface cooling during renal artery clamping facilitated longer, more complicated resection and reconstruction without exacerbating kidney injury. With these technical advances, the 1970s and 1980s was the pivotal era when large centers began recommending

partial nephrectomy for patients with a normal, contralateral kidney [31, 32].

One of the major advances in the technique for partial nephrectomy was the introduction of the concept of the non-clamping, nonischemic, partial nephrectomy – a procedure originated and developed by Libertino. He demonstrated, in the solitary kidney model, that avoiding ischemic injury (non-clamping) to the kidney protected and provided the best long-term renal functional outcome possible (see Chap. 12).

Despite improved experience and techniques, the urologic community harbored concerns regarding the oncologic success of partial nephrectomy compared with radical nephrectomy. Vermooten identified the encapsulation of renal tumors and promoted the oncologic safety of partial nephrectomy in patients with renal insufficiency. Critics cited microscopic invasion of the tumor capsule that could compromise oncologic outcomes, but Vermooten's pathologic specimens showed no such microscopic capsular penetration in small renal tumors, and his patients did not experience local recurrence [29]. Further concerns are developed after a publication by Mukamel et al., who reported occult multifocal renal tumors in 20% of nephrectomy specimens, most of which had primary tumors less than 5 cm diameter [33]. This finding raised the specter of retained tumors in the spared kidney parenchyma, but reassurance came in the form of clinical outcomes. In 1993, Licht and Novick reported only 2 recurrences and 95% disease-specific survival in a meta-analysis of 241 partial nephrectomies with an average 3 years of follow-up [34]. Two larger studies with 10-year follow-up reinforced the safety and efficacy of partial nephrectomy for renal masses less than 4 cm, with Herr reporting 97% disease-free survival and 93% overall survival [31] and Fergany reporting 100% cancer-specific survival [32]. The debate regarding appropriate tumor size cut off for partial nephrectomy and tumor enucleation versus wider margins was discussed as early as Vermooten and continues into contemporary practice. But regardless of subtle differences in technique, partial nephrectomy has been firmly established as a safe and effective tool for urologic surgeons.

Modern Renal Surgery

The first laparoscopy was performed in 1910 by Hans Christian Jacobaeus of Sweden, but this technique did not find its way into the field of renal surgery until 1990 when Ralph Clayman performed the first laparoscopic nephrectomy at Washington University in St. Louis [35]. The following few years saw adoption of laparoscopic or retroperitoneoscopic approach for nephroureterectomy and partial nephrectomy. The laparoscopic approach reduced hospital stay, blood loss, and narcotic requirement compared with open renal surgery, but critics cited concerns about longer operative time and questionable oncologic equivalence. Ultimately follow-up data showed equivalent disease-free survival compared to open approach [36], leading to increased adoption. This scenario is demonstrated by the review from Johns Hopkins showing that 9% of renal cancers were removed laparoscopically in 1994 and up to 55% in 2000, only a decade after the first laparoscopic nephrectomy [37].

With the introduction of the robotic surgical system in 2004, robot-assisted laparoscopic renal surgery has steadily been adopted, utilizing the increased degrees of freedom to improve renorrhaphy and ease the learning curve for laparoscopic renal surgery. Further pushing the limits of laparoscopic surgery, work has been done on natural orifice transluminal endoscopic surgery (NOTES) and laparoendoscopic single-site surgery (LESS), which will surely continue to evolve as instruments and other technologies advance.

In addition to newly developed surgical platforms for minimally invasive renal surgery, other technologies have advanced that assist with renal surgery. Ever improving quality of preoperative CT or MRI facilitates surgical planning with fine visualization of renal vasculature as well as number and size of lesions. Intraoperative ultrasound probes can be deployed laparoscopically to delineate completely endophytic tumors. A variety of hemostatic agents have been developed to reduce the risk of postoperative hemorrhage. Additionally,

fluorescence imaging can confirm tumor ischemia when performing polar artery clamping, to name a few new technologies.

While much has changed since Gustav Simon's first successful nephrectomy nearly 150 years ago, renal surgery continues to push for optimal oncologic control and maximal preservation of renal function. The courageous surgeons and patients of the bygone era overcame many obstacles and used innovation and careful consideration of their outcomes to chart the path to our current techniques. The duty remains for all urologic surgeons to continue to improve upon our current gold standards and enhance the care for this lethal disease.

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12 The Surgical Approaches to Renal Masses and Their Impact on Postoperative Renal Function

John A. Libertino and Robert Hamburger

Introduction

The data in the literature are confusing and conflicted as to the role of various surgical maneuvers and their impact on postoperative renal function. The aim of this chapter is to review the current literature and to present my own personal experience, regarding the role of warm ischemia and the volume of renal parenchyma preserved on the ultimate postoperative renal functional outcome following partial nephrectomy (PN).

Nephrectomy Versus Partial Nephrectomy: The Rationale for Partial Nephrectomy and Preservation of Renal Function

It is estimated that approximately 30 million Americans are living with chronic kidney disease (CKD) [1]. In addition, the increased incidence of obesity, heart disease, hypertension, and diabetes puts millions more Americans at risk for developing chronic kidney disease. It is also estimated that 30% of patients diagnosed with a renal mass already have chronic kidney disease (CKD). Chronic kidney disease (CKD) also develops in many patients who undergo a radical nephrectomy (RN) [2, 3]. Although radical nephrectomy for kidney cancer cures one disease (kidney cancer), it can often cause another disease chronic kidney disease (CKD) that may be just as ominous. This notion is underscored by the fact that the average 60-year-old patient is expected to live another 21 years, as opposed to a 60-year-old patient on dialysis who has an average life expectancy of 4.6 years [1]. In addition to requiring renal replacement therapy, many patients with moderate to severe chronic kidney disease have an increased incidence of cardiovascular events [4]. Patients with GFR less than 45 are 11 times more likely to experience a major cardiovascular event than those with normal renal function [4]. Therefore, radical nephrectomy, although it provides a good oncologic cure for *small renal masses*, should be avoided in these patients because of the significant probability of their developing CKD following radical nephrectomy.

When compared with radical nephrectomy, partial nephrectomy provides better renal functional outcomes in similar patients (Table 12.1) [3].

As a result, the *AUA guidelines* recommend partial nephrectomy for tumors under four centimeters in size and up to 7 cm in size in those patients who are in need of preserving kidney function. This concept of renal preservation takes

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Table 12.1 Summary of renal functional changes according to type of management for renal mass (numerical values in percentages)

Surgery	Ipsilateral parenchyma removed (%)	Total parenchyma preserved (%)	Median loss of renal function (%)	% Developing new-onset CKD (GFR < 45)
RN	100	Approximately 50	35	35–43
PN with extended ischemia (>30 min)	25 (15–60)	Approximately 70–90	19	19
PN with regional hypothermia	20 (15–40)	Approximately 75–92	11	10
PN with limited ischemia (<30 min)	20 (10–40)	Approximately 80–95	12	10
PN without ischemia	10 (0–20)	Approximately 90–100	5–10	7
TA	0	Approximately 90–100	0–10	NA
AS	0	100	0–5	NA

on added significance when one considers that Bijol and colleagues reviewed a series of specimens for patients undergoing radical nephrectomy and found that apart from the tumor, 62% of the specimens showed microscopic signs of renal disease in the non-tumor portion of the kidney [5].

Additional factors supporting the role of partial nephrectomy rather than radical nephrectomy, were demonstrated by Huang and associates, who in a series of 662 patients with *small renal masses*, a normal contralateral kidney, and normal serum creatinine levels, found that 26% had preexisting CKD as evidenced by an e-GFR of less than 60 by the MDRD method [2]. In addition, they found that chronic kidney disease develops in 50–60% of patients following radical nephrectomy.

Motivated by these observations, several series reported the successful use of partial nephrectomy in tumors even larger than 7 cm in diameter. This collective experience, fortified by my own observations in a large series of patients, has led me to conclude that the preservation of functioning renal parenchyma that remains, and not the size of the tumor, should be the main determinant for performing partial nephrectomy, especially in solitary kidneys.

This concept is evident in the case below, where a non-clamping, nonischemic, tissue sparing partial nephrectomy was performed on the patient's solitary kidney, rather than a radial nephrectomy, dialysis, and a renal transplant. Bench surgery and an autotransplant were also a potential option, but would have been technically difficult because of the three arteries supplying this kidney and would have exposed the kidney to ischemic injury. The partial nephrectomy provided this patient with a good functional outcome (preoperative e-GFR = 53 ml/min; postoperative e-GFR of 35 ml/min), rather than the potential risks associated with the alternative approaches. This, in spite of a large, complex, centrally located lesion (nephrometry score of 12) (Fig. 12.1a, b).

Illustrative Case: Large Tumor in Solitary Kidney

Therefore, despite tumor size, partial nephrectomy is the treatment of choice when mandated by the clinical situation and is technically feasible. Unfortunately, in the USA currently, 54% of patients with *small renal masses* still undergo radical nephrectomy rather than partial nephrectomy [6].

The major goals of PN are as follows:

- Obtain the best possible oncologic outcome.
- Maximally preserve renal function.
- Minimize surgical complications.

There are certain factors that are modifiable and others that are not alterable when considering a partial nephrectomy. These factors are listed in Table 12.2.

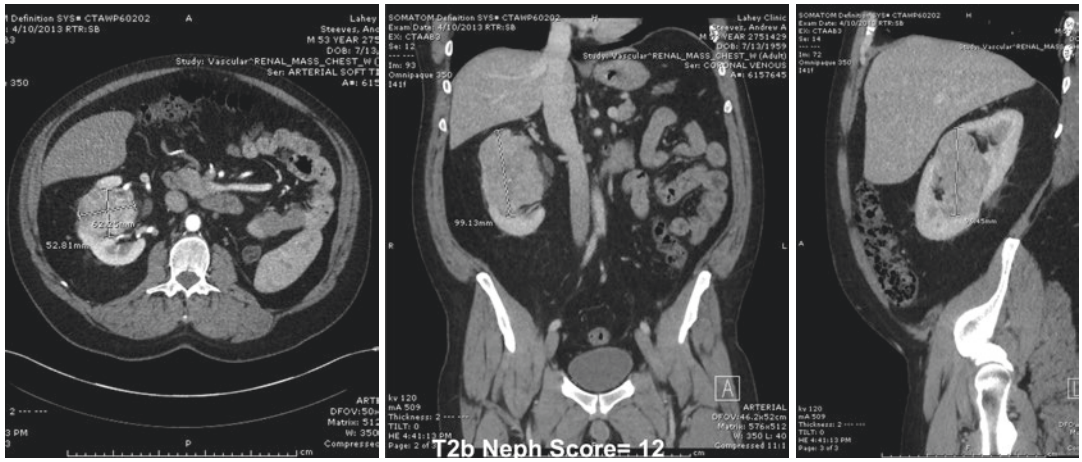


Fig. 12.1 Solitary kidney

Table 12.2 Modifiable and nonmodifiable factors when considering a partial nephrectomy

Nonmodifiable	Modifiable
Renal tumor size	Surgical margins
Preexisting renal function	Ischemia time
	Volume of kidney tissue resected
	Or injured by the procedure itself

The factors that influence renal function after partial nephrectomy are as follows: *lower preop GFR, solitary kidney, smaller volume of kidney preserved, longer warm ischemia time (WIT), larger tumor size, and older age*. These are independent predictors of reduced GFR postoperatively.

Role of Preoperative CKD on Postoperative Renal Function Following Partial Nephrectomy

Takagi and associates assessed whether adequately functioning parenchyma is preserved in patients with preexisting chronic kidney disease (CKD) who undergo a partial nephrectomy (PN) when compared to those who underwent a radical nephrectomy (RN). Ninety-five azotemic patients were analyzed, who underwent curative surgery for pathological T1a–T2 NOMO renal cell carcinoma, with a 24-month follow-up period. Moreover, 51 patients underwent RN, and 44 patients had a PN. Renal function was assessed using estimated GFR (e-GFR). These investigators demonstrated that the PN patients with a 2-year follow-up had a 64% freedom from progression of CKD class, as opposed to 22% who had freedom from progression of CKD class following radical nephrectomy [7].

This work demonstrated that, even in patients with CKD and an e-GFR of between 45 and 59 ml/min, there is value in preserving renal parenchyma by performing a PN as illustrated in Case 1.

Role of Warm Ischemia on Postoperative Renal Function Following Partial Nephrectomy

Vincenz Czerny, from Heidelberg University, originally described the technique for partial nephrectomy in 1887. For over 100 years, the renal hilum was clamped as originally described. While the technique allowed preservation of renal parenchyma and renal function, our group while dealing with a large population of patients with renal tumors and CKD, began to question the need for routine clamping of the renal hilum. This question was stimulated by a publication in 1992 from Schumer et al., who described the morphologic,

biochemical, and molecular evidence for apoptosis during the reperfusion phase, even after brief periods of renal ischemia [8]. Application of these analytical techniques to renal vascular injury has distinguished that brief periods of complete ischemia initiates a form of cell death (apoptosis) during a subsequent reperfusion phase that is drastically different from cellular necrosis induced by prolonged severe ischemia. Motivated by this research, I began to develop methods for the non-clamping, nonischemic partial nephrectomy.

In the late 1990s, our institution began working with a German company to develop 3D CT imaging. This technology allowed us to obtain 3D images of the renal vasculature in a noninvasive way, thus obviating the need for selective renal angiography prior to partial nephrectomy. This, in conjunction with the evolution of newer hemostatic agents, at about the same time, allowed us to visualize the intrarenal vascular anatomy noninvasively and carry out partial nephrectomies without hilar clamping.

From a historical perspective, the author originated and developed the technique of the non-clamping, nonischemic partial nephrectomy in the mid-1990s and has successfully used it since that time. We reported our technique and presented our initial results at the 2005 AUA meeting entitled: "Does Thrombin Sealant Allow Nephron Surgery without Renal Artery Occlusion? Description of Technique and Initial Results" [9].

At the 2008 AUA meeting, we presented two other related reports entitled: "Non-Clamped, Non-Ischemic Partial Nephrectomy in Patients with Compromised Pre-Operative Renal Function or with a Solitary Kidney" [10] and "Non-Clamped, Non-Ischemic Partial Nephrectomy: The New Gold Standard" [11]. These presentations resulted in two publications, one dealing with the "non-clamped partial nephrectomy: techniques and surgical outcomes" [12] and the other "the comparison of hilar clamping and non-hilar clamping for tumors involving a solitary kidney" [13]. In the initial publication, we compared clamping (116 PNs) versus non-clamping (192 PNs) and evaluated postoperative GFR after a 1-year follow-up. The clamped group had a decline in GFR of 12.3% and non-clamped of 9.8% ($p = 0.037$) which did not appear to be statistically significant in the patients with two kidneys. However, in the subset of patients with a solitary kidney, we noted a 21% decrease in GFR in the clamped group as opposed to the 4% decrease in GFR in the non-clamped group [10]. This observation leads us to review our solitary kidney experience in detail. In our publication dealing with 104 patients with solitary kidneys, the non-clamping group had a significantly smaller percent decrease in late GFR 11.8% versus 27.7% in the clamped group ($p = 0.01$) [13]. In a subsequent review of 188 patients, from our institution, who underwent partial nephrectomies in solitary kidneys, the non-clamped group had a 13% decreased e-GFR, and the clamped group had a 30% decreased e-GFR® (unpublished data) (Fig. 12.2).

After these original observations, other investigators began to evaluate the role of ischemia in patients undergoing partial nephrectomy. Notably, Thompson and colleagues investigated the safe duration of warm ischemia during partial nephrectomy [14]. Their aim was to evaluate the short- and long-term renal effects of warm ischemia on renal function in patients with a solitary kidney. A total of 362 patients with a solitary kidney who underwent open (319) or laparoscopic (43) partial nephrectomy, using warm ischemia with hilar clamping, had the association of warm ischemic time (4–55 min) and renal functional outcome evaluated. Postoperative acute renal failure occurred in 70 patients (19%), including 58 patients (16%) who had a GFR of <15 ml/min within 30 days of surgery. Among 226 patients with a preoperative GFR > 30 ml/min, an additional 38 patients (17%) developed new-onset stage IV CKD. Their conclusion was that longer warm ischemia time is associated with short- and long-term renal consequences. These results suggested that every minute counts when the renal hilum is clamped [14] (Fig. 12.3).

The findings of Thompson and his group confirmed our original observations that renal ischemic injury is temporarily related to hilar clamping in solitary kidneys and damages postoperative renal function following partial nephrectomy.

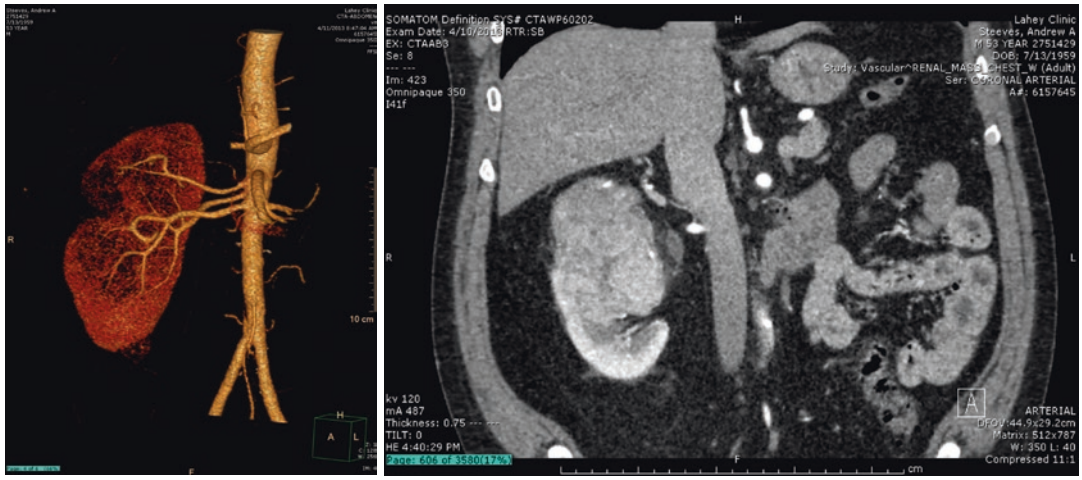


Fig. 12.2 Solitary kidney decrease in GFR: non-clamping versus clamping

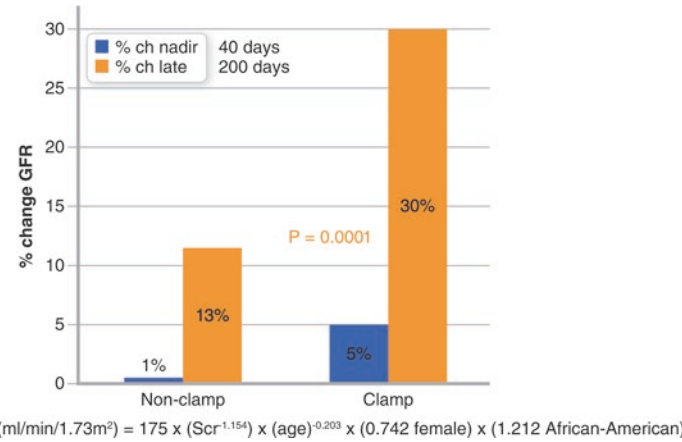


Fig. 12.3 Risk of developing new-onset stage IV CKD for patients with >25 min versus <25 min of warm ischemia. GFR = glomerular filtration rate. (Modified from [14])

Many publications have stated that in patients with two kidneys, hilar clamping versus non-clamping has minimal effect on postoperative renal function following partial nephrectomy. Unfortunately, many of these publications have only *short-term follow-up* data available. However, even in patients with two kidneys, who underwent partial nephrectomy with warm ischemia, Mikkamalla and Assoc [15] noted in the Kaplan–Meier curves that the overall freedom from clinically significant CKD progression is 50% at 10 years (Fig. 12.4). The two most important predictive parameters are preoperative GFR values and length of warm ischemia time (Figs. 12.5 and 12.6). They reported that when warm ischemia exceeds 22 min, only 30% of patients were free of progressive CKD at 10 years. Stated another way, 70% of patients with warm ischemia >22 min had progression of CKD class at 10 years. In addition, preoperative azotemia (with GFR <79 cc/min) also compromised post-operative renal function, and 70% of these patients had progression of CKD class at 10 years.

The role of warm ischemia compromising post-operative renal function following partial nephrectomy is clearly established, even in patients with two kidneys, with long-term not short-term follow-up.

Regardless of these findings, the debate continues in the literature regarding the benefits of

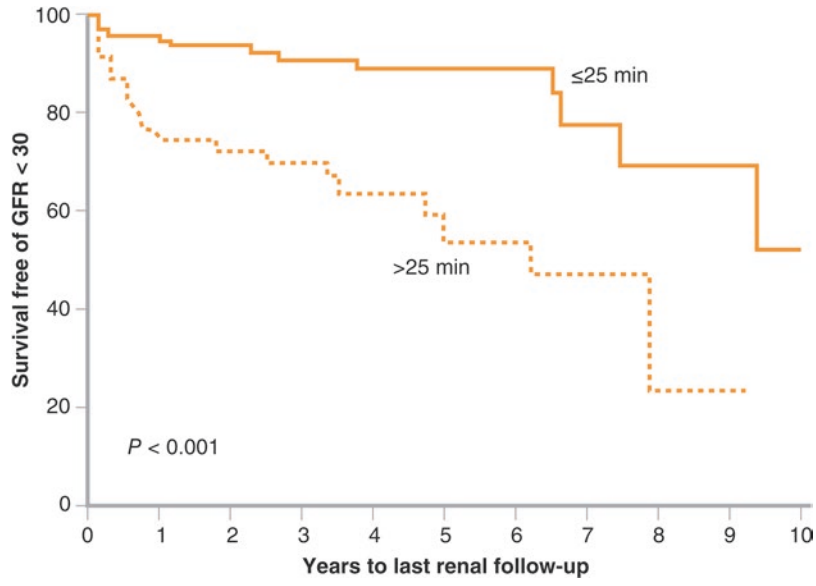


Fig. 12.4 Overall freedom from progression in CKD class in all patients. (Modified from [15])

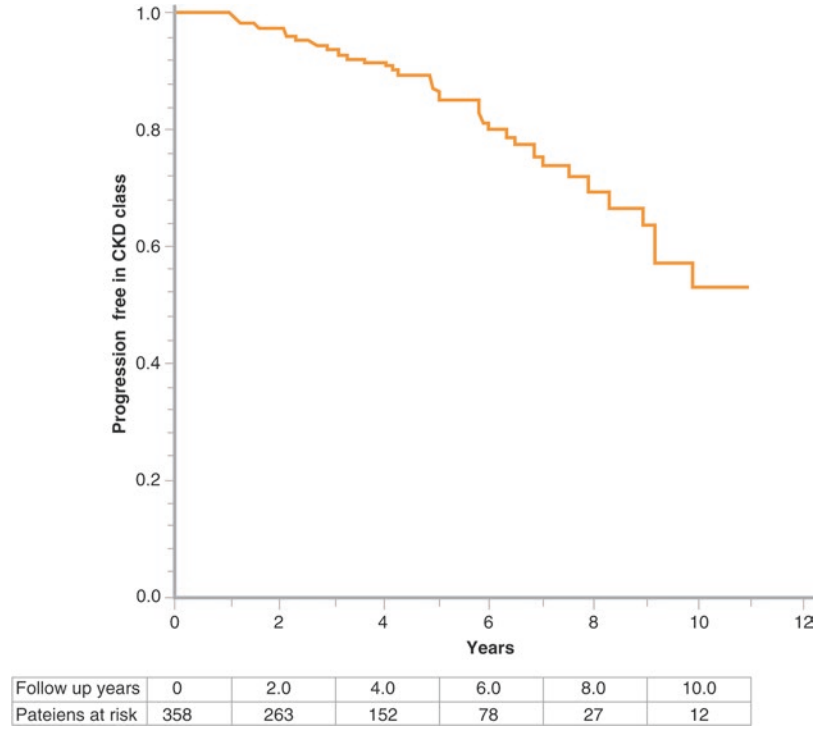
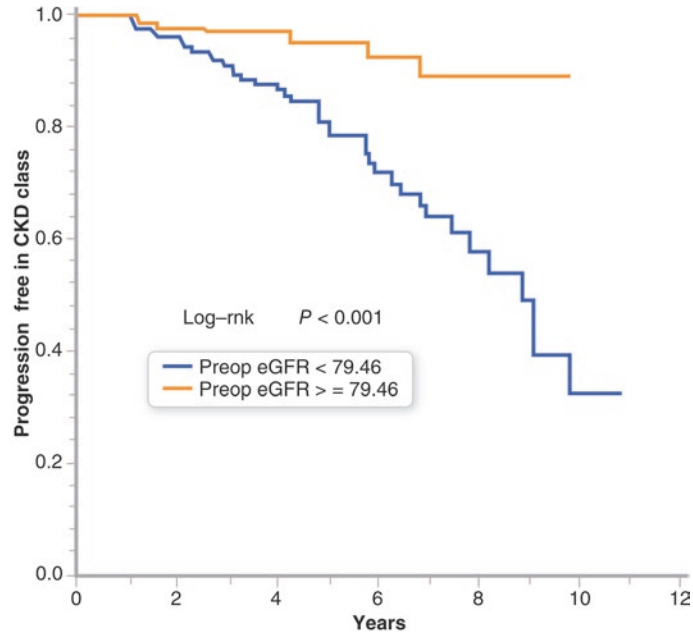


Fig. 12.5 Impact of preoperative e-GFR from freedom of progression of CKD class. (Modified from [15])

clamping versus non-clamping in robotic partial nephrectomy. Daniel Rosen et al. presented, at the 2018 AUA meeting, a series of 668 patients with two kidneys who underwent partial nephrectomy with hilar clamping and noted that there was a strong association between warm ischemia time (WIT) and acute kidney injury (AKI). A threshold of WIT > 20 min was identified as a significant risk factor for developing AKI at the time of discharge, while 15 min WIT was identified as a cut-off for a worse e-GFR outcome with long-term follow-up. *These authors also agree that every effort should be made to limit every minute of warm ischemia during a robotic PN and keep the WIT under 15 minutes* ® [16]. This idea is obviously true in open partial nephrectomy as well.



Patients at risk time	0	2.0	4.0	6.0	8.0	10.0
Below median	179	150	89	42	16	5
Above median	179	145	106	36	26	26

Fig. 12.6 Impact of WIT on freedom from progression of CKD class. (Modified from [15])

There is little doubt as to the importance of renal ischemia and its long-term effect on postoperative renal function following partial nephrectomy, even in patients with two kidneys. The two-kidney model is not as ideal a setting to study the effect of ischemia on kidney function as the solitary kidney model, and long-term follow-up is mandatory in analyzing the current literature regarding clamping versus non-clamping partial nephrectomy. *That being said, if less WIT is better, then no ischemia is the best method of avoiding long-term renal ischemic injury in any patient undergoing a partial nephrectomy, open or minimally invasive*.

Role of Volume on Postoperative Renal Function Following Partial Nephrectomy

In addition to ischemic injury, the percent of volume preserved is another primary determinant of the renal functional outcome following partial nephrectomy. Steve Campbell and his colleagues carried out an elegant study, of a novel method, to estimate the percentage of functional volume preserved in order to assess its effect on renal functional outcomes [17]. They studied the GFR outcome based on the MDRD score in 38 patients who had normal preoperative serum creatinine and who underwent open or laparoscopic partial nephrectomy. A cylindrical volume ratio method was used to estimate the percentage of functional volume preserved on CT images obtained before and after partial nephrectomy. A model to predict the postoperative estimated GFR was based on multiplying the preoperative GFR by the percentage of volume preserved, followed by adjustment for the functional contribution of the contralateral kidney. Correlation and multiple regression analysis were done to test this model. On multivariate analysis, the preoperative glomerular filtration rate ($p < 0.001$) and ischemia time ($p = 0.02$) correlated with the nadir glomerular filtration rate, and the preoperative glomerular filtration rate ($p < 0.001$) and the percent of functional volume preservation ($p = 0.04$) correlated with the late glomerular filtration rate. These data support the notion that preoperative nephron endowment and the percentage of functional volume preserved are primary determinants of the long-term functional

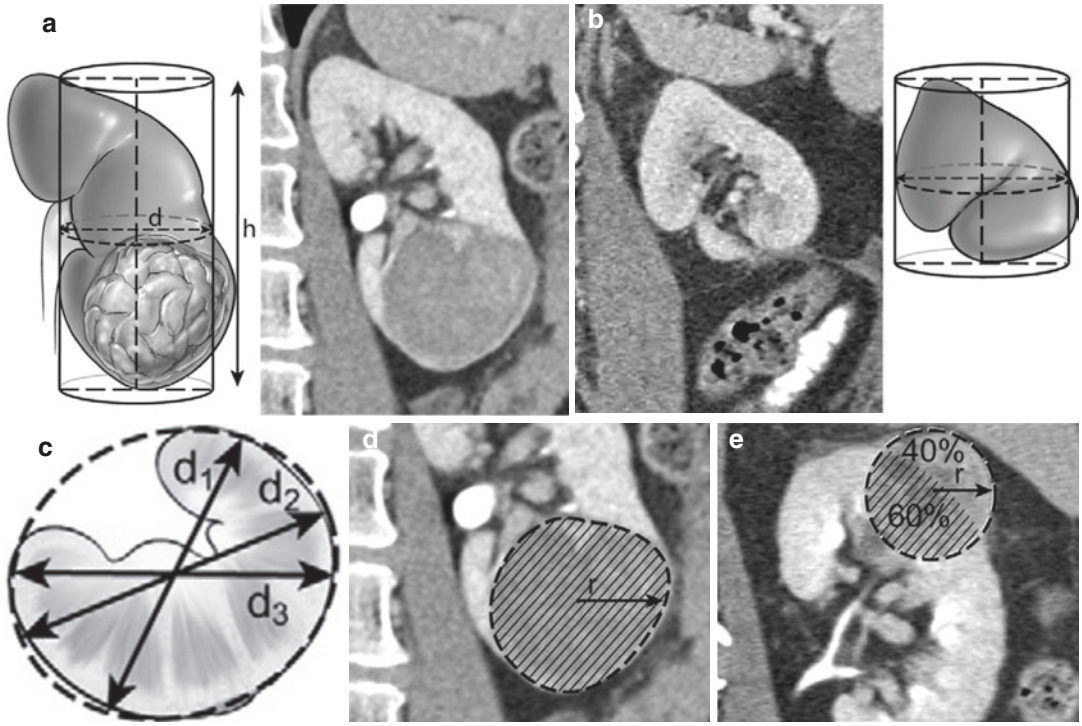


Fig. 12.7 Method for calculating residual renal parenchyma following partial nephrectomy. (Reprinted with permission from Simmons et al. [17])

outcome after partial nephrectomy in patients with normal preoperative kidney function who also have an ischemia time within acceptable limits. What is difficult to discern, from this study, is how much of the kidney tissue preserved was damaged by hilar clamping and renal ischemic injury (Fig. 12.7).

It seems reasonable to conclude that warm ischemia and the volume of functioning renal tissue that remains are both critical in determining postoperative kidney function following partial kidney. WIT needs to be minimized or eliminated and volume maximized in order to obtain the best renal functional outcome for the patient.

Combined Role of Ischemia and Volume on Renal Function Following Partial Nephrectomy

We have demonstrated that ischemia and volume are independent factors determining renal functional outcomes following partial nephrectomy. What about the combined role of nonischemia and preservation of renal parenchymal volume (enucleation rather than wedge resection) on renal function following partial nephrectomy?

For many years, we have combined the non-clamping, nonischemic partial nephrectomy approach with renal tumor enucleation, in order to maximize renal function following partial nephrectomy. We have recently reviewed our series 1422 partial nephrectomies where tumor enucleation was utilized, 434 clamped versus 988 non-clamped. As expected, there was more blood loss in the non-clamped cohort (600 cc vs. 250 cc). However, even in patients with two kidneys, long-term follow-up demonstrated a 35% decrease in renal function in the clamped group and an 18% in the non-clamped group as measured by changes in pre- and postoperative creatinine and e-GFR, again clearly demonstrating better preservation of renal function in the non-clamped group (unpublished data). These results were confirmed by the University of Michigan group, alluded to above, who

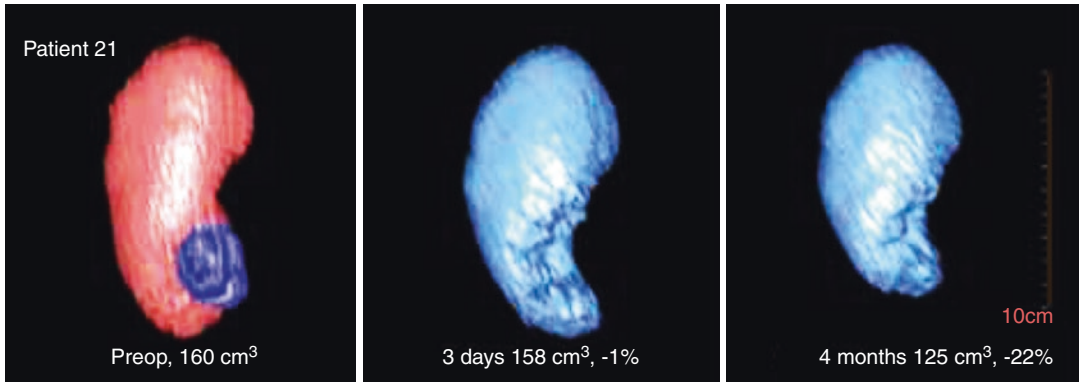


Fig. 12.8 Loss of renal parenchyma following robotic partial nephrectomy. (Adapted from AUA News Dec. 2017)

reported that even in patients with two kidneys, with long-term follow-up (10 years), approximately 50% of patients developed clinically significant progression of CKD class following robotic partial nephrectomy [15]. Our results are even clearer in patients with solitary kidneys. In our series of 188 partial nephrectomies in solitary kidneys, there was a 13% decreased GFR in the non-clamped group and a 30% decreased GFR in the clamped group at day 200 (® unpublished data).

These results clearly underscore the value of non-clamping, nonischemic tissue sparing technique, which I believe provides the optimal renal functional outcome following partial nephrectomy. As can be seen in this text, many other researchers have also confirmed our original observations that avoiding ischemic injury and sparing renal parenchyma are key determinants of renal function following partial nephrectomy.

One final technical point is the avoidance of large mattress sutures in both open and minimally invasive partial nephrectomy. These mattress sutures compromise residual parenchymal volume and therefore impair postoperative renal function. This observation is clearly demonstrated in a recent study of 20 patients who had a robotic partial nephrectomy [18, 19]. As seen in the illustration and chart below, after 1 year of follow-up, there is a significant (24%) reduction in the remaining renal parenchymal volume because of large mattress sutures (Fig. 12.8).

Conclusion

Regardless of whether the partial nephrectomy is performed open or minimally invasively, the data, in my opinion, very strongly supports that "The Non-Ischemic Tissue Sparing Technique" *provides the best long-term renal functional outcome, in patients with either two functioning kidneys or a solitary kidney at the time of surgery*.

Surgical Approach to Multifocal or Bilateral Renal Tumors

Managing patients with bilateral, multiple tumors or tumors in a solitary kidney adds another dimension of complexity. Many patients with hereditary renal syndromes, such as Von Hippel–Lindau, Birt–Hogg–Dube, hereditary leiomyomatosis and renal cell cancer, hereditary renal papillary carcinoma, succinate dehydrogenase deficiency, tuberous sclerosis, familial oncocytoma, and familial renal cancer, *often present with multifocal, bilateral renal tumors synchronous or asynchronous in nature*. For patients with these conditions, the surgical approach requires cure of the cancer while maximizing renal function. These patients generally present with tumors at a younger age, and the clinician needs to be forward thinking. The goal in these patient populations is to prevent cancer dissemination, maximize renal function, limit the number of surgeries

performed, and minimize ischemia, while at the same time maximizing the remaining renal parenchyma.

> Decisions on timing of genetic testing, the order of surgery, optimal method for partial nephrectomy, and surveillance of de novo lesions are critically important in managing patients with multifocal or bilateral disease. Information obtained from nuclear scans may help more accurately delineate split renal function and help with planning of the surgical approach. For synchronous, bilateral tumors, the timing of surgery is debatable. Three major surgical options exist, they include:

1. Concomitant bilateral partial nephrectomies
2. Staged partial nephrectomy with the larger, more complex side first
3. Staged partial nephrectomy with the smaller less complex side first [20]

Each surgeon or center advocates its own surgical approach. My personal preference to use is option (3), the staged open partial nephrectomy approach doing the less complicated lesions first. This process allows the kidney containing the more complicated lesion or lesions to remain as a backup dialysis unit during the immediate postoperative period in the event that the more complex tumor may require a subsequent radical nephrectomy. If done in the opposite order, and radical nephrectomy is performed initially, ischemia in the remaining solitary kidney after the partial nephrectomy may place the patient at greater risk for renal complications.

While it is possible to carry out minimally invasive surgery on patients with multiple or bilateral tumors, ischemia becomes a significant potential problem due to the prolonged clamping time required and the need for bilateral renal artery occlusion. *That is why, I prefer a non-clamping, nonischemia, tissue sparing open partial nephrectomy as the preferred approach in patients with multiple, bilateral tumors or tumors in a solitary kidney*, as illustrated in the following case studies.

Case Study 1

The patient is a 60-year-old male who underwent a left radical nephrectomy in 2007. He developed a tumor in his solitary right kidney and underwent a right partial nephrectomy in 2011. In 2018, he was referred for surgery of two recurrent tumors in his solitary right kidney. His preoperative creatinine was 1.3. He underwent a non-clamping, tissue sparing partial nephrectomy with removal of the two tumors in his solitary kidney seen in the following MRI and CT scans and studies (Fig. 12.9a–d). The vessels supplying the tumor are ligated in continuity (Fig. 12.9d). Note that the entire kidney has normal blood flow during the non-clamping partial nephrectomy. The middle pole tumor was excised initially. One can see the upper edge of the lower pole tumor through the enucleation site of the first tumor (Fig. 12.9e). After both tumors were excised, the kidney was reconstructed as seen in (Fig. 12.9f). His postoperative creatinine remains 1.3.

Case Study 2

The patient is a 52-year-old female who was in good general health until she noted persistent right flank pain and gross hematuria with passage of clots. A CAT scan demonstrated a large right renal tumor and a midpolar tumor in the left kidney (Fig. 12.10a, b). She initially underwent a non-clamping, nonischemic, tissue sparing partial nephrectomy (Fig. 12.10e, f). Thereafter, she had a right radical nephrectomy. Her postoperative BUN is 10, creatinine 1.1, and GFR > 60. The final pathology of the left partial nephrectomy revealed a clear cell renal cell carcinoma grade 2 of 4. Stage PT 1b be with negative surgical margins and no evidence of lymphovascular invasion. The pathology of the right thoracoabdominal radical nephrectomy was clear cell carcinoma Fuhrman grade 3–4 stage PT 3a with extension into the perirenal fat, negative surgical margins and negative for lymphovascular invasion.

Case Study 3

The patient is a 60-year-old male, who was referred with bilateral renal tumors. Outside studies revealed a large tumor in the left kidney (Fig. 12.11a) and a tumor in the lower pole of the right kidney (Fig. 12.11b). He was also noted to have what was thought to be perihilar nodes in

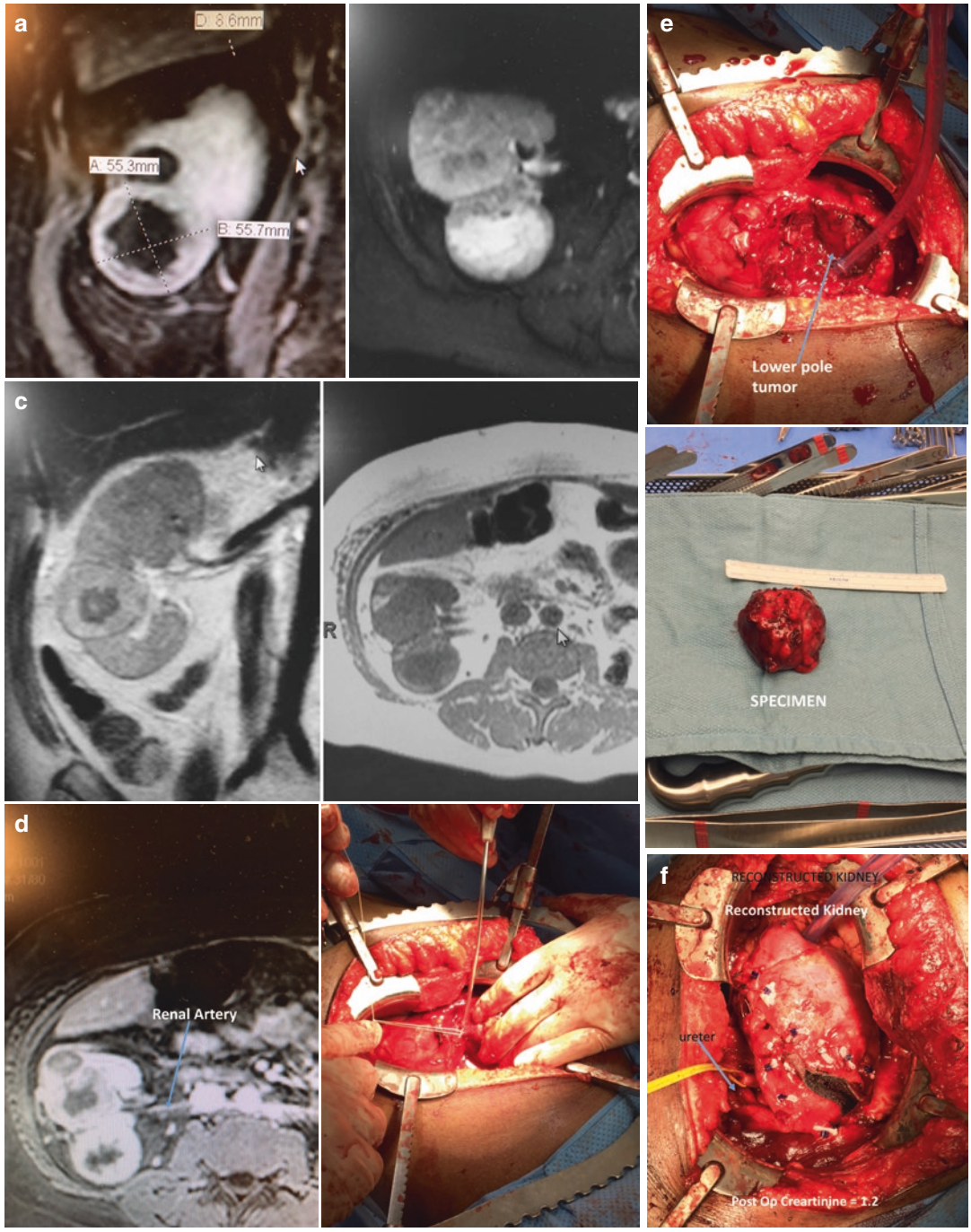


Fig. 12.9 Case Study 1. (**a**) Preoperative CT scan of two recurrent tumors in a solitary kidney. (**b**) Preoperative MRI of two recurrent tumors in a solitary kidney. (**c**) MRI – 2 Recurrent in solitary right kidney. (**d**) Intraoperative view – ligating segmental renal artery in continuity without clamping the main renal artery. (**e**) Tumor bed after resection of the first renal tumor, arrow points to the upper border of the second renal mass before removal. (**f**) Reconstructed solitary kidney after non-clamping partial nephrectomy

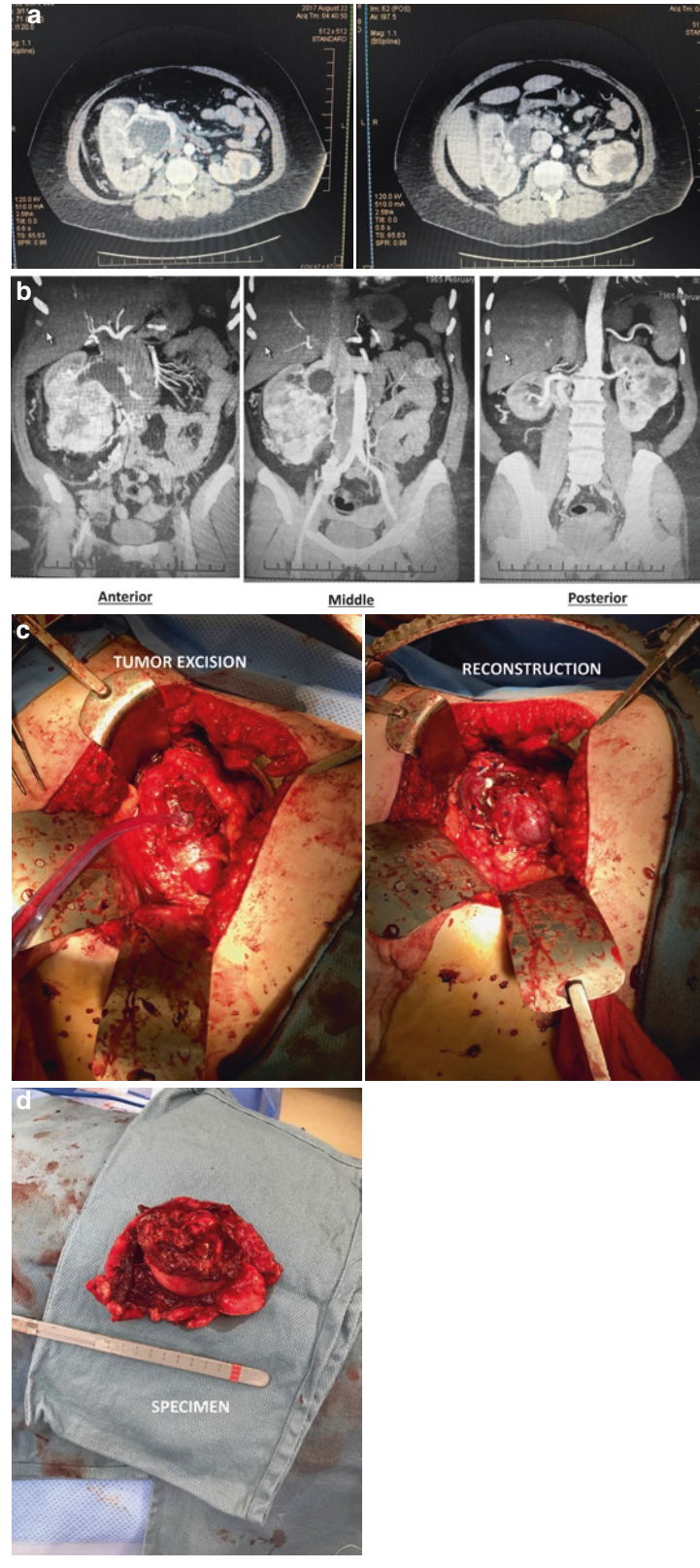


Fig. 12.10 Case Study 2. (**a**) Preoperative CT scan demonstrating large right renal tumor and midpolar left renal tumor. (**b**) Preoperative CTA scan of large right renal tumor and midpolar left renal tumor, without evidence of adenopathy or venous involvement. (**c**–**d**) The intraoperative photographs of the midpolar partial nephrectomy site, reconstruction of the kidney and the excised renal tumor

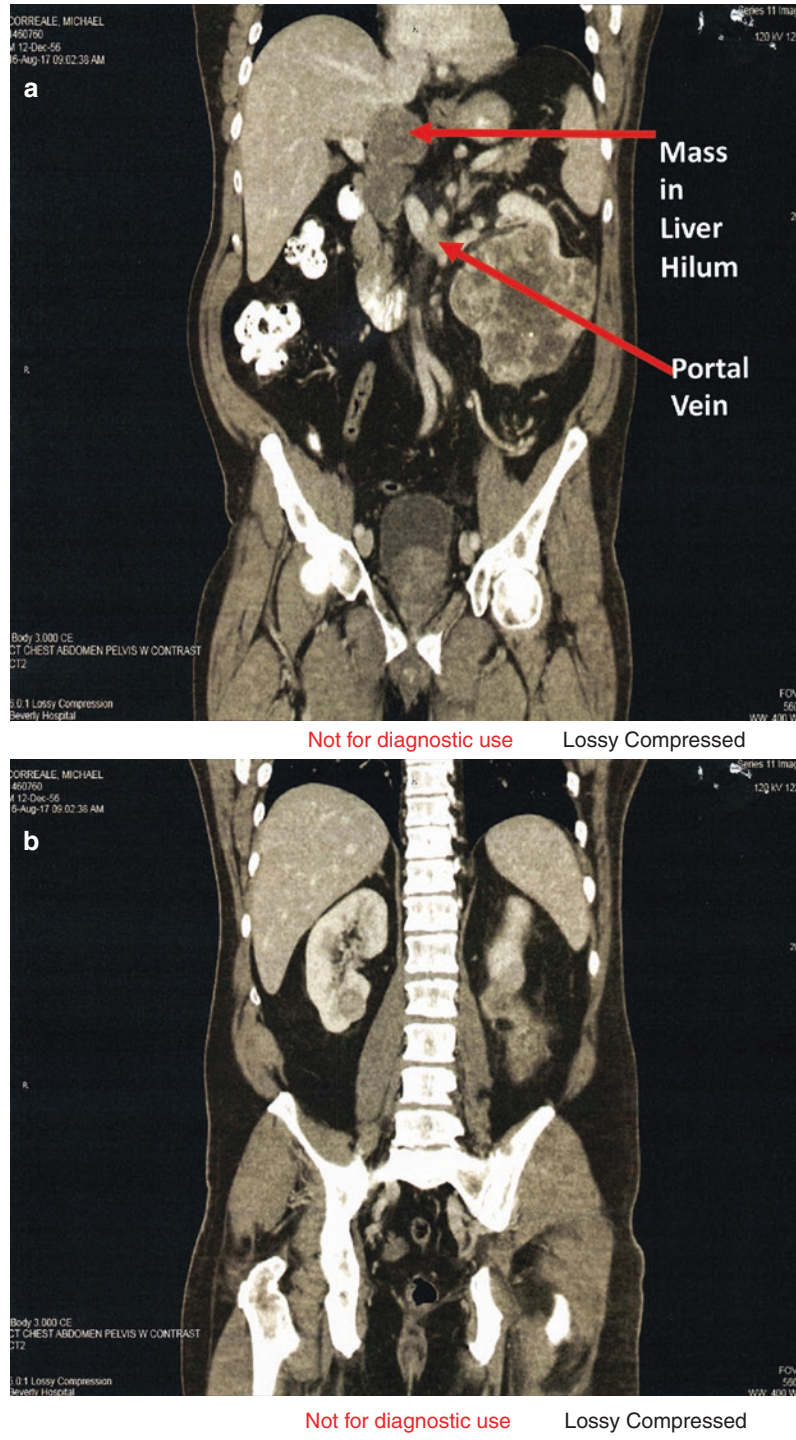
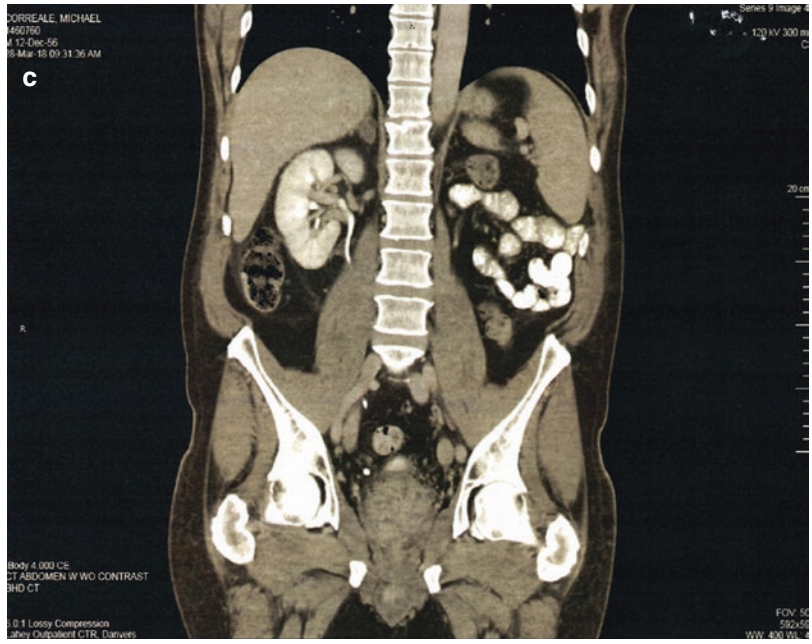


Fig. 12.11 Case Study 3. (**a**) Preoperative CT scan demonstrating a large left renal tumor and an additional mass surrounding the portal vein. (**b**) Preoperative CT scan demonstrating a right lower pole tumor. (**c**) Postoperative CT scan following a left radical nephrectomy and a right lower pole partial nephrectomy

Fig. 12.11 (continued)



the hilum of the liver surrounding the portal vein (Fig. 12.11a). Because of the unusual nature of periportal lymph node metastasis, we evaluated this mass with a liver scintigram which demonstrated a hemangioma of the caudate lobe of the liver. The lesions were biopsied, and the diagnosis of hemangioma of the caudate lobe was confirmed. The patient underwent sequential right lower pole non-clamping, nonischemic, tissue sparing partial nephrectomy followed 6 weeks later by a left radical nephrectomy. The postoperative image is noted in Fig. 12.11c. His preoperative creatinine was 1.3 and GFR > 60 ml/min. His postoperative creatinine is 1.5, and his GFR equals 55 ml/min.

Summary

In essence, the non-clamping, nonischemic, tissue sparing partial nephrectomy, in my experience, provides the best long-term outcome in patients with two kidneys or those with a solitary kidney, especially in those patients with multiple or bilateral synchronous tumors.

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Open Partial Nephrectomy

13

Marianne M. Casilla-Lennon, Patrick A. Kenney, Matthew Wszolek, and John A. Libertino

Introduction

Despite broader acceptance of active surveillance and ablative approaches, surgical excision remains an excellent option for treatment of locally confined renal cell carcinoma (RCC). Historically, radical nephrectomy (RN) was utilized to treat locally confined RCC, regardless of tumor size and complexity. RN remains overutilized for RCC amenable to partial nephrectomy (PN) despite contemporary studies demonstrating equivocal oncologic outcomes between PN and RN for T1 RCC. Comparable oncologic outcomes coupled with contemporary studies correlating RN with increased cardiovascular morbidity, development of chronic kidney disease (CKD), and inferior overall survival have led to more widespread acceptance of nephron-sparing surgery (NSS). To this end, the 2017 American Urologic Association and 2014 European Association of Urology guidelines recommend PN for T1 RCC when technically feasible especially when there is a need to preserve renal function [1, 2].

PN however remains a challenging endeavor requiring complete tumor resection with a negative margin and maximal preservation of functioning renal parenchyma. The chief advantages of PN compared to RN include avoiding the overtreatment of benign renal masses without compromising oncologic efficacy in malignant tumors and preserving renal function to minimize postoperative CKD, morbidity, and mortality. This chapter will provide a detailed discussion of the rationale for PN as well as its current indications. The importance of minimizing renal ischemia and other predictors of postoperative CKD will be discussed. The techniques of open PN will be described as will perioperative management. Minimally invasive approaches, ablative therapies, and active surveillance will be discussed in other chapters.

Historical Perspective

In 1887, Vincenz Czerny (1842–1915) performed the first planned PN for a renal tumor (angiosarcoma) over 15 years after Gustav Simon (1824–

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1876), his predecessor at Heidelberg Germany, performed both the first planned nephrectomy and PN for nonmalignant renal pathology [3]. Initial interest in PN, however, weaned due to concerns about complications including intraoperative hemorrhage, delayed bleeding, and urinary fistulae [4]. The observation that a patient could survive with one functioning kidney after nephrectomy also diminished early interest in NSS [3]. In the early twentieth century, nephrectomy was considered a standard therapy for malignant renal tumors due to the technical challenges associated with advanced clinical stage at presentation and concerns about perinephric tumor extension, although PN was occasionally employed in the treatment of benign conditions such as cysts, infarcts, caruncles, calculi, or localized hydronephrosis [3]. In the late twentieth century, the necessity of radical Halstedian resections for renal cancer was questioned by pathological studies demonstrating the noninvading, expansile local growth of renal tumors [3] as well as studies reporting a low rate of metastasis from small renal tumors [5]. In 1950, Vermooten notably questioned the necessity of RN in all cases of RCC, even in the presence of a functioning contralateral kidney, and established the basis for the modern approach of NSS for RCC [6]. For the next several decades, however, PN was rarely performed even in patients with solitary kidneys, renal dysfunction, or bilateral tumors [7]. As researched by Herr, surgical textbooks written between 1937 and 1970 do not mention PN for renal cancer [3]. Surgical advancements in the 1960s and 1970s, more specifically renal hypothermia and resection techniques based on segmental blood supply, which permitted resection and reconstruction in a bloodless field, as well as published favorable local recurrence rates (4–10%) and survival rates comparable to RN in patients with solitary kidneys and bilateral tumors perked interest in widespread use of PN in RCC [3, 8].

In the late 1970s and 1980s, progressive urologists increasingly questioned the rationale of removing an entire kidney for a small renal mass leading to the modern era of routine elective PN. As mentioned previously, the concept was not novel. However, advancements in technique and anatomical knowledge, promising local recurrence rates and survival outcomes in preliminary studies of essential PN, and a downward stage migration resulting from more frequent axial imaging provided the foundation for the preliminary experiences of elective PN for patients with RCC and normal contralateral renal function. As often true for any dramatic paradigm shift, the change was not immediate or unanimous. Opponents raised concerns over inadequate excision of the primary tumor and possible occult tumor in the renal remnant. Licht and Novick in 1993 published their short-term experience of 241 PNs in patients with a normal contralateral kidney. They reported a <1% local recurrence rate and 95% survival rate [9]. Subsequent publications with longer follow-up validated these results and solidified the role of PN in the treatment of small renal masses with a normal contralateral kidney [10, 11]. With continued technical advancements including intraoperative ultrasound and more effective hemostatic agents, urologists have expanded indications for NSS to include larger tumor size, multiple tumors in a single operation, and complex locations such as hilar, endophytic, and centrally located lesions. The role of NSS has been further solidified by the observation that RN compared to PN is associated with an increased risk of CKD and non-cancer-related morbidity and mortality [12, 13]. In recent years, urologists have focused on techniques to minimize ischemic injury and also lessen surgical morbidity by minimally invasive approaches, as well as avoidance of surgery through the use of active surveillance or ablation in appropriate cases.

Epidemiology of Small Renal Masses

Kidney cancer is the 12th most common malignancy worldwide with 338,000 new cases in 2012 [14]. In the United States, there will be an estimated 65,340 new cases and 14,970 deaths from renal tumors (including RCC and urothelial renal pelvis tumors) in 2018 [15]. For cases with pathological confirmation in the US Surveillance,

Epidemiology, and End Results (SEER) database, over 90% of "renal tumors" were RCC while the majority of the remaining tumors were urothelial tumors of the renal pelvis [16]. For malignant renal tumors, the clear cell (conventional) type constitutes approximately 70% of cases with papillary, chromophobe, renal medullary and collecting duct comprising the remaining cases [17]. Established risk factors for RCC include increasing age [16, 18], male sex [14], geographic location (higher in the United States and Europe) [19], race (lower in Asian/Pacific descendent than in the United States) [16, 18], smoking [20], obesity [21–23], and hypertension [21].

Total kidney cancer incidence increased for an approximately 20-year period from the 1970s to the 1990s, but has plateaued or declined recently in many countries worldwide [19, 24]. In the United States, where histologic information is available unlike many cancer registries, the rates of renal pelvis urothelial tumors have declined while RCC rates have continued to rise among all age classifications, tumor sizes, and racial groups [18]. The increased incidence of RCC has been attributed to the incidental diagnosis of small, asymptomatic renal masses due to more frequent usage of axial imaging. Contemporary studies support this observation. A study from the US National Cancer Database (NCDB) between 1993 and 2004 showed a significant increase in Stage I RCC with a corresponding decrease in Stage II–IV RCC [25]. Furthermore, the mean size of Stage I RCC decreased from 4.1 in 1993 to 3.6 cm in 2003 with a particular increase in incidence of tumors <3 cm [25, 26]. Stage migration may account for the recent plateauing of RCC mortality rates in Europe [24] and the United States [16, 18]. Other factors are likely also contributing to this trend, as the survival of RCC patients with more advanced disease has improved recently as well. Possible explanations include early detection of all stages through incidental diagnosis and recent therapeutic advancements including targeted therapy [16, 18].

There is adistinct relationship between tumor size and risk of malignancy. Smaller lesions are more likely to be benign tumors such as oncocytoma, angiomyolipoma, papillary adenoma, and metanephric adenoma. In the Mayo Clinic, 6.3% of tumors >7 cm were benign compared with 46.3% of tumors <1 cm [27]. Furthermore, larger tumor size was associated with an increased risk of high compared to low grade and clear cell compared to papillary RCC [27]. For renal masses <4 cm treated surgically, upstaging to T3 and advanced grade was associated with increasing tumor size, especially for tumors >3 cm [28, 29]. The relationship between tumor size and risk of metastasis at presentation has been established. Patients with tumor 1 cm or less, 1.1–2 cm, 2.1–3 cm, and 3.1–4 cm had prevalence of metastasis at diagnosis of 1.4%, 2.5%, 4.7%, and 7.4%, respectively, in a recent SEER study [30]. The most rapid increase in both the prevalence of metastases at diagnosis and disease-specific death occurred for tumor sizes between 4 and 12 cm [30]. A similar pattern to the increased risk of metastasis at presentation with tumors >3 cm was evident in the probability of de novo asynchronous metastatic RCC in postsurgical patients [31].

Oncologic Efficacy of Partial Nephrectomy

Traditionally, RN was the treatment of choice for renal cortical tumors. PN was performed only in "essential" cases, such as patients with solitary kidneys, bilateral renal tumors, or severe chronic renal insufficiency with a goal of avoiding dialysis dependence. Consistent with trends across other surgical disciplines favoring organ preservation, the American Urologic Association (1) and European Association of Urology (2) now recommend PN as a treatment for T1 (<7 cm) RCC in patients with two functioning kidneys. The rationale driving this paradigm shift was multifactorial, including concerns over the relationship between CKD and non-RCC-related mortality as well as a downward stage migration in RCC resulting in an increased detection of renal cortical tumor amenable to PN. Since the goal of any oncologic procedure is local cancer control, the aforementioned factors would be irrelevant if PN was inferior to RN in oncologic outcomes.

There is a significant selection bias in early retrospective studies comparing the oncologic efficacy of PN versus RN as many of the PNs were performed in "essential" cases. A group from Mayo Clinic reported a case-control study comparing PN with RN in elective cases with unilateral RCC with a normal contralateral kidney. Each group contained 164 patients and was matched for tumor size, pathological stage (97% T1), grade, age, sex, and year of surgery. The 10-year cancer-specific survival (96% RN vs. 98% PN) or metastasis-free survival (95% RN vs. 98% PN) was similar between the two groups, and no difference was noted in 10-year overall survival (74% RN vs. 73% PN) [32].

The EORTC Intergroup (EORTC 30904) conducted a non-inferiority Phase III trial comparing PN and RN for <5 cm solitary tumors suspicious for RCC in patients with normal contralateral kidneys. The study has been noted to have several shortcomings. Foremost, the analysis was underpowered due to poor accrual (541 patients enrolled with 1300 patients required), and there was a >10% crossover rate following randomization. There was also a small number of total deaths (117) and cancer-related deaths (12), limiting meaningful comparative statistics relating to survival. In the intent to treat analysis, RN unexpectedly had superior overall survival compared with the PN (81.1% vs. 75.7%, $p = 0.03$). In the secondary analysis of RCC patients only, and clinically and pathologically eligible patients, the trend in overall survival was not statistically significant. The estimated risk of RCC-related death and 10-year progression rates (3.3% after RN and 4.1% after PN, $p = 0.48$) were similar between the two groups. Since only 3% of the PN patients died from RCC, this study may be interpreted as supporting the oncologic efficacy of NSS for T1 disease [33].

The remainder of this section will detail pertinent literature relating to the oncologic efficacy of PN compared with RN based on primary tumor stage (Table 13.1). Table 13.2 summarizes many of the studies reporting oncologic outcomes in T1 RCC.

Table 13.1 TNM staging of renal cancer

T1: Tumor <7 cm in greatest dimension, confined to kidney
T1a: Tumor <4 cm, confined to kidney
T1b: Tumor between 4 and 7 cm, confined to kidney
T2: Tumor >7 cm in greatest diameter, confined to kidney
T2: Tumor >7 cm in greatest diameter, confined to kidney
T2a: Tumor >7 cm but ≤10 cm, confined to kidney
T2b: Tumor >10 cm, confined to kidney
T3: Tumor extends into major veins or perinephric tissues but not into ipsilateral adrenal gland or beyond Gerota fascia
T3a: Tumor grossly extends into the renal vein or its segmental branches, or tumor invades perirenal and/or renal sinus fat
T3b: Tumor grossly extends into the vena cava below the diaphragm
T3c: Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4: Tumor invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland)
N: Regional lymph nodes
NX: Regional lymph nodes cannot be assessed
N0: No lymph node metastasis
N1: Metastasis in regional lymph nodes
M: Distant metastases
MX: Metastases cannot be assessed
MO: No distant metastases
M1: Distant metastases

Adapted from Edge et al. [120]

T1a Tumors

A competing-risks population-based SEER analysis comparing oncologic outcomes after PN ($n = 1622$) versus RN ($n = 5658$) for T1aN0M0 was recently published. There was no difference in the 5-year cancer-specific mortality rate after adjusting for other causes of mortality (1.8% for PN vs. 2.5% for RN, $p = 0.5$) [34]. An international multi-institutional retrospective analysis of T1a also showed no difference in the rate of cancer-specific deaths (2.2% vs. 2.6%, $p = 0.8$) or local recurrence (0.8% vs. 0.6%, $p = 0.6$) after PN ($n = 314$) compared with RN ($n = 499$) [35]. Single-institution studies have published comparable 5-year disease-specific survival (95–96.1%) and local recurrence rates (0–0.9%) [36, 37].

Table 13.2 Oncologic outcomes of open PN for T1 TCC (NR – not reported)

	Study	# of patients	Follow-up (months)	Local recurrence	Five-year disease-specific survival (%)
T1a	Crepel et al.	1622	24	NR	98.2
	Patard et al.	314	51	0.8%	97.8
	Antonelli et al.	176	59	0.6%	96.1
	Lee et al.	79	40	0	95.0
T1b	Crepel et al.	275	40	NR	93.8
	Patard et al.	65	51	3.6%	97.8
	Weight et al.	212	49	NR	93.0
	Antonelli et al.	52	54	1.9%	99.0
	Joniau et al.	67	40	4%	95.8
	Pahernik et al.	102	56	1.7%	

Adapted from Refs. [34–41]

T1b Tumors

A recent SEER population-based analysis of T1bN0M0 RCC compared matched PN ($n = 275$) and RN ($n = 1100$) groups. In regression models controlling for age, tumor size, and year of surgery, there was no difference in 5-year cancer-specific survival between PN and RN (91.4% vs. 95.3%, $p = 0.2$). Competing risk regression analysis also failed to demonstrate a difference in cancer-specific mortality [34]. A bi-institutional Mayo Clinic and Memorial Sloan Kettering study compared outcomes between RN ($n = 286$) and PN ($n = 873$) for T1b tumors. Type of surgery was not a significant factor in multivariate modeling of death from RCC (Hazard Ratio [HR] for RN vs. PN: 1.97, $p = 0.079$) [42]. A retrospective study from seven international centers had similar findings. In this study, the RN ($n = 576$) and PN ($n = 65$) groups had similar rates of cancer-specific death (9% vs. 6.2%, $p = 0.6$, respectively) and local recurrence (2.3% vs. 3.6%, $p = 0.5$, respectively). Type of surgery had no influence on survival in multivariable analysis ($p = 0.8$) [35]. Single-institution retrospective studies have published comparable local recurrence of 1.7%–4.0% and 5-year cancer-specific survival rates of 93.0–99.0% [36, 39–41].

>T1 Tumors

PN plays a vital role in treating select patients with >T1 RCC, such as those who would be rendered dialysis dependent after RN. The European Association of Urology recommends NSS for T2 RCC in selected patients [2]. In general, the available literature relies on pathologically diagnosed T2-3b and may not be unequivocally applicable to patients with clinically evident T2-3b disease prior to PN. The data from several studies reporting the oncologic outcomes of PN for T2-T3b RCC are reported in Table 13.3. A study from MD Anderson Cancer Center compared the oncologic efficacy of RN ($n = 567$) with PN ($n = 34$) for locally advanced RCC. The RN group had larger tumors with more advanced pathological stage. To control for the more advanced features in the RN group, multivariable Cox modeling was performed. In this analysis which included stage, grade, size, histology, and procedure type, PN versus RN was not an independent indicator of disease recurrence or RCC-specific mortality [43]. Breau et al. published a study comparing outcomes between RN ($n = 207$) and PN ($n = 69$) in populations matched for stage, tumor size, baseline renal function, age, and gender. There was no difference in the risk of cancer-specific survival (HR 0.80, $p = 0.5$) or overall survival (HR 1.11, $p = 0.6$) between the two groups [44].

The preceding data support a role for PN in select cases of advanced RCC. Unlike T1 RCC, however, the oncologic efficacy of PN remains uncertain due to the inherent selection biases in the aforementioned studies. In general, PN should be utilized in locally advanced RCC only in cases that are favorable for NSS and/or in patients where RN would result in hemodialysis dependence.

Table 13.3 Oncologic outcomes of open PN for >T1 RCC

Study	Number of patients per pathological stage	% elective	Follow-up (months)	Local recurrence	Disease-specific survival
Margulis et al.	T2–8	27%	62	0%	78%
	T3a – 22				
	T3b – 4				
Breau et al.	T2–32	42%	38	6%	83%
	T3a – 28				
	T3b – 9				
Karellas et al.	T2–34	86%	17	NR	89%
	T3a – 0				
	T3b – 0				

Adapted from Refs. [43–45]

Preserving Renal Function: The Rationale Behind PN

The risks and benefits of treatment options for localized RCC extend beyond simply perioperative morbidity and cancer-specific outcomes. Understanding the influence of RN versus PN on postoperative CKD is central to this discussion, as advanced stages of CKD have been associated with increased mortality and morbidity [46]. Table 13.4 defines the stages of CKD per National Kidney Foundation Disease Outcomes Quality Initiative CKD classification. The renal transplantation literature has been frequently cited as evidence to support the use of RN in patients with normal contralateral renal function, as kidney donors have similar risks of hypertension, renal dysfunction, and death compared with matched populations [47–49]. The donor nephrectomy and RCC populations are considerably different, however, as kidney donors tend to be young and lack medical comorbidities. On the contrary, 26% of patients with a renal mass and a normal contralateral kidney have preoperative Stage III–V CKD [12] while over 50% of patients with a renal mass in a solitary kidney have preexisting Stage III–V CKD [50, 51]. Pathological studies of nonneoplastic parenchymal tissue in nephrectomy specimens also show frequent evidence of underlying comorbidities. In a study of 110 specimens, only 38% had normal renal parenchyma, of which a majority exhibited pathologically evident vascular disease [52]. A greater decrement in renal function 6 months after surgery was demonstrated in patients with substantial pathological abnormalities compared to those with normal renal parenchyma [52]. The prevalence of preoperative CKD in RCC patients combined with the frequency of histologically evident renal parenchymal and vascular abnormalities in nonneoplastic tissue at the time of nephrectomy indicates a potential for significant post-nephrectomy renal impairment.

Table 13.4 National kidney foundation disease outcomes quality initiative CKD classification

Stage	Description	GFR (mL/min/1.73 m^2)
I	Kidney damage with normal or ↑ GFR	≥90
II	Kidney damage with mild ↓ GFR	60–89
III	Moderate ↓ GFR	30–59
IV	Severe ↓ GFR	15–29
V	Kidney failure	<15 (or dialysis)

Adapted from Ref. [53]

In 2004, Go et al. published a landmark paper demonstrating a graded association between degree of CKD and risk of cardiovascular events, hospitalization, and death [46]. This study included 1,120,295 adult patients in the Kaiser Permanente Renal Registry with a follow-up interval of 2.84 years. GFR was estimated using the Modification of Diet Renal Disease (MDRD) equation. Multivariable analysis controlling for demographics and comorbidities was performed to elucidate the relationship between CKD stage and adverse patient outcomes. A GFR >60 mL/min/1.73m^2 was used as the reference. As GFR

decreased, the risk of death increased (HR 1.2, 1.8, 3.2, and 5.9 for GFR 45–59, 30–44, 15–29, and <15 mL/min/1.73m^2, respectively). The adjusted HR for cardiovascular events and hospitalization also increased inversely with respect to GFR [46]. A study of 15,837 randomly selected patients from the Third National Health and Nutrition Examination Survey confirms the association between CKD and cardiovascular health. After adjustment in multivariable analysis, the presence of increasing numbers of cardiovascular risk factors was associated with a GFR <60 mL/min/1.73 m2 (odds ratios 1, 3.7, and 10.4 for 0, 1, and 2 risk factors, respectively, $p \leq 0.001$) [54].

In the early 2000s, investigators from both Memorial Sloan Kettering and Mayo Clinic reported a higher rate of renal failure (defined as serum creatinine >2.0 mg/dl) after RN compared to PN [32, 55]. Huang et al. published a retrospective cohort study from Memorial Sloan Kettering using the MDRD equation to estimate GFR in 662 patients with a single ≤4 cm renal tumor and normal contralateral renal function. They found that RN was associated with a lower 3-year postoperative probability of freedom from both GFR <60 mL/min/1.73m^2 (35% vs. 80%, $p < 0.0001$) and GFR <45 mL/min/1.73m^2 (64% vs. 95%, $p < 0.0001$) than PN. RN was an independent risk factor for the development of both GFR <60 mL/min/1.73m^2 (HR 3.82, $p < 0.0001$) and GFR <45 mL/min/1.73m^2 (HR 11.8, $p < 0.0001$) [12].

Several investigators have addressed whether enhanced renal preservation via NSS translates into improved overall survival and decreased risk of cardiovascular events compared to RN. Huang et al. performed an analysis of SEER-Medicare consisting of 2547 RN patients and 556 PN patients with T1a RCC. On multivariable analysis, RN was independently associated with an increased risk of cardiovascular events (HR 1.4, $p < 0.05$) and overall mortality (HR 1.38, $p < 0.001$). There was no association between RN and cardiovascular death or time to first cardiovascular event [13]. In a study from Mayo Clinic of ≤4 cm renal tumors, no difference was observed in overall survival when analyzing the entire cohort. In patients <65 years, however, RN was associated with an increased risk of overall mortality (relative risk 2.16, $p = 0.02$) after adjusting for comorbidities, preoperative creatinine, and year of surgery [56]. The trend toward improved overall survival with PN compared with RN has been studied in T1b renal tumors as well. Weight et al. performed a retrospective study of 212 PN and 298 RN patients with preoperative GFR > 60 mL/min/1.73m^2 and a normal contralateral kidney. New onset CKD was defined as postoperative GFR < 60 mL/min/1.73m^2. RN increased the odds of new onset CKD (odds ratio 3.4, $p < 0.001$) when controlling for gender, age, comorbidities, and preoperative renal function. Cancer-specific survival was equivalent between the two groups when adjusted for stage and grade. Multivariable models indicated that PN (HR 0.47, $p = 0.03$) and graded stratification of postoperative renal function ($p = 0.003$) independently predicted overall survival when controlling for pathological stage, age, and comorbidities [39].

Although the preceding evidence suggests that relative renal preservation by PN is associated with improved overall survival, several questions remain. Foremost, EORTC 30904 failed to show a survival benefit with PN [33]. Future studies will be required to elucidate the relative contributions of "surgically induced" renal failure and the continued effects of medical renal disease in postoperative patients. When planning surgery in RCC patients, urologists must consider the effects of surgical approach (RN vs. PN) on both oncologic control and renal function given the deleterious effects of CKD on postoperative morbidity and mortality.

Underutilization of PN

Despite equivalent oncologic outcomes and the potential benefits of minimizing postoperative CKD risk, PN remains underutilized. Data from the Nationwide Inpatient Sample compiled from 2003 to 2008 demonstrates that RN consisted of 79.3% of renal surgeries while PN comprised the remaining 20.7% [57]. There was a trend toward increasing PN use over the

study interval ($p < 0.001$) [57], and also the overall percentage of PN increased from a previous Nationwide Inpatient Sample study from 1988 to 2002 [58]. The Nationwide Inpatient Sample does not include information on tumor size, location, or histology. Given the downward stage migration of RCC, however, one would assume that a greater portion of detected renal masses would be amenable to NSS than the 20.7% frequency of PN reported in this sample. A retrospective study analyzing the NCDB stratified PN rates by clinical stage (cT1a, cT1b, and T2a), all of which they found to increase over time. They reported that the rate of PN for cT1a RCC tumors increased from 46.4% in 2004 to 76.8% and for cT1b RCC tumors increased from 13.7% to 37.1% in 2013 [59]. Despite these trends, PN remains underutilized in these stages, where it is considered standard of care in most cases [1, 2].

Although not the only criteria impacting PN feasibility, tumor size is an important determinant in tumor complexity and is available in the SEER database. Dulabon et al. reported the use of PN in 18,330 patients from the SEER registry with ≤4 cm renal tumors from 1999 to 2006. A total of 6460 (35%) patients underwent PN, and the ratio of PN to RN increased every year ($p < 0.001$) with PN comprising 45% of renal surgeries in 2006. Additional analysis demonstrated noteworthy disparities in PN utilization in women, elderly, rural patients, patients with an earlier year of surgery, and patients with a larger tumor size [60].

Compared with population-based studies, tertiary care centers perform a higher percentage of PNs for T1 renal tumors. In a study of six European centers from 2004 to 2007, PN comprised 86.3% of renal surgeries for <2 cm tumors, 69.3% of renal surgeries for 2.1–4 cm tumors, and 35.3% of renal surgeries for 4.1–7 cm tumors [61]. Investigators from Memorial Sloan Kettering reported a similar trend with an increasing usage of PN from 2000 to 2007. In 2007, the frequency of PN was 89% for tumors ≤4 cm and 60% for tumors 4.1–7 cm [62]. Future endeavors aimed at understanding the underlying rationale for PN underutilization, and addressing these issues is paramount for widespread acceptance of PN throughout the urologic community.

Adoption of Minimally Invasive Techniques

Minimally invasive surgery has been increasingly common overall, because of similar long-term outcomes with shorter recovery times in many surgeries. This scenario is the case for renal surgery, where traditionally open procedures are increasingly being replaced with laparoscopic or robotic-assisted partial or radical nephrectomies when feasible.

One cross-sectional study of renal surgical from state records in Maryland analyzed the trends in surgical approaches in renal surgery. Consistent with other literature [57–59], this study reported an increase in PN utilization for small renal tumors [63]. Despite the increase in PN overall, the proportion of laparoscopic RN also increased, whereas rates of laparoscopic PN remained low [63], likely related to the steep learning curve and technical difficulty of the procedure [64]. By contrast, the wider use of robotic technology for PN drastically increased over a very short time, from just 2% of all PNs in 2008 to 44% of PNs [64].

Despite the enthusiasm for minimally invasive techniques due to advantages such as shorter hospital stay and lower blood loss and shorter warm ischemia time [65], the adoption of minimally invasive techniques may not have been uniformly beneficial, with recent studies positing a correlation between minimally invasive techniques and increased rates of positive surgical margins [59, 66, 67]. A separate study found that positive surgical margins after partial nephrectomy were associated with increased risk of recurrence in masses with high-risk features [68]. It is clear that there is a role for both open and minimally invasive partial nephrectomy. The findings emphasize the critical role of proper patient selection for RN and PN.

Objective Analysis of Tumor Complexity

In the 2017 AUA Renal Mass and Localized Renal Cancer Guideline, it states that for clinical T1 renal masses, nephron-sparing approaches should be prioritized whenever intervention is indicated [1]. Partial nephrectomy feasibility was not defined. Differences in opinion between surgeons regarding the feasibility of partial nephrectomy may contribute to the variability in use of partial nephrectomy described above. An important characteristic that determines whether or not partial nephrectomy is feasible is the technical complexity of the tumor [68]. Traditionally, tumors were described with nonstandardized, subjective terms such as central, hilar, deep, superficial, exophytic, or endophytic. This descriptive approach was not quantifiable for research or comparative studies, making it impossible to compare series, techniques, or surgeons with rigor. Inability to quantify tumor complexity may contribute to lack of uniformity in the assessment of partial nephrectomy feasibility and, consequentially, may lead to variability in care of the small renal mass.

Starting in 2009, three systems were introduced that aimed to quantify the anatomic characteristics of renal masses in a reproducible way with meaningful clinical correlation: the RENAL nephrometry score, the Centrality Index (C-Index), and the PADUA classification [69–71]. The RENAL nephrometry scoring system was described by Uzzo in 2009 ([69], Table 13.5). Points are assigned to four morphometric tumor variables: diameter, exophytic versus endophytic properties, proximity to collecting system or renal sinus, and the tumor's location relative to the polar lines and axial midline (Fig. 13.1). Points are added together with total scores of 4–6, 7–9, and 10–12 corresponding to low, moderate, and high tumor complexity, respectively. A qualitative descriptor "h" is added after the nephrometry score if the lesion abuts the main renal artery or vein. A second descriptive term is added to describe the tumor's anterior (a) or posterior (p) location (or "x" if it the tumor cannot be described as anterior or posterior).

The Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) classification schema shares many similarities with the RENAL nephrometry score [71]. Points are also assigned to anatomical features, and an "a" or "p" classifier is also used to denote anterior or posterior location, respectively (Table 13.6).

The C-Index also aims to quantify the complexity of renal masses, but does so with a geometric approach [70]. The C-Index assesses the proximity of the tumor center to the kidney center and puts this value in context of the tumor size (Fig. 13.2). This schema makes use of the Pythagorean theorem in which the square of the hypotenuse (c) of a right-angle triangle is equal to sum of the squares of the other two sides (a and b) of the triangle (i.e., $a^2 + b^2 = c^2$). Using axial imaging, the vertical distance from the kidney center to the level of the maximum tumor diameter is measured, as is the horizontal distance from the kidney center to the tumor center. The hypotenuse is then

Table 13.5 RENAL nephrometry scoring system

Variable	1 point	2 points	3 points
Diameter (cm)	≤4	>4 and <7	≥7
Exophytic	≥50%	<50%	100% endophytic
Nearness to collecting system or renal sinus (mm)	≥7	>4 and <7	≤4
Anterior/posterior	Qualitative descriptor of "a," "p," or "x"; no points		
Location relative to polar lines	Above upper or below lower polar line	Crosses polar line	More than 50% across polar line, entirely between polar lines, or crosses axial midline

Kutikov and Uzzo [69]

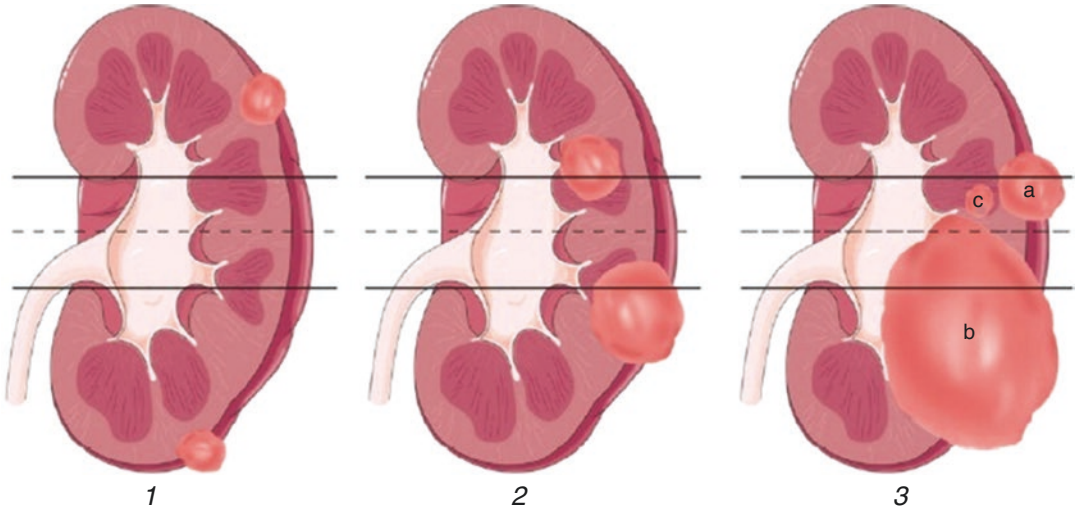

Fig. 13.1 The L component of RENAL nephrometry score characterizes a tumors' location relative to the polar lines. A sagittal depiction of the kidney demonstrates the polar lines (solid) and renal axial midline (dashed), with the points (1, 2, or 3) that would be assigned to each tumor. The RENAL nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location, and depth. (J Urol. 2009;182(3):844–53)

Table 13.6 The PADUA classification scoring schema

Variable	1 point	2 points	3 points
Polar location	Polar	Interpolar	–
Exophytic	≥50%	<50%	100% endophytic
Renal rim	Lateral	Medial	–
Renal sinus	Uninvolved	Involved	–
Collecting system	Uninvolved	Displaced or invaded	–
Diameter (cm)	≤4	>4 and ≤ 7	>7

Adapted from Ref. [71]

the distance from the kidney center to the tumor center (c). The tumor radius (r) is measured. The C-Index is calculated, where C-Index = c/r. A C-Index of 0 indicates that the tumor center is in the kidney center, while a C-Index of 1 indicates that the tumor periphery abuts the kidney center. The larger the C-Index, the further is the tumor center from the kidney center.

There is retrospective evidence that these morphometric systems correlate with clinical markers of complexity, specifically a surgeon's choice of operation and approach, surgical technique including ischemia time and parenchymal preservation, as well as surgical outcomes and pathology. In a 2009 survey of members of the American Urologic Association, respondents were shown eight tumors with RENAL nephrometry scores ranging from 4 to 10 [68]. On multivariate analysis, each additional RENAL nephrometry score point increased the odds of a surgeon choosing to perform a radical nephrectomy instead of partial nephrectomy (OR 1.59, 95% CI 1.27–1.95). Respondents who were more likely to choose partial nephrectomy were high volume kidney surgeons (OR 1.57), high volume partial nephrectomy surgeons (OR 3.7), younger (OR 1.64), and in academic practice (1.80). The willingness of a surgeon to perform partial nephrectomy appears to be linked to tumor complexity, but the complexity threshold that triggers radical nephrectomy appears to vary among surgeons.

These findings are supported by retrospective data from clinical practice. In a single-institution retrospective review, Broughton et al. assessed 154 patients with clinical T1a renal tumors, of whom 120 (77.9%) had a planned partial nephrectomy [72]. Independent predictors of planned partial nephrectomy included tumor size, with each 1 cm decrease in diameter increasing the OR of partial nephrectomy 2.2-fold ($p = 0.011$). Tumor complexity was also an independent predictor, with each 1 point decrease in RENAL nephrometry score increasing the OR

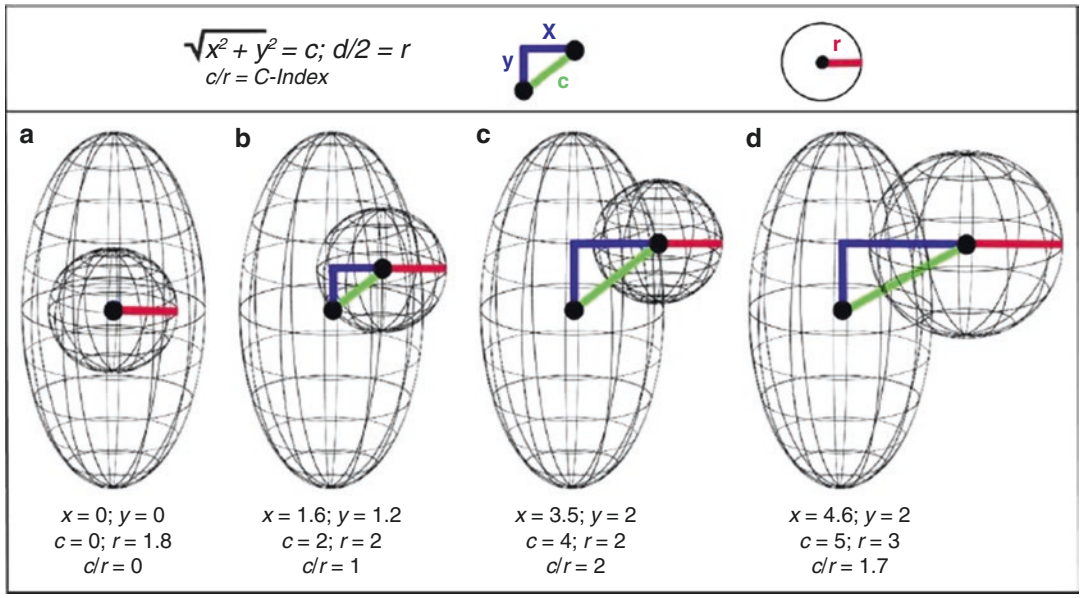

Fig. 13.2 The C-Index method uses the Pythagorean theorem to measure the distance between kidney center and tumor center, c (green line), which is the hypotenuse of a triangle formed by x and y (blue lines). Dividing c by r (red line) yields the C-Index kidney tumor location measurement using the C-Index method. (J Urol. 2010;183(5):1708–13)

of partial nephrectomy 2.4-fold ($p < 0.001$). Similar retrospective studies have shown that increasing RENAL nephrometry score is significantly associated with the use of radical instead of partial nephrectomy, and open instead of minimally invasive partial nephrectomy [73, 74].

The morphometric systems have also been found to correlate with technical aspects of partial nephrectomy including ischemia time and percentage of functional kidney volume preserved [75–78]. In a single-institution retrospective review, Simmons et al. calculated RENAL nephrometry score and C-Index for 237 partial nephrectomy patients and estimated the percentage of functional kidney volume that was preserved using postoperative imaging [78]. They noted that increasing tumor complexity was associated with parenchymal loss, with each 1 unit increase in RENAL nephrometry score correlating with a 5% decrease in functional volume preservation. Similarly, each 0.5 unit decrease in C-Index correlated with a 3% decrease in functional volume preservation.

Higher PADUA and RENAL nephrometry scores and lower C-Index have been associated with a higher risk of overall complications, including urine leak [71, 75, 76, 79, 80]. In addition, the morphometric systems may also be predictive of renal functional outcomes. For instance, the rate of ≥30% decrease in estimated GFR was significantly higher among patients with a C-Index ≤2.5 than those with C-Index >2.5 (70% vs. 32%, $p < 0.01$) [76].

It appears that quantitative scoring of tumor complexity by RENAL nephrometry score, PADUA classification, and C-Index may be a valuable addition to the clinical research armamentarium. The relative predictive abilities of the three systems remain unclear. Comparative research is needed, as are efforts to delineate the role of these systems in determining the feasibility of partial nephrectomy in moderate and highly complex lesions.

Preoperative Evaluation

A thorough preoperative evaluation is essential for patients undergoing open partial nephrectomy. The goals of the preoperative evaluation

are clinical TNM staging, identifying and treating comorbid disease, selecting the proper patients for surgery, as well as reducing the risk of perioperative complications.

Cardiopulmonary Evaluation

Preoperative vigilance may identify patients at elevated risk of cardiopulmonary complications and allow for presurgical intervention. It has been recommended that cardiologists should evaluate and treat patients with unstable angina, decompensated heart failure, arrhythmias, substantial heart valve disease, and known or suspected coronary artery disease prior to noncardiac surgery [81]. A urologist should also inquire about cardiovascular symptoms and risk factors and refer for evaluation accordingly. Risk stratification tools such as the Revised Cardiac Risk Index may be helpful for preoperative risk stratification. The Revised Cardiac Risk Index is composed of six independent predictors of cardiac complications after major noncardiac surgery: high-risk surgical procedure (intraperitoneal, intrathoracic, suprainguinal vascular), ischemic heart disease, congestive heart failure, cerebrovascular disease, preoperative insulin use, and preoperative serum creatinine >2 mg/dL [82].

Predictors for pulmonary complications following noncardiothoracic surgery include chronic obstructive pulmonary disease, age >60 years, smoking, American Society of Anesthesiologists (ASA) Class ≥2, inability to perform activities of daily living, congestive heart failure, pulmonary hypertension, and low serum albumin [83, 84]. Patients without these risk factors may still be at risk for pulmonary complications due to surgical positioning and the surgical wound, since upper abdominal surgery and surgery that lasts >3 hours are both independent predictors of pulmonary complications [84]. A pulmonary evaluation with chest x-ray, arterial blood gas, pulmonary function tests, and consultation by a pulmonologist may benefit some of these patients. Smokers should quit prior to surgery [83]. An anterior surgical approach may be preferable to a flank approach in patients with pulmonary risk factors.

Renal Evaluation

Assessment of renal function by urinalysis and serum creatinine is mandatory before partial nephrectomy, especially in light of the high rate of preexisting chronic kidney disease among patients with renal tumors [12] Methods of estimating kidney function include serum creatinine, 24-hour creatinine clearance, radionuclide imaging such as technetium-99 diethylenetriaminepentaacetic acid, or estimating GFR using equations such as the Modification of Diet in Renal Disease (MDRD) equation [85]. Although serum creatinine and estimates of GFR based on serum creatinine such as the MDRD equation may not be as accurate as a 24-hour urine collection or radionuclide imaging, they are commonly employed, relatively inexpensive, and typically adequate for clinical purposes.

Imaging

Adequate preoperative imaging is mandatory to identify locally advanced tumors or metastatic disease as well as to define regional anatomy and to characterize the renal vasculature. Renal angiography used to be commonly employed prior to partial nephrectomy, but it has been replaced by 3D CT angiography (CTA) at most centers. CTA is noninvasive and provides detailed anatomic images by incorporating arteriography, venography, excretory urography, and CT data into a single imaging modality. CTA can delineate renovascular anatomy including the subsegmental branches supplying the tumor, as well as renal tumor location, depth, and proximity to the collecting system [86]. In addition, preoperative imaging helps identify surgically relevant anatomic variants such as multiple renal arteries, retroaortic or circumaortic left renal vein, and duplex collecting system.

Prophylaxis

Partial nephrectomy patients should have a preoperative urinalysis and culture to screen for bacteriuria. If a urinary tract infection or bacteriuria is discovered, antibiotics should be administered

to sterilize the urine prior to surgery, especially in lesions in which collecting system entry is anticipated. The American Urologic Association recommends mechanical VTE prophylaxis (intermittent pneumatic compression devices or compression stockings) in all patients undergoing open surgery and consideration of pharmacologic VTE prophylaxis in patients with elevated risk for VTE [87, 88]. The use of pharmacologic VTE prophylaxis in partial nephrectomy is controversial [89]

Surgical Techniques

Broadly speaking, the steps of performing open partial nephrectomy are incision and surgical approach, isolation and control of the renal hilum, mobilization of the kidney while preserving the perinephric fat overlying the tumor, and tumor excision. This process is followed by renorrhaphy with hemostasis, collecting system repair if needed, and repair of the parenchymal defect.

Approach

Choosing a favorable surgical approach is the first step in a successful partial nephrectomy. The ideal approach provides excellent access to the kidney, renal vasculature, and tumor while minimizing wound-related morbidity. The position of the kidney relative to the ribs impacts the level of a flank incision and should be assessed on preoperative radiographic studies. Other factors to consider include the tumor location and size.

There are numerous surgical approaches to the kidney. For partial nephrectomy, the primary approaches are the supracostal flank, transcostal (classic) flank, and anterior subcostal incisions. Turner–Warwick described a rib-sparing extraperitoneal, extrapleural supracostal flank incision that is favored at some institutions [90]. For very large upper pole tumors, a thoracoabdominal approach can be useful. An 8-cm "mini-flank" supra 11th rib incision has been described as an effective alternative for radical or partial nephrectomy [91]. Other approaches to the kidney such as anterior midline, the dorsal lumbotomy, and subcostal flank incision are rarely if ever the most favorable approach for partial nephrectomy.

Vascular Control

After the surgical approach is complete and retraction is in place, controlling the renal pedicle is the initial priority with rare exceptions. The main renal artery and vein should be carefully dissected from surrounding structures. Vessel loops can be used to encircle the renal artery and vein without compromising blood flow. Establishing control of the renal vasculature gives the surgeon the ability to rapidly occlude the artery if necessary to stop unanticipated and uncontrolled bleeding.

Kidney Mobilization

Having established vascular control, one can proceed with mobilizing the remainder of the kidney. Gerota's fascia is opened. The ureter should be identified to reduce risk of ureteral injury. It can be tagged with a vessel loop for identification. Great care should be taken to avoid injuring its blood supply. The kidney is mobilized within the perirenal fat, though the fat overlying the tumor should be left undisturbed in case there has been occult fat invasion. Mobilizing the kidney within the fat can be performed sharply or with cautery. It can be time-consuming and challenging in patients with prior kidney infections or other inflammatory processes that result in "sticky fat." Nevertheless, adequate mobilization of the kidney is an essential step in a high-quality, safe partial nephrectomy.

Vascular Clamping

During tumor excision and portions of renorrhaphy, the segmental artery supplying the tumor or the main renal artery is temporarily occluded with a vascular clamp. The purpose of clamping is to reduce intraoperative bleeding and improve visualization. Another proposed benefit is to ease

access to intrarenal structures by reducing tissue turgor.

Traditionally, mannitol is given intravenously 5–10 minutes before temporary renal arterial occlusion [92–94]. Recent research, including a randomized controlled trial, however, found that mannitol administration did not impact long-term renal function 6 months after partial nephrectomy [95, 96]. Anticoagulation to prevent intrarenal thrombosis is not necessary. The renal vein is not clamped, which may permit some oxygenation despite arterial occlusion [97–99]. In open partial nephrectomy, the kidney may be cooled immediately after clamping to protect against ischemic renal injury. The entire kidney is surrounded by ice slush for 10–15 minutes to obtain a core kidney temperature of approximately 20 ° C, which permits as much as 3 hours of ischemia time [94]. In cases where ischemia time is anticipated to be short, warm ischemia may be a reasonable option. Safe limits of warm ischemia have been proposed. Limits of 20 and 35 minutes have recently been advocated as safe [93, 100]. The clinical impact of ischemia time, if limited, remains unclear. The ischemia time itself may be a secondary variable with the quality and quantity of the preserved nephrons being the most important variable. Nonetheless, some data suggest that there is no safe limit of warm ischemia, with each additional minute increasing the risk of acute renal failure, chronic kidney disease, and end-stage renal disease [101].

An open non-clamping technique has been described in detail [50, 102] to eliminate the potential impact of ischemia. The kidney is mobilized as described above. Similar to clamping partial nephrectomy, the hilar vessels are dissected out, and nonocclusive control is obtained with vessel loops in case vessel clamping is needed (Fig. 13.3). The perirenal fat overlying the tumor is left in situ (Fig. 13.4). Margins are marked out with the aid of intraoperative ultrasound.

The renal capsule is opened either sharply with tenotomy scissor or with handheld electrocautery. The renal parenchyma is opened with a tenotomy scissor circumferentially. Penfield dissectors are used to split the parenchyma, leaving a thin rim of grossly normal parenchyma on the tumor (Fig. 13.5). A Frazier pediatric suction is used to keep the base of the nephrotomy free of blood. It also serves to locate cortical vessels which can be either coagulated if small or tied with 4-0 absorbable suture and divided

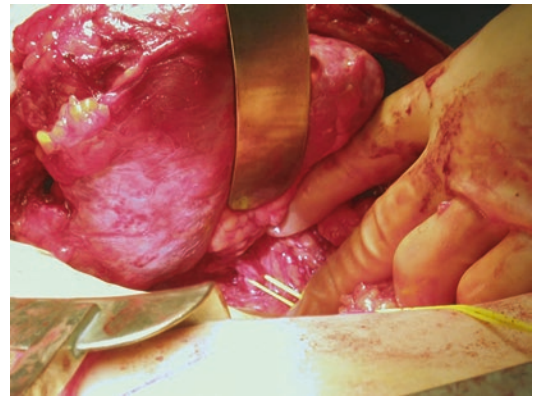

Fig. 13.3 Vascular control

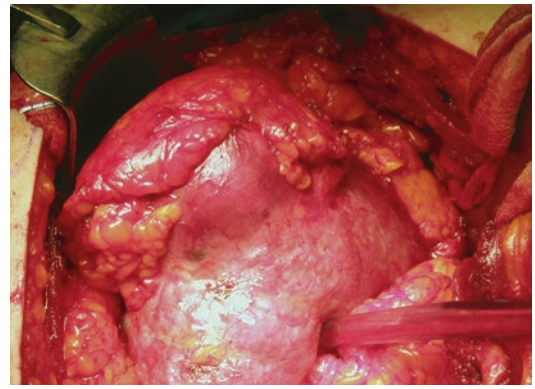

Fig. 13.4 Preservation of perinephric fat

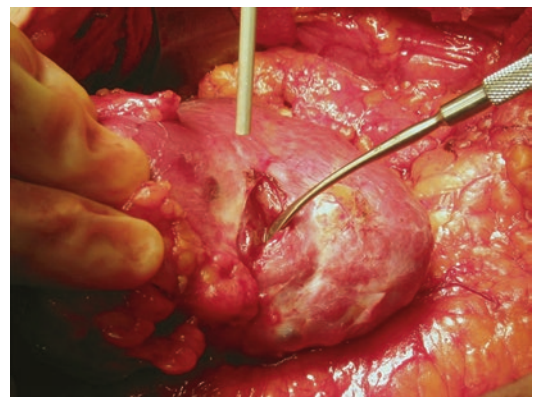

Fig. 13.5 Cleavage plane between tumor and normal parenchyma

(Fig. 13.6). At the base of the tumor, the specimen is gently lifted, and the remaining larger vessels can be clamped with a small right-angle clamp, divided and tied (Figs. 13.7, 13.8, and Video 13.1). The specimen is inked to grossly evaluate resection margins. Frozen sections can be obtained if there is any question of a positive margin. In the case of a positive margin, additional tissue can be resected. Hemostasis and renorrhaphy proceed as described above. One advantage of non-clamping is that indigo carmine can be given intravenously to permit evaluation for openings in collecting system. In cases of brisk hemorrhage, which is rare with experience, the surgeon can either clamp the renal vessels, apply manual compression adjacent to the cut renal parenchyma, or apply pressure with a Kittner dissector to a bleeding vessel. The non-clamping technique allows excellent preservation of normal parenchyma, even with entirely endophytic tumors which can be approached through the hilum and sinus using Gil–Vernet's techniques and selective ligation of tertiary and quaternary arteries or via a capsular nephrotomy.

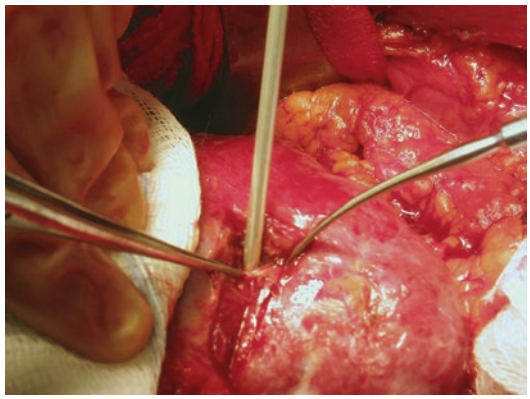

Fig. 13.6 Coagulation of small arteries at the corticomedullary junction

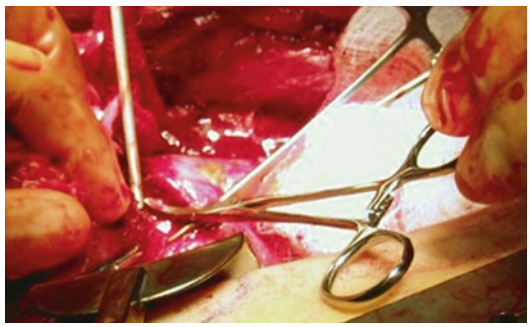

Fig. 13.7 Ligation of larger intrarenal arteries at the tumor base

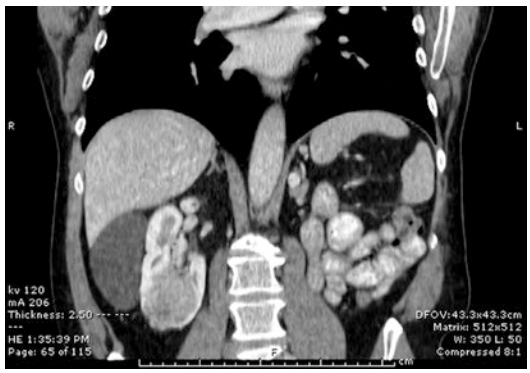

Fig. 13.8 Lower pole tumor—solitary kidney

Excision of the Tumor

Once clamped and cooled, partial nephrectomy can proceed. There are various techniques of partial nephrectomy that can be employed, but all aim to fully excise the tumor with reliably negative margins and maximal preservation of functional parenchyma. There are a variety of partial nephrectomy techniques which include simple enucleation, polar nephrectomy, hemi-nephrectomy and wedge resection, or resection of the tumor with a thin rim of normal parenchyma.

In enucleation, the tumor is separated from the surrounding normal parenchyma along a natural plane provided by the tumor pseudocapsule. No margin of normal parenchyma is taken. Most often, this technique is employed in patients with an inherited kidney cancer syndrome or multiple tumors [103]. Enucleation has traditionally been avoided in sporadic RCC due to concerns about local recurrence, as the tumor may extend for several millimeters through the pseudocapsule [104–107]. When enucleation is employed, it may be beneficial to ablate the resection margin to reduce the risk of recurrence [108]. In most cases, techniques that remove the tumor along

with a margin of normal parenchyma are preferable to enucleation.

Polar nephrectomy can be employed for tumors that are limited to one pole of the kidney. Traditionally, this technique involved ligating and dividing the segmental apical or basilar artery supplying the upper or lower pole of the kidney, respectively. This selective vascular control results in a line on the kidney surface demarcating the ischemic pole from the rest of the kidney that remains perfused. The ischemic, tumor-bearing pole of the kidney is then excised along the line of ischemia. An alternative approach that we favor is to define the limits of resection by a thin rim of normal parenchyma around the tumor and not by the territory supplied by the segmental artery. This process permits preservation of polar parenchyma that is uninvolved by tumor. Large tumors that extensively involve the upper or lower portion of the kidney should be excised by heminephrectomy.

Centrally located tumors can prove particularly challenging given their intimate association with the renal hilum and collecting system. One option is to create an overlying radial or Y-shaped nephrotomy to expose the underlying tumor, which can then be excised by enucleation or with a thin rim of parenchyma. Alternatively, the tumor can be approached via the hilum using the intrarenal surgical techniques of Gil–Vernet. Small intrarenal venous branches can be ligated to improve exposure without compromising venous return. Segmental arteries supplying the tumor are divided. The tumor is excised, along with neighboring renal sinus fat if possible. Often no normal adjacent tissue can be excised, and the tumor is essentially enucleated from the sinus.

Regardless of the surgical technique employed in partial nephrectomy, complete tumor excision should be confirmed in the operating room. Intraoperative ultrasound can be employed to prospectively delineate resection margins and to identify additional occult tumors that are a source of ipsilateral recurrence [109, 110]. Frozen section can be employed to evaluate for margin status. As long as the margin is negative, the size of the negative margin is not thought to be important [111]

Renorrhaphy

After excision of the tumor, the transected blood vessels on the renal surface are secured with figure-of-eight 4-0 Monocryl sutures. The argon laser can used to achieve hemostasis on the renal cortex, but it should be used with caution as it may disrupt sutures or injure the collecting system. Openings in the collecting system should be carefully repaired with 4-0 Monocryl sutures. One can improve identification of collecting system defects by injecting methylene blue or indigo carmine either intravascularly or directly into the renal pelvis. Although it is rarely necessary, a ureteral stent can be placed in a retrograde fashion at the start of the procedure if significant repair of the intrarenal collecting system is anticipated. Alternatively, a stent can be placed antegrade over a wire through the opening in the collecting system.

Once suturing of vessels and collecting system is complete, a bolster can be placed in the defect, though this is often not necessary if the cortical edges can be adequately opposed. The bolster can be composed of rolled Surgicel® or other absorbable hemostatic products. Floseal® (Baxter International Inc., Deerfield, IL, USA) or other hemostatic gels can also be used. The edges of the renal cortex are reapproximated, over the bolster if one is used, with pledgeted interrupted 2-0 polygalactic sutures, ensuring that the renal vessels are not kinked or obstructed. These edges can be secured with knots or with a Weck clip (Pilling Weck Canada, L.P., Markham, ON, Canada) and a Lapra-Ty® clip (Ethicon Endosurgery, Cincinnati, OH, USA). If the renal artery was clamped, then it can be unclamped immediately after obtaining hemostasis or after the entire renorrhaphy is complete. A retroperitoneal drain should be placed, but can be omitted in small, superficial tumors in which the collecting system was not entered [112].

Addressing the Adverse Impact of Ischemia

Partial nephrectomy can be associated with a postoperative decline in renal function [97, 113, 114]. Numerous factors contribute to the decline

in GFR after partial nephrectomy, including those that are not modifiable such as older age, female gender, larger tumor size, as well as solitary kidney and preexisting renal dysfunction [97, 113, 114]. Modifiable factors that contribute to decreased GFR include reduction in functional renal parenchyma and ischemic injury [92, 101, 114–116]. Even when accounting for the percentage of functional renal parenchyma preserved after partial nephrectomy, renal ischemia is independently associated with postoperative renal dysfunction [116]. In a bi-institutional study of nephron-sparing surgery in solitary kidneys, warm and cold ischemia were associated with higher risk of acute ($p < 0.001$) and chronic ($p = 0.027$) renal failure, need for temporary dialysis ($p = 0.028$), as well as urine leak ($p = 0.006$) when compared with partial nephrectomy without clamping [100].

To address the adverse impact of renal ischemia, several investigators have proposed performing partial nephrectomy with the kidney fully perfused and described above [50, 117–119]. In a partial nephrectomy series in 158 patients with solitary kidneys when nadir GFR was measured during postoperative days 7–100, the non-clamping cohort was found to have a lower percentage decrease versus the clamping cohort (11.0% vs. 16.1%, $p = 0.08$) [50]. Additionally, when measured during postoperative days 101–365, there was a 27.7% decrease in GFR from preoperative GFR in the clamping group compared to 11.8% in the non-clamping group ($p = 0.01$). These data suggest a progressive renal insult after 100 days in the clamping group [50]. Despite this analysis, it remains unclear if zero ischemia has a clinically significant benefit over traditional short-duration warm ischemia.

A multivariate analysis of patients undergoing PN, which included tumor size, location, and focality as well as CKD risk factors, found that clamping was the only significant covariate. However, this study did not control for the percentage of functional parenchyma preserved [116]. Further analysis by the same authors suggests that ischemia is a secondary factor when accounting for the percentage of parenchyma that is preserved, which is a more important indicator [116]. There was no difference in median estimated blood loss between the non-clamping and clamping groups (900 vs. 1000 mL, $p = 0.86$). The 5-year RCC-specific survival (excluding patients undergoing cytoreductive nephrectomy) was also similar between the non-clamping and clamping cohorts (79% vs. 75%, $p = 0.68$). Of note, while it is theorized that clamping may improve visualization, this process has not lead to better surgical margins. In patients with two functioning renal units, margin rates were similar between the clamping and non-clamping groups (6% vs. 4.7%) [117].

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14 Minimally Invasive Partial Nephrectomy and Ablative Procedures for Small Renal Masses

Shanta T. Shepherd, Egor Parkhomenko, and David S. Wang

Introduction

The advent of computed tomography (CT) and magnetic resonance imaging (MRI) in the twenty-first century has resulted in an increased identification of incidental findings such as small renal masses (SRMs) [1]. Traditionally, contrast-enhancing renal masses on cross-sectional imaging were treated with a radical nephrectomy. In an effort to accommodate for the increased incidence of SRMs, and reduce the morbidity of a radical nephrectomy, nephron-sparing techniques such as a partial nephrectomy (PN) and ablative therapy have risen. PN provides comparable oncological outcomes for T1–T2 renal tumors while preserving the renal parenchyma and reducing the incidence of cardiovascular events [2–4]. The American Urological Association (AUA) currently recommends a PN for renal masses <4 cm [5]. Initial indications for minimally invasive partial nephrectomy (MIPN) were limited to SRMs, but improved technology and skill set has evolved to include more complex lesions [6]. Other nephron-sparing procedures are also available without compromising oncologic outcome [7, 8]. Improvements in technique and histological assessment have affected the surgical approach by way of a renal biopsy. In addition, technological advances in the form of augmented and virtual reality are beginning to enter the operating room and improve preoperative. In this chapter, we provide an update on the minimally invasive surgical techniques of laparoscopy and robotic-assisted laparoscopy, ablative techniques, as well as associated complications.

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Laparoscopic Partial Nephrectomy

Patient Selection

There are several factors which should be taken into account when selecting a patient for minimally invasive partial nephrectomy (MIPN). These factors are similar when performed laparoscopic partial nephrectomy (LPN) as well as robot-assisted laparoscopic partial nephrectomy (RALPN). Medical comorbidities such as cardiac and pulmonary disease can affect a patient's ability to tolerate pneumoperitoneum. Patients with severe chronic obstructive pulmonary disease are at risk for developing severe hypercarbia and acidosis [9]. The increased intraabdominal pressure induced by peritoneal insufflation is transmitted to the thoracic cavity decreasing cardiac performance [10]. Surgical history should be carefully reviewed when determining the appropriate surgical approach, as it may affect port site location. Some cases may require extensive lysis of adhesions as well as potentially conversion to open procedure. Obese patients present an additional

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challenge in that anatomic landmarks may be shifted [11]. Eaton et al. [12] demonstrated that there was a correlation between obesity and intraoperative blood loss; however, there is an overall difference in intraoperative time and transfusion rate. LPN can safely be performed in obese patients without increased morbidity [12–14]. A preoperative magnesium citrate bowel preparation has historically been given to all patients to reduce the potential risk of infection, though this is increasingly being challenged with evidence showing no difference in infection risk or return of bowel function [15, 16]. In our experience, the bowel preparation is also preferred as it provides bowel decompression which improves intraoperative visualization.

Cross-sectional imaging should be carefully reviewed for identification of tumor location and proximity to the collecting system, number of vessels, and lymphadenopathy. The RENAL nephrometry score may be used to further classify renal lesion complexity [17].

Patient Positioning

Prior to positioning patient, a time-in is performed confirming patient identity, team members, medication concern, and laterality of surgery. Once general endotracheal anesthesia is induced, it is the authors' preference to perform a flexible cystoscopy with the placement of an open-ended catheter into the ipsilateral ureter. Dilute methylene blue can then be injected in a retrograde fashion in ordered identify entry into the collecting system and ensure adequate closure and prevention of urine leak. Bove et al., however, demonstrated no difference in urine leak with use of ureteral catheter versus no catheter [18].

In the transperitoneal approach, the patient is placed in a 45° modified flank position, as opposed to full flank position in the retroperitoneal approach with the ipsilateral side facing upward. The table is maximally flexed. Arms are then positioned on padded arm boards and secured in place in order to avoid brachial plexus injury. An axillary roll is typically used. The contralateral lower extremity is bent 90° and ipsilateral leg straight with pillows placed between the legs. All bony prominences are also carefully padded. Lower extremity sequential compression devices are utilized on all patients. The flank and shoulder are also supported, and the shoulders, hips, and lower extremities are secured with towels and tape in order to prevent movement with table rotation. The head is placed in a neutral position. Prior to propping and draping the patient, laterality is again confirmed. The patient's abdomen and flank are prepped widely including the ureteral stent and foley catheter, which are secured with tegaderm in order to allow for injection of methylene blue. Wide preparation also allows for potential conversion to open surgery.

Positioning of the patient is critical to the prevention of rhabdomyolysis and neuropathies, though despite careful attention to positioning, rhabdomyolysis has been reported [19, 20].

Access

Transperitoneal

As mentioned above, the patient is placed in a 45° modified flank position. A 12-mm incision is made at the ipsilateral border of the rectus muscle at a midpoint between the umbilicus and the anterior superior iliac spine. We prefer to obtain intraperitoneal access is obtained via Veress technique; however, Hassan (open) may also be used. Pneumoperitoneum is achieved to 15 mmHg [21]. Remaining trocars are placed under direct vision. Depending on laterality of tumor, a 12-mm subcostal port is placed on the contralateral side for the surgeon's hand. The camera port is placed also using a 12-mm trocar, medial and caudal to the subcostal trocar. A 12-mm trocar is placed for the assistant along the anterior axillary line. A 5-mm subxiphoid trocar is inserted for liver retraction in cases of right-sided tumor (Fig. 14.1).

Retroperitoneal

In full flank position, a 12-mm incision is made in the posterior axillary line between the iliac crest and the tip of the 12th rib, and a working

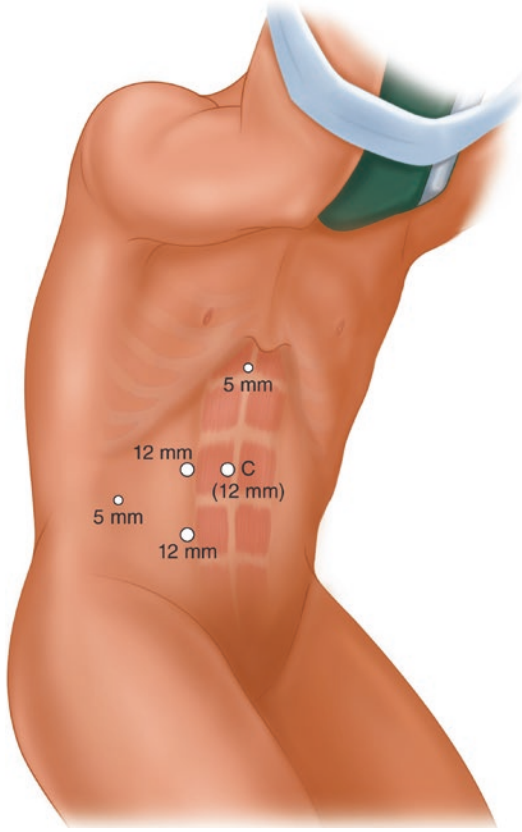

Fig. 14.1 Transperitoneal laparoscopic partial nephrectomy. (Original work submitted by the authors.) Key: C – camera port

space is created using blunt dissection; a blunt tip trocar is then inserted through the incision. A 5-mm port is placed at the tip of the 12th rib, a 12-mm port along the axillary line at the level of the umbilicus, and a 12-mm port in the midaxillary line just superior to the umbilicus [22] (Fig. 14.2). While retroperitoneal access is technically more challenging due to reduced working space, it is ideal for posterior tumors and avoids the risk of bowel injury, particularly in patients with prior abdominal surgery. Transperitoneal and retroperitoneal approaches have been shown to have similar outcomes, including blood loss, complications, and postoperative creatinine [23].

Hand-Assisted

Hand-assisted LPN allows for hand-facilitated dissection, suturing, and hemostasis, while maintaining the cosmesis of minimally invasive surgery. When the surgeon's dominant hand is contralateral to the tumor side, a periumbilical working port is made for the nondominant hand [24]. However, in ipsilateral cases, for instance, when right-handed surgeons operate on right-sided tumors, the hand incision is made in the ipsilateral lower quadrant for the dominant hand. In order to preserve pneumoperitoneum, the incision made is based upon the size of the surgeon's hand. Our institution uses the GelPort Laparoscopic System (Applied Medical, Rancho Santa Margarita, CA) to further prevent loss of pneumoperitoneum. Two or three additional ports may be placed dependent upon tumor location and surgeon preference. An example of trocar placement at our institution for a right-sided case is as follows: a 12-mm camera trocar is placed lateral to the rectus above the umbilicus. After using a 30-degree lens to ensure successful initial port placement, an additional 12-mm trocar is placed in the subxiphoid area, right midaxillary line, and right anterterior axillary line above the level of the umbilicus. The hand port is placed in the right lower quadrant as described above (Fig. 14.3).

Procedure

After access is obtained, the first step in the transperitoneal approach is medial mobilization of the colon (ascending or descending). For right-sided tumors, the hepatic flexure is mobilized and the duodenum is Kocherized. The gonadal vessels and ureter are identified, and the ureter is retracted laterally while keeping the gonadal vein medial adjacent to the inferior vena cava. On the left, the splenorenal, splenocolic, and splenophrenic ligaments are released, and the spleen and pancreas tail are mobilized medially. The gonadal vessels and ureter are identified and retracted laterally. Prudent dissection of the ureter is critical to preventing devascularization. The renal hilum is dissected with care taken to identify accessory vessels. Hyams et al. [25] describe the use of Doppler ultrasound to aid in the identification of these vessels not previously seen on cross-sectional imaging, whereas Wang et al. [26]

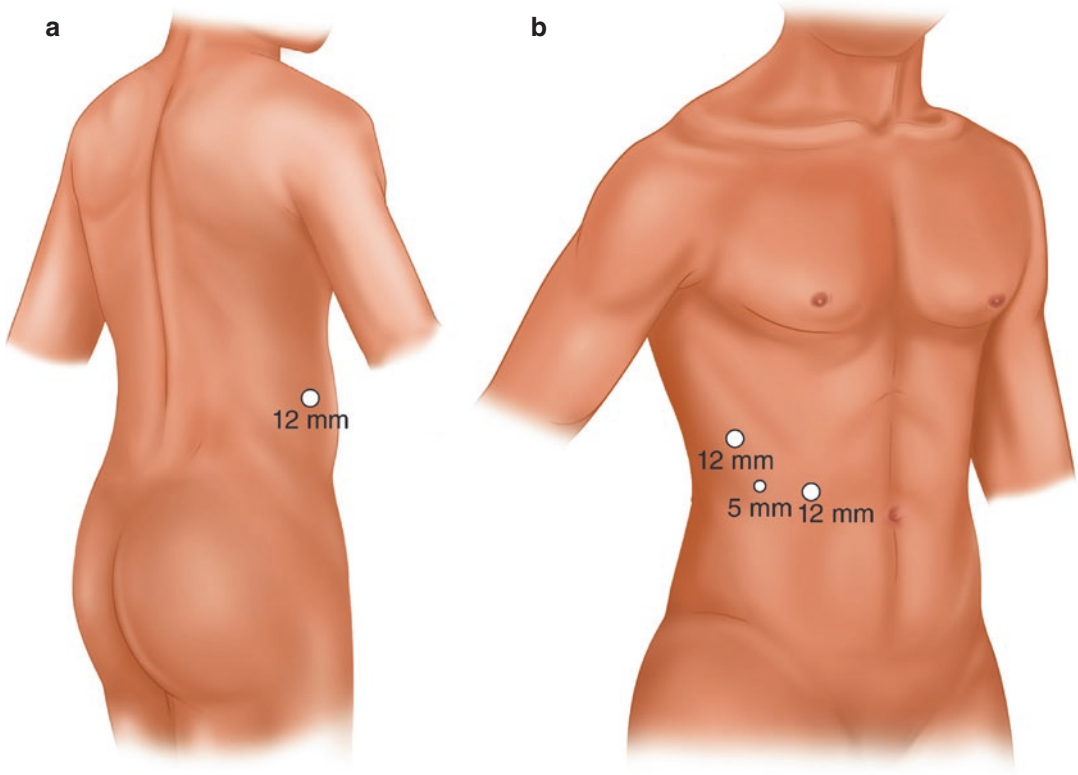

Fig. 14.2 (**a**–**b**) Retroperitoneal laparoscopic partial nephrectomy. (Original work submitted by the authors)

found that there was a 96% correlation rate between 3-D magnetic resonance angiogram and intraoperative findings. Once the hilar vessels are adequately exposed, Gerota's fascia is dissected and the tumor identified, preserving a portion over the tumor for T3 staging. This portion of Gerota's fascia may also serve as a handle during tumor excision. The 2017 American Urologic Association update on renal mass and localized renal cancer recommend adrenalectomy if preoperative imaging suggest metastasis or direct invasion into the adrenal gland [27]. Otherwise, the adrenal gland is separated from the upper pole. Patients with clinically regional lymphadenopathy should undergo lymph node dissection for staging purposes [27], as there is no survival benefit of lymph node dissection in patients with stage 1 renal cell carcinoma and no clinically concerning lymph nodes [28]. Nonetheless, despite the controversy, some still advocate for lymph node dissection for patients with large T1b tumors in order to detect and cure micrometastasis [29, 30].

Hilar Clamping

There are various devices utilized for hilar clamping: a Satinsky clamp for en bloc clamping, or bulldog clamps for selective clamping. Clamping technique varies by surgeon preference. Artery-only clamping has been described, with reported findings of similar blood loss [31]. Gong et al. [31] found that clamping the artery and vein resulted in increased postoperative creatinine compared to artery-only clamping, though there was no significant difference in the development of renal insufficiency in patients with normal preoperative renal function.

In attempts to minimize cellular oxidative damage during renal ischemia, renal hypothermia and administration of intravenous diuretics

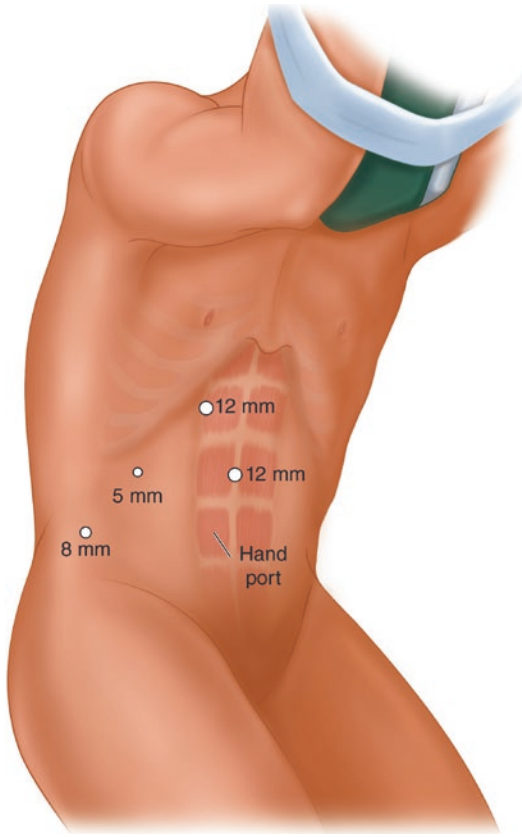

Fig. 14.3 Hand-assisted laparoscopic partial nephrectomy (right). (Original work submitted by the authors)

have been employed. There are various methods for inducing renal hypothermia, including perfusing renal arteries with cold crystalloid, infusion of retrograde transurethral saline, and intraperitoneal ice slush [32–34]. Mannitol and/or Lasix may be given prior to clamping, though recent studies suggest there may not be benefit to use of intraoperative diuretics. In a double-blind, randomized clinical trial, Spaliveiro et al [35] found that in patients with normal renal function there is difference in postoperative eGFR of patients who received mannitol.

Reduction in warm ischemia time can be achieved with early unclamping with the removal of the clamp immediately after the initial central running suture is placed and prior to placement of mattress or bolster sutures [36]. V-Loc (Covidien, Mansfield, MA, USA), a barbed unidirectional suture for this running anastomosis, may be used. Vicryl (Ethicon, Somerville, NJ, USA) sutures are then placed for hemostasis. Similar intraoperative blood loss was reported by Nguyen et al. [36], in a series of 100 patients comparing early unclamping to the standard technique. Compared with the average clamping times for open partial nephrectomy at 20 minutes [37], the average clamp time in the early unclamping group was 6 minutes shorter.

Performance of LPN without the use of a clamp has also been described. In a retrospective comparison of clamping and off-clamping techniques in 26 patients, Guillonneau et al. [38] described an off-clamping technique with the use of ultrasonic shears and bipolar electrocautery for hemostasis of the tumor bed. Similar complication rates were reported, and all patients had negative margins. Conversely, Rais-Bahrami et al. [39] found in their series of 126 patients that the off-clamp group had significantly more blood loss but had similar rates of transfusions compared to the clamped group. At 6 months follow-up, the off-clamp group had significantly less changed postoperative creatinine.

Selective clamping involves the microdissection of tumor-specific arterial branches, thus eliminating global ischemia. Gill et al. [40] described this technique with the use of preoperative three-dimensional (3D) CT imaging and color Doppler ultrasonography. In a meta-analysis performed by Cacciamani et al. [41], off-clamp, selective clamp, and early unclamp techniques were found to be safe and feasible in attaining hilar control with similar perioperative and oncologic outcomes.

Tumor Resection

Once the kidney is fully mobilized, the tumor is identified. An intraoperative ultrasound may be used to determine the depth and location of endophytic or more centrally located tumors. The tumor is circumferentially demarcated using electrocautery. Cold cutting is then utilized to excise the tumor, while maintaining a rim of normal parenchymal tissue. Minimal surrounding

peritumor tissue is necessary for adequate control [42], with reported rates of positive surgical margins after MIPN ranging from 0.7% to 5.7% [43]. There appears to be minimal metastatic or recurrence risk associated with positive surgical margin [44], though long-term data remain lacking. Frozen section and random tissue sampling from the tumor bed remain controversial [44–46], however, may play a role in cases of suspected remaining tumor, as data suggest that gross inspection provides an accurate margin assessment [47].

After tumor excision, methylene blue may be injected in order to determine collecting system entry. The excised mass is placed in a specimen retrieval bag and set aside for removal prior to fascial closure.

Reconstruction of the Collecting System

Tumors abutting or invading the collecting system often require entry into the collecting system. Methylene blue may be injected in a retrograde fashion through an open-ended ureteral catheter. If the kidney is perfused, intravenous indigo carmine may also be used. The collecting system can be closed with 2-0 Vicryl or a 3-0 unidirectional barbed suture with a Lapra-Ty (Ethicon Endo-Surgery, Cincinnati, OH, USA) at the end. Methylene blue is again injected to confirm a watertight closure. Bylund et al. [48] described an alternative closure technique using a fibrin glue absorbable gelatin sponge sutured in place without formal collecting system reconstruction and reported a urine leak rate of 2/104 patients.

Hemostasis of the Tumor Bed

The most common postoperative complication requiring a secondary intervention is delayed hemorrhage [37]. As such, hemostasis is a critical step. At our institution, a central running Vicryl may be placed to oversew any bleeding vessels. Watertight closure of the collecting system is also performed. Renorrhaphy is then performed with 2-0 Vicryl sutures with a Weck Hem-o-lok clip (Teleflex Medical, Kenosha, WI) on one end, using four to six sutures placed in a mattress fashion. The sutures are then secured with a Weck Hem-o-lok clip and a Lapra-Ty. Hemostatic agents or a bolster may also be utilized [49], with bolsters aiding particularly with cases in which apposition of the sides of the renal bed are not possible.

Closure

Ensuing the confirmation of hemostasis, Gerota's fascia is re-approximated, and the specimen is removed. Resumption of pneumoperitoneum allows reconfirmation of hemostasis. A Blake or Jackson-Pratt drain is then delivered through the most lateral port site. Under direct visualization, all remaining trocars are removed, and local anesthesia is injected into the port sites. The fascia is then closed with 0 Vicryl. A Carter-Thomason device may then be used to close the remaining 12-mm trocar sites. Monocryl (Ethicon, Somerville, NJ, USA) is used to seal the skin and adhesives may be applied.

Robotic-Assisted Laparoscopic Partial Nephrectomy (RALPN)

RALPN improves depth perception by use of 3D visualization as well as full range of motion via articulating instruments, thus enhancing precision and dexterity. Aboumarzouk et al. [50] performed a systemic review comparing LPN and RALPN, finding similar outcomes including conversion rates, operative time, intraoperative blood loss, duration of hospital stay, positive margins, and complications. The robotic group demonstrated shorter warm ischemia time. Recent studies demonstrate similar findings [51, 52].

Patient Positioning

The positioning of the patient mirrors the transperitoneal laparoscopic approach at a modified 45° flank position [52]. However, the patient's

posterior is placed near to the edge closer to the robot rather than being centered on the table to improve the reach of the robotic arms. For retroperitoneal access, the patient is in full flank position with the umbilicus at the break of the table, and the table maximally flexed [53]. Lower extremity positioning and securing the patient are similar to the laparoscopic approach described in the section above.

Access

In general, four robotic ports are utilized with an assistant port arranged between the left robotic trocar and the camera trocar, though three-arm approaches have been described. As with LPN, an additional liver retractor can be placed at the subxiphoid for tumors on the right side. There must be sufficient distance between the trocars, with at least 8-cm distance between trocars and camera in order to ensure adequate instrument working room. First, a 12-mm para-umbilical incision is made through which the 30°-down laparoscope is placed. Three 8-mm ports are then arranged at the ipsilateral edge of the rectus muscle, midline approximately 3 cm beneath the umbilicus (robotic left arm for renal tumors on the right side), and cephalad to the camera port (robotic right arm for renal tumors on the right side). The robot is docked nearly perpendicular to the table.

Counter retraction may be provided by the fourth arm with a prograsper during bowel takedown and hilar dissection. The fourth arm may assist in kidney and tumor dissection.

Retroperitoneal access with an incision made at the tip of the 12th rib through the external oblique fascia. After careful dissection through the internal oblique muscle fibers, an incision is made through the internal oblique fascia and a space is created. Porrecca et al. describe blind creation of a space using a finger and a glove connected to a nasogastric tube for inflation thereafter [53]. While retroperitoneal access may be more technically challenging with the potential for disorientation due to unfamiliar landmarks and limited working space, it does offer the advantages of direct access to the renal hilum, the order of vessel identification changed with the renal artery being encountered before the renal vein [53–55]. The lack of bowel manipulation allows for earlier return of bowel function and reduced risk of ileus, which in turn minimizes the length of stay, as well as significantly reduces the risk of potential bowel injury [55].

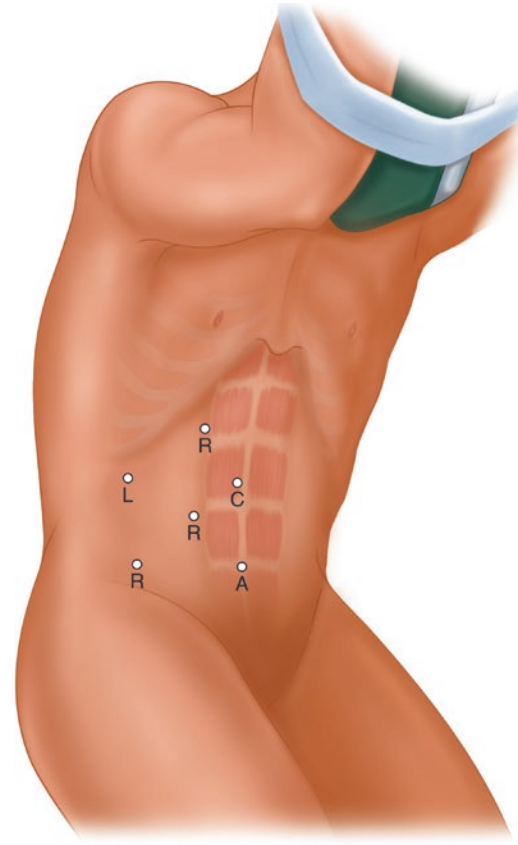

Fig. 14.4 Transperitoneal robotic-assisted laparoscopic partial nephrectomy. (Original work submitted by the authors.) Key: L – liver, R – robot port, A – assistance port, C – camera port

Figure 14.4 demonstrates an example of retroperitoneal robotic access.

Procedure

The techniques described for transperitoneal and retroperitoneal laparoscopic partial nephrectomy can be used in a similar fashion for the da Vinci (Intuitive Surgical, Sunnyvale, CA, USA) robotic surgical system. Technically challenging

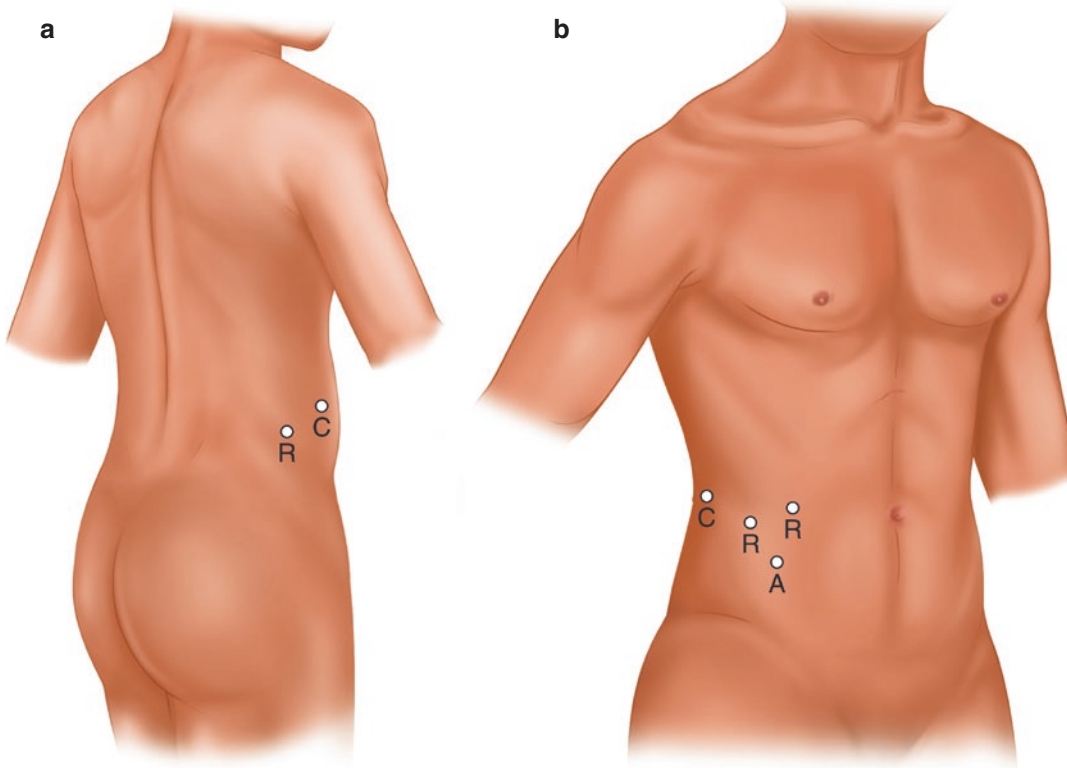

Fig. 14.5 (**a**–**b**) Retroperitoneal robotic-assisted laparoscopic partial nephrectomy. (Original work submitted by the authors.) Key: R – robot port, A – assistance port, C – camera port

steps, such as closure of the collecting system, may be performed more easily with the robot due to the use of articulating arms. The bedside assistant is responsible for suctioning, delivery of sutures, placement of clips, and possibly placement of the hilar clamp (Fig. 14.5).

Ablative Techniques

Minimally invasive thermal ablative (TA) therapies for renal tumors have typically been performed percutaneously with real-time imaging guidance in an interventional radiology suite. These techniques are technically less challenging than a partial nephrectomy as there is no need for hilar clamping, collecting system reconstruction, renorrhaphy, or adjacent organ dissection. Ablative therapy is typically limited to clinical cT1a (<3 cm) tumors and patients with increased surgical risks [5]. The American Urological Association recommends a tissue diagnosis prior to treatment as the ablative process destroys the tissue and prevents a definitive diagnosis [5]. The two most commonly studied and utilized methods are cryoablation (CA) and radiofrequency ablation (RFA). Cryoablation causes cellular damage from both the freezing temperatures induced by iceball formation from rapid expansion of high-pressure argon gas and subsequent reperfusion injury during thawing. RFA utilizes alternating current transmitted to cells via electrodes. The energy causes agitation resulting in tissue heating to temperatures over 60 °C. At this temperature, irreversible cell damage and necrosis occur. The choice of approach, open, laparoscopic, or percutaneous, depends on tumor location and its proximity to the bowel, adjacent organs, and the great vessels. Complication rates and oncologic outcomes between percutaneous and laparoscopic approaches appear to be equivalent [56–58]. In patients with recurrent disease,

ablative therapy did not preclude radical nephrectomy [59, 60].

A number of studies and systematic reviews have compared MIPN (LPN or RALPN) to TA [56, 61–67]. These studies have demonstrated similar oncological outcomes (local recurrence-free and metastatic-free survival) between partial nephrectomy (PN) and TA, but a superior metastases-free survival for PN when compared to RFA. Of note, the overall survival favors PN, but these studies have a high selection bias – PN patients tend to be younger and healthier. Thompson et al. presented 1424 cT1a patients that underwent PN (n = 1057), RFA (n = 180), and CA (n = 187) with a median follow-up of 5.2, 3.6, and 1.9 years, respectively [68]. The PN recurrence-free survival and metastasis-free survival was comparable to CA (98% vs 98%, and 99% vs 100%, respectively), but a superior metastasis-free survival was noted for PN compared to RFA (99% vs 93%, respectively). Similarly, patients with cT1b (n = 379) managed with PN (n = 326) and CA (n = 53) had comparable oncological outcomes. A recent review by Pierorazio et al. identified an inferior 1-year recurrence-free survival for patients undergoing TA compared to PN; however, a secondary TA procedure eliminates this difference [63]. The perioperative side effect profile appears more favorable for TA compared to PN, but the renal function outcomes for either procedure are similar [61–63]. Moreover, RFA and CA appear to share similar oncological, perioperative, and functional outcomes, but further data are required to delineate differences between the two techniques. Thoughtful consideration is necessary when comparing MIPN and ablative therapies as the indications for each vary and the patient populations are often significantly different with the MIPN population being younger and healthier [66]. At the present time, minimally invasive ablative procedures require further validation prior to widespread utilization.

New treatment modalities such as high-intensity focused ultrasound (HIFU) and microwave therapy remain investigational. The latter is beginning to gain ground as it has been shown in a few studies to be safe and as effective as PN, but further data are required [6, 7]. An international group has reported their experience with extracorporeal and laparoscopic HIFU demonstrating its feasibility and safety [69, 70]. Further trials with optimized device settings and longer-term follow-up are needed to demonstrate the oncologic safety and efficacy of these novel techniques.

Postoperative Management

In the immediate postoperative period, patients are continued on intravenous fluids and started on a clear liquid diet. Postoperative day 1, patients are transitioned to a regular diet and intravenous fluids are stopped once the patient has had adequate oral intake. Pain control is managed with intermittent intravenous and oral analgesics, and antibiotics are continued for 24 h. Laboratory data are checked postoperatively and postoperative day 1. For deep vein thrombosis (DVT) prophylaxis, sequential compression devices are worn at all times, subcutaneous heparin is administered, and early ambulation is encouraged. Our institution utilizes the Caprini Score for determination of postoperative DVT risk. Patients with elevated risk of DVT are transitioned to enoxaparin depending on renal function and risk of bleeding, which is determined by intraoperative blood loss.

A drain is placed for monitoring of bleeding or urine leak, and if drain output is elevated, the fluid is checked for creatinine. The Foley catheter is typically removed postoperative day 1 and the drain is removed prior to discharge from the hospital, on average postoperative day 2 at our institution. Given minimal intraoperative bowel manipulation, full return of bowel function is not required for diet advancement or discharge. In a 90-patient series presented by Shah and Abaza, a clinical pathway was proposed in which 94% patients were discharged on postoperative day 1, with a 5% readmission rate of 5% [71]. Minimal data exist regarding perioperative of antiplatelet use. In a retrospective review of 430 consecutive cases, Leavitt et al. found no significant difference in major postoperative complications or

intraoperative blood loss in patients for whom aspirin was continued when performing laparoscopic partial nephrectomy [72]. Generally, antiplatelet agents are safely resumed within 7–10 days.

Complications of Minimally Invasive Partial Nephrectomy

Previously reported complication rates for LPN and RALPN ranged from 11% to 36% and from 8.5% to 35.3%, respectively. Cacciamani et al. [51] performed a meta-analysis reviewing 20,282 cases of open, LPN, and RALPN from 2000 to 2016, and found overall postoperative complication rates of 23.4% for LPN, and 19.2 for RALPN.

Intraoperative Complications

Vascular Injury

Renal hilum injuries can result in significant morbidity and mortality if not managed in a timely fashion. Hemostatic agents such as Surgiflo (Ethicon, Somerville, NJ, USA) or Floseal (Baxter, Deerfield, IL, USA), or direct pressure with Surgicel (Ethicon, Somerville, NJ, USA) may be sufficient to treat small venous bleeding. Adequate hemostasis is confirmed by decreasing pneumoperitoneum. Larger venous injuries may be oversewn with nonabsorbable suture such as 4-0 Prolene (Ethicon, Somerville, NJ, USA); however, significant injury may require completion nephrectomy.

Injury to Intra-abdominal Organs

Bowel injury may occur in a traumatic fashion, such as during access, or thermal with the use of electrocautery. Minor thermal injury may be managed with simple imbrication, whereas major thermal injury may require bowel resection and re-anastomosis. In rare cases, diversion is indicated. Postoperative identification of bowel injury often requires surgical exploration. Clinical presentations of bowel injury include peritonitis, nausea, vomiting, signs, and symptoms of sepsis. Excessive bowel manipulation may also increase the risk of postoperative ileus. Early adhesion formation may also cause small bowel obstruction.

Pancreatic and splenic injuries typically occur during left-sided procedures [73]. Injury to the pancreatic tail is most common. Most commonly, pancreatic injury is identified during the postoperative period with increased, often milky-appearing drain output. Confirmation is by obtaining drain fluid and serum amylase and lipase. Management includes elemental diet or total parenteral nutrition, nasogastric tube placement, somatostatin to suppress pancreatic exocrine function, and percutaneous drainage. Minor splenic injuries are typically managed conservatively with hemostatic agents and/or tamponade. Rarely, splenectomy is performed in cases of significant splenic laceration.

Diaphragmatic injury is rare in laparoscopic renal surgery, occurring in 0.4% of cases [74]. Intraoperatively, clinical signs of pleural entry may include changes in respiratory requirements or simply billowing of the diaphragm. Repair can be performed intraoperatively using laparoscopy. If there is a clinical concern for diaphragmatic injury and no defect is visualized, an upright chest X-ray may be obtained postoperatively in the recovery area. However, routine postoperative chest X-rays are not required [75].

Postoperative Complications

Hemorrhage

Pseudoaneurysm (PA) and arteriovenous fistula (AVF) are rare, but potentially fatal causes of postoperative hemorrhage. However, delayed hemorrhage is the most common complication requiring secondary procedure after LPN [37]. In a systematic review by Jain et al., the mean presentation occurred 14.9 days after surgery, and 87.3% presented with gross hematuria [76]. Other symptoms patients may have include flank pain and potentially ecchymosis, particularly in

cases with significant retroperitoneal hematoma formation. Patients diagnosis may be made with CT angiogram; however, in some cases depending on severity, the patient may be taken directly by Interventional Radiology for angiography and angioembolization [77]. Selective angioembolization is the preferred method of treatment of PA and AVF however, in some cases, complete renal embolization and even re-exploration and potentially completion nephrectomy are performed.

Urine Leak

Larger or more endophytic tumors may require intentional entry into the collecting system. As a result, great care is taken to ensure that during repair, the collecting system is adequately closed. The use of methylene blue assists with closure, as mentioned above. However despite prudent efforts, a urine leak may occur. Zorn et al. demonstrated that collecting system entry alone does not correlate with increased risk of leakage of urine [78]. A drain placed intraoperatively aids in the diagnosis of both hemorrhage and urine leak. Clinic symptoms include abdominal or flank pain, ileus, increased serous-appearing drain output, and rising serum creatinine. Urine leak may be confirmed by checking a drain fluid creatinine, which would reveal an elevated value when compared to serum. Treatment includes conservative management with ureteral stent, drain, and foley catheter for bladder decompression. Occasionally a percutaneous nephrostomy tube is required, and rarely a second surgery for closure is indicated. Antibiotics may be indicated if there is concern for infection with fevers or leukocytosis.

Future Directions

In line with the principle of "no surgery is the best surgery," renal mass biopsy (RMB) is beginning to gain ground. It has been documented that nearly a quarter of renal masses removed are benign [8]. When considering the rigorous cancer guidelines set forth for other organ systems, the lack of a definitive tissue diagnosis prior to surgical management remains unique to renal masses. Technological and histological advancements provide a high diagnostic accuracy with acceptable morbidity for RMB, and the procedure itself does not preclude surgical therapy [79]. It is our suspicion that the future of renal cancer will be guided by renal mass biopsies.

Another noteworthy development is the use of advanced imaging technology in the form of augmented (AR) and virtual reality (VR). AR is the overlay of virtual images onto the real world, whereas VR is the simulation of the real world. AR has already entered the clinical field and has been used intra-operatively to improve surgical outcomes, particularly negative margins in a PN and the preservation of the normal ischemia by guiding selective arterial clamping [2, 3]. Moreover, VR has the potential to further improve surgical outcomes by creating an accurate and detailed mental map of the surgical anatomy prior to surgery. Wake et al. illustrated that experienced surgeons, after reviewing a CT scan, fail to identify the correct location of a renal tumor on a 3D reconstructed kidney [4]. Interestingly, studies on VR from the University of California, Irvine, investigated the use of a VR head-mounted display along with hand-motion tracking for preoperative planning for a PN. Their use of VR technology allows the surgeons to peer inside and interact with patient-specific 3D-VR models. Experienced surgeons indicated that the review of the VR model provides superior anatomical understanding compared to CT alone. Additionally, the VR experience improved surgical confidence for the planned PN and altered the operative approach on numerous occasions [80]. Although the AR and VR technologies are promising, further studies are required to evaluate their clinic impact and address the time constraints that come with creating these advanced images.

Conclusion

Minimally invasive nephron-sparing techniques have proven similar oncologic outcomes while reducing morbidity and improving outcomes

[37]. While LPN remains the gold standard nephron-sparing approach for SRMs, RALPN has emerged as a safe, effective, and widely used technique among many surgeons who otherwise may not be facile with laparoscopy. Current literature suggests that RALP has equivalent and potentially superior outcomes when compared to LPN and OPN.

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15 Surgery for Renal Cell Carcinoma with Thrombus Extension into the Vena Cava

John A. Libertino, Chad Wotkowicz, and Jason R. Gee

Introduction

Since the last edition of this textbook, new, important observations regarding the management of renal cell carcinoma involving the venous system have emerged and will be incorporated into this revised chapter.

Renal cell carcinoma (RCC) has a tendency, within the natural course of progression, to infiltrate into the venous system of the affected renal unit with rates of extension varying between 4% and 10% [1].

Within this subgroup, an additional 1% of patients may have thrombus extending into the right atrium [2]. The increased utilization of imaging studies will no doubt lead to a decrease in these numbers in the future; however, the gold standard of RCC treatment will remain surgical intervention as first described by Robson in 1969 [3].

Although the radiographic appearance of these renal masses and associated tumor thrombus can be alarming, their removal can be performed in a safe and effective fashion by following the surgical tenets to be discussed in this chapter. In addition to discussing the management of these tumors, we will also present the first author's (JAL) personal outcomes data from 359 patients treated with venous tumor thrombi. Despite the tremendous improvements in cancer therapeutics, the basic tenets of surgical oncology have been constant in our algorithm for managing these complicated cases.

Like most malignancies, the outcomes are improved significantly if there is no invasion of the surrounding structures and absence of lymph node metastasis. Studies suggest 5-year survival rates of between 40% and 68% following radical nephrectomy with tumor thrombectomy [4, 5]. The level of tumor extent has been shown in some studies to correlate with survival, and at our institution we have published our results indicating improved survival for patients with renal vein involvement versus involvement of the IVC suggesting the need for revision of the current TNM system, which occurred in the latest revision of the TNM system [6]. Different institutions have devised a variety of categories based on thrombus extension, and for the purposes of this text, we will refer to our employed system. The operative approach for the most part can be based on level of extension: renal vein, infrahepatic IVC, and suprahepatic IVC/atrial. Although a host of'

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authors have proposed a variety of classification systems, the primary outcome in most cases will depend on the biology of the tumor, the surgical experience, and confidence of the surgeon.

Renal cell carcinoma has long been called the internist's tumor because of the myriad of symptoms this particular malignancy can present with (Chart 15.1) [7]. More concerning are the symptoms that tumor thrombi can produce (Chart 15.2). It is also worth noting that surgeons need to become familiar with the venous anatomy of' the kidney and retroperitoneum which can often vary based on collateral drainage associated with venous tumor thrombus (Fig. 15.1).

The presentation and diagnostic evaluation of RCC and tumor thrombus have been described elsewhere in this text and will not be discussed in detail in this section. Some of the more common imaging studies preferred by our group include 3D-CT reconstructions and MRI with dedicated venous phases (Fig. 15.2). MRV can delineate between bland and tumor thrombus which assists greatly in surgical planning and often dictates the need to start presurgical anticoagulation to limit the risk of clot embolus. Traditional cavagrams are also performed at the time of preoperative renal artery embolization (Fig. 15.3). Additionally we employ preoperative TEE, and coronary angiography if indicated, to assess the potential for cardiac revascularization which we have occasionally performed concomitantly. The primary goal of preoperative imaging is to determine the level of the tumor thrombus and to evaluate for metastatic disease. Zini and colleagues have suggested that preoperative measurements of renal vein and IVC diameters with associated tumor thrombus can correlate with rates of ostial wall invasion [8]. The presence of metastatic disease does not necessarily preclude an aggressive approach as data has been accumulating to suggest that solitary metastectomy and cytoreductive procedures improved survival rates [9].

Chart 15.1 Clinical manifestations of Renal Cell Carcinoma

Renal cell carcinoma – paraneoplastic manifestations
Stauffer syndrome – elevated liver function tests with fever and hepatic necrosis
Neuromyopathy
Neuromyopathy
Polycythemia – increased erythropoietin production
Hypertension – increased renin production
Elevated erythrocyte sedimentation rates
Anemia of chronic disease
Cachexia and weight loss
Fever of unknown origin
Elevated alkaline phosphatase
Hypercalcemia – increased parathyroid-related hormone/osteolytic bone mets

Chart 15.2 Renal Cell Carcinoma Thrombus-signs and symptoms

Renal cell carcinoma thrombus signs and symptoms
Caput medusae
Pulmonary embolus
Budd-Chiari syndrome (hepatomegaly, abdominal pain, and ascites)
Varicocele
Bilateral lower extremity edema
Proteinuria

venous extension [31].

Preoperative Renal Embolization

As discussed earlier in this text, we have found preoperative renal artery angioinfarction to be beneficial in dealing with large renal cell carcinomas with tumor thrombus. We prefer to perform our embolization 2–4 weeks prior to planned nephrectomy (Fig. 15.4). The primary purpose of this technique is to provide some insurance against excessive blood loss and to facilitate ligation of the renal vein prior to the artery. In some instances the embolization can result in tumor shrinkage and thrombus regression. The natural response to embolization often creates a moderate degree of edema (tissue hypoxia and necrosis) which can actually enhance dissection around the renal pedicle, especially in patients with extensive hilar adenopathy. This same process can induce tumor necrosis that activates natural killer cells [10, 11]. Embolization success can often be determined by assessing the venous system via renal vein palpation. Postinfarction syndrome (5% of patients) is often characterized by flank pain, fevers, chills, malaise, hematuria, transient hypertension, and hyponatremia [12]. In our

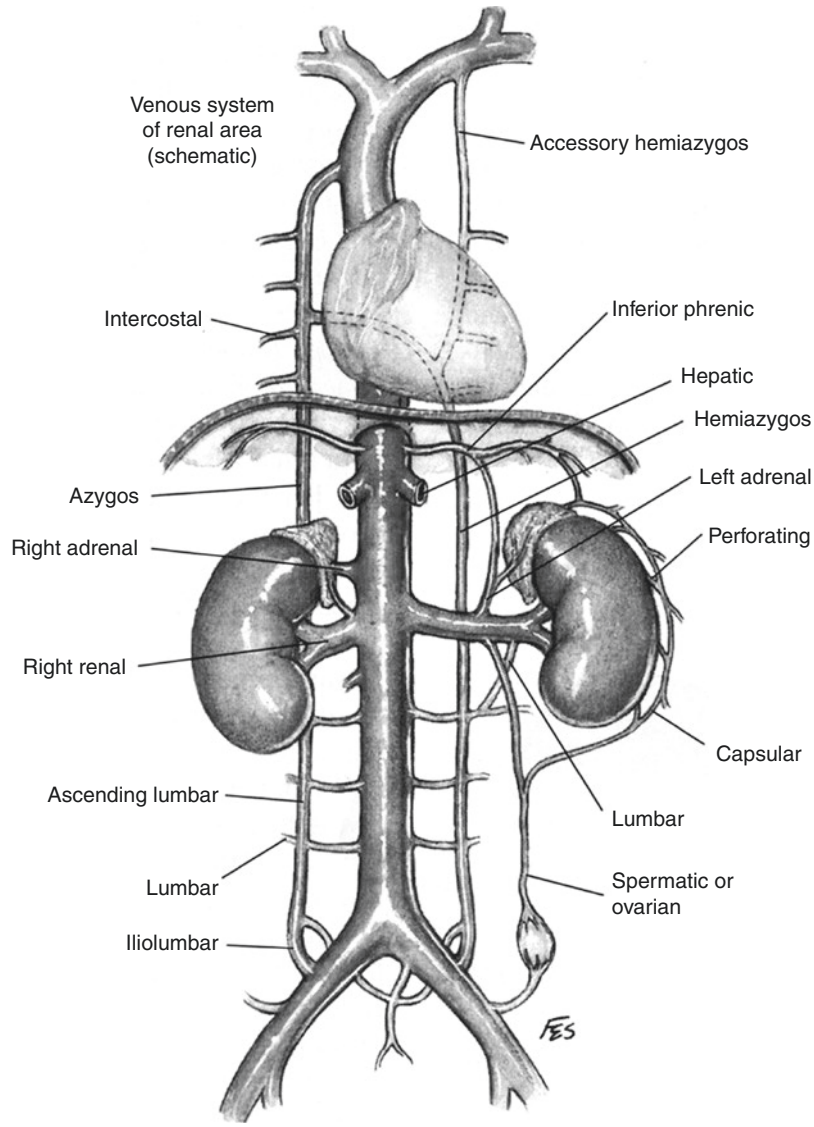


Fig. 15.1 Relevant venous anatomy of the kidney and retroperitoneum

experience younger, healthier patients tend to present with more severe symptoms which may require hospitalization for analgesics and monitoring; however, all symptoms are eventually self-limiting.

Renal Vein Tumor Thrombus

Tumors with renal vein thrombus can be managed with an approach similar to a radical nephrectomy; however, we do advocate a thoracoabdominal incision with generous exposure to provide insurance against blood loss (Fig. 15.5). After exposure is obtained, the kidney and renal pedicle are exposed as well as the inferior vena cava. As mentioned previously the renal artery is palpated to assure that a successful embolization has been completed. The tumor thrombus can usually be palpated and in some instances milked out of the IVC to provide room for placement of two Satinsky clamps at the confluence of the renal vein and IVC. A scalpel is used at the level of the IVC to circumscribe the renal vein ostium, and the Satinsky clamp nearest the renal vein is removed leaving a cuff of IVC above the second

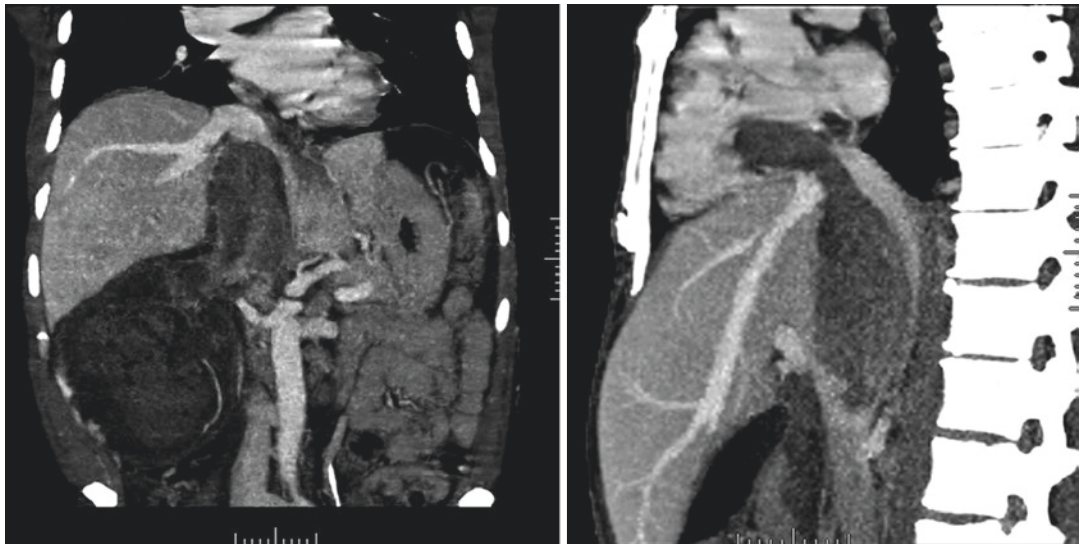


Fig. 15.2 Imaging reconstructions demonstrate extension of a large right renal cell carcinoma with tumor extension into the right atrium

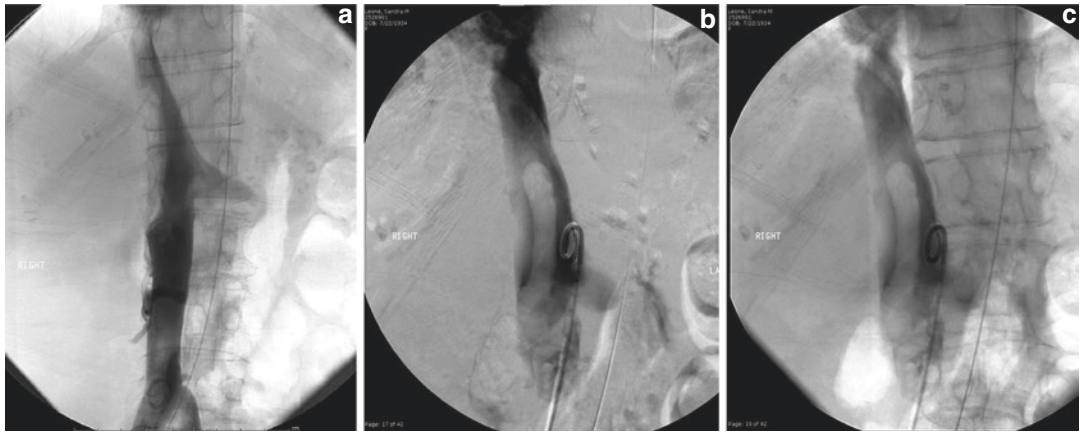


Fig. 15.3 Cavagram series demonstrating thrombus within the inferior vena cava. MRI is used in conjunction to differentiate tumor from bland thrombus

clamp in place to facilitate reconstruction of the IVC with 4-0 polypropylene suture in a running fashion (Figs. 15.6, 15.7, 15.8, and 15.9).

Infrahepatic Tumor Thrombus

As discussed earlier the preoperative imaging is crucial to establish the distal extension of the thrombus and rule out the need for cardiopulmonary bypass. The anesthesiologist should perform transesophageal echocardiography prior to the start of the case. We have published our approach to these tumors multiple times over the past 20 years and still approach most of these thrombi with a thoracoabdominal incision in the majority of cases [13, 14]. Upper pole masses can be mobilized more easily with a thoracoabdominal incision. With left-sided tumors, posing some difficulty because of the length of the renal vein and associated collaterals that tend to develop, these patients will also undergo renal angioin-

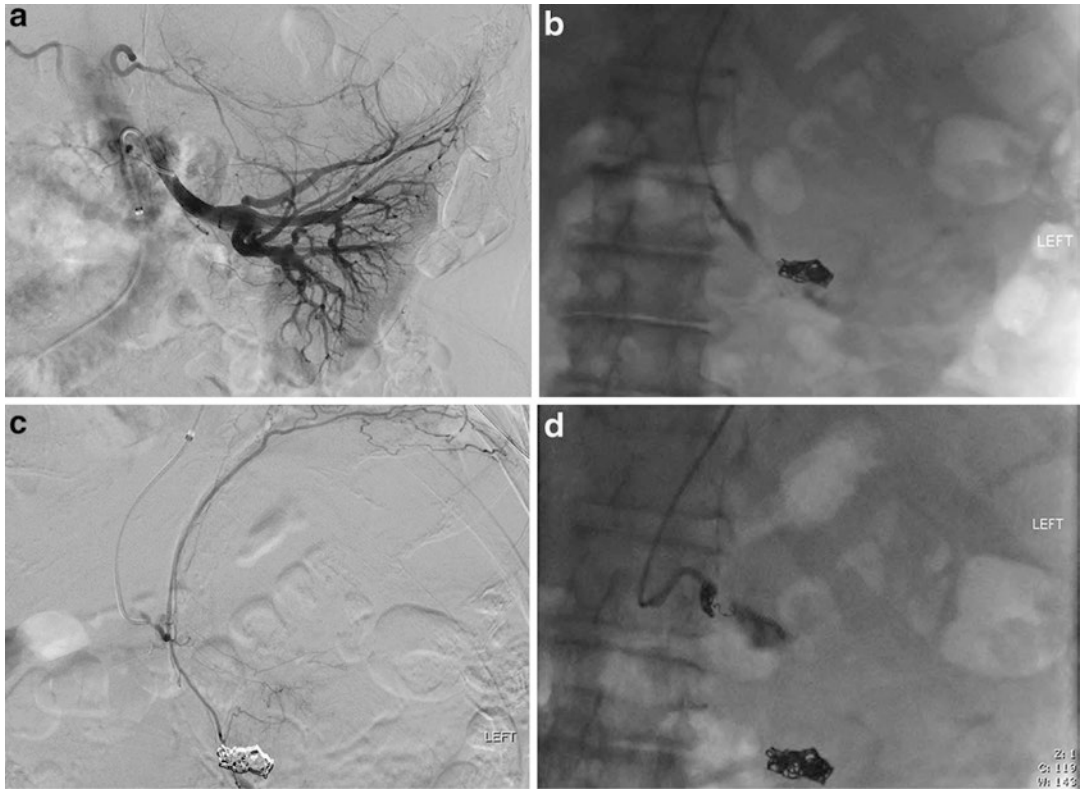


Fig. 15.4 (**a**) Left aortogram demonstrating hypervascular left renal mass. (**b**) Left brachial artery was accessed for embolization of left renal artery using purified ethanol followed by platinum coils. (**c**) Inferior phrenic artery was cannulated and demonstrated tumor vascularity. Embolization performed with purified ethanol and coils. (**d**) Successful embolization of inferior phrenic artery with diminished flow to left kidney

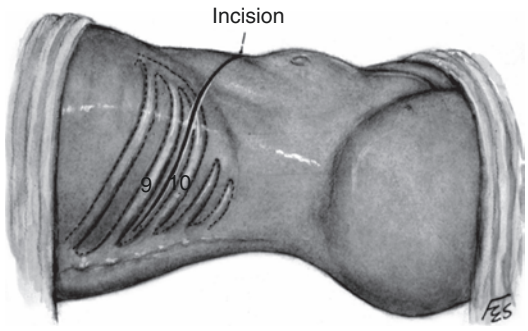


Fig. 15.5 Thoracoabdominal incision for renal vein tumor thrombus. Curve-linear supratenth incision extending to the midline

farction prior to resection. We usually approach left-sided tumors through a chevron incision. It should be mentioned that these cases can be prolonged and the initial placement of Bookwalter retractors must be done with caution to prevent excessive pressure on the bowel and most importantly the liver. A liver hematoma can occur during the case and become somewhat troublesome to deal with at the end of the case. The caudate lobe will need to be exposed and retracted, often exposing the portal hepatis. Perforating minor hepatic veins can be sacrificed with impunity to improve mobility of the caudate lobe and IVC. Simple lacerations to the liver can be treated with argon laser or electrocautery with larger defects requiring Surgicel or Gelfoam bolsters.

Unlike cases involving cardiopulmonary bypass and renal vein thrombi, the portion of the IVC with thrombi should be approached with a "no-touch technique," as much as possible, until the Rummel tourniquet has been placed cephalad and caudal to the thrombus with an additional tourniquet on the contralateral renal vein (Fig. 15.10). Inadvertent injuries to the IVC will

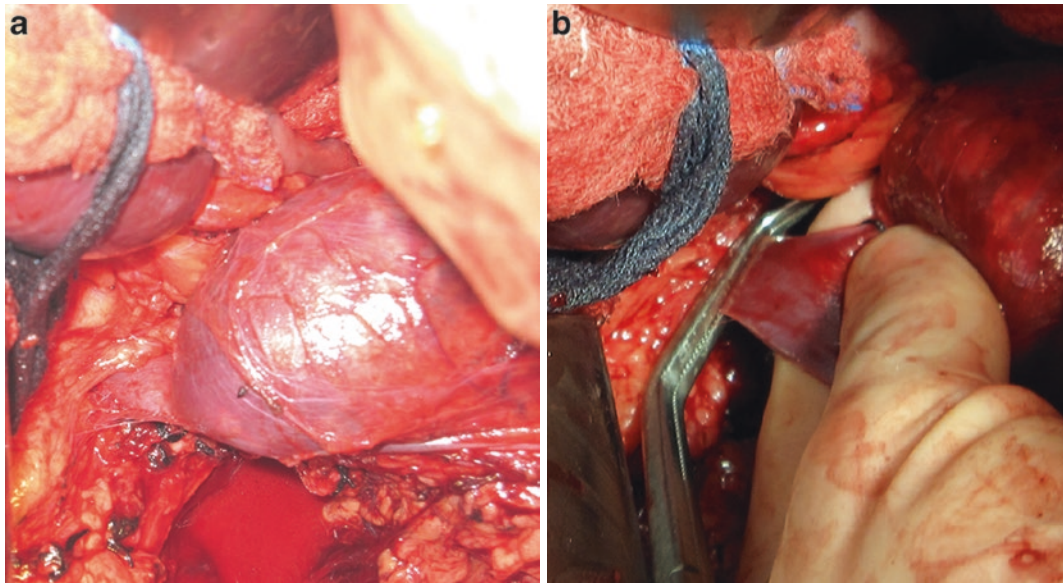


Fig. 15.6 Large renal vein thrombus is milked back to expose the confluence of the RV/IVC for placement of the Satinsky clamp

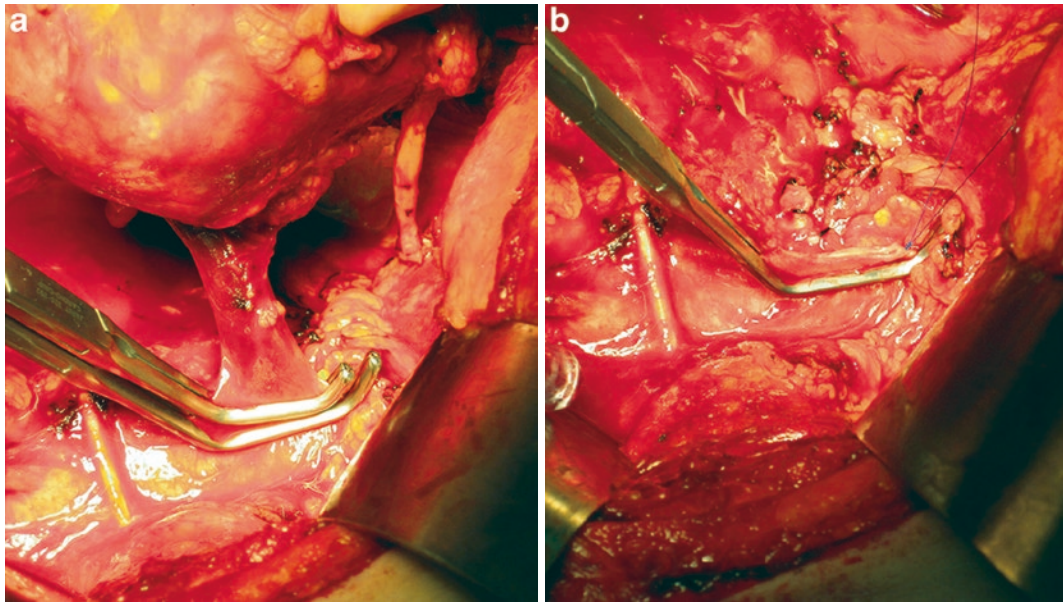


Fig. 15.7 A second Satinsky clamp is placed taking caution not to limit the circumference of the IVC following caval reconstruction

occur if one performs enough resections, and these injuries are best dealt with utilizing gentle pressure proximally and distally. We advocate utilizing sponge spicks for pressure and Allis clamps to reapproximate the defect before oversewing with 4-0 Prolene sutures. Likewise, inadvertent damage to the aorta is best approached with gentle pressure and closure with Prolene figure-of-eight pledgeted sutures and placement of Surgicel or Gelfoam over the repair. A common sense approach when dealing with injuries of large vessels is to avoid making more than one hole at a time.

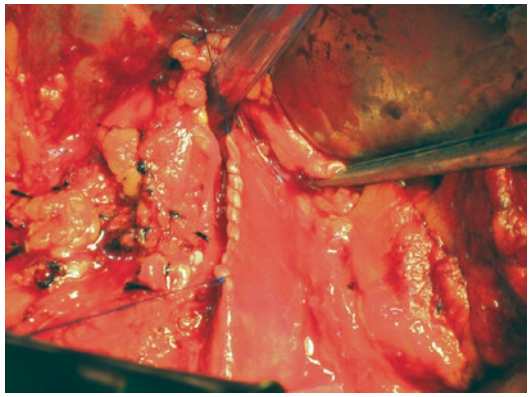


Fig. 15.8 Closed cavatomy with running 4-0 polypropylene (Prolene)

In many instances, preoperative imaging will detect significant lumbar veins that deserve respect during dissection. Once these major venous tributaries are isolated the surgeon can then address the-ipsilateral renal artery. Although our colleagues in radiology have certainly perfected the embolization technique, we still palpate the renal artery to rule out incomplete embolization. If any question exists, one can utilize intraoperative Doppler. If there is still concern we strongly advocate isolation, ligation, and division of the renal artery before tumor thrombectomy with large Hem-o-Lok clips-or Suture ligation.

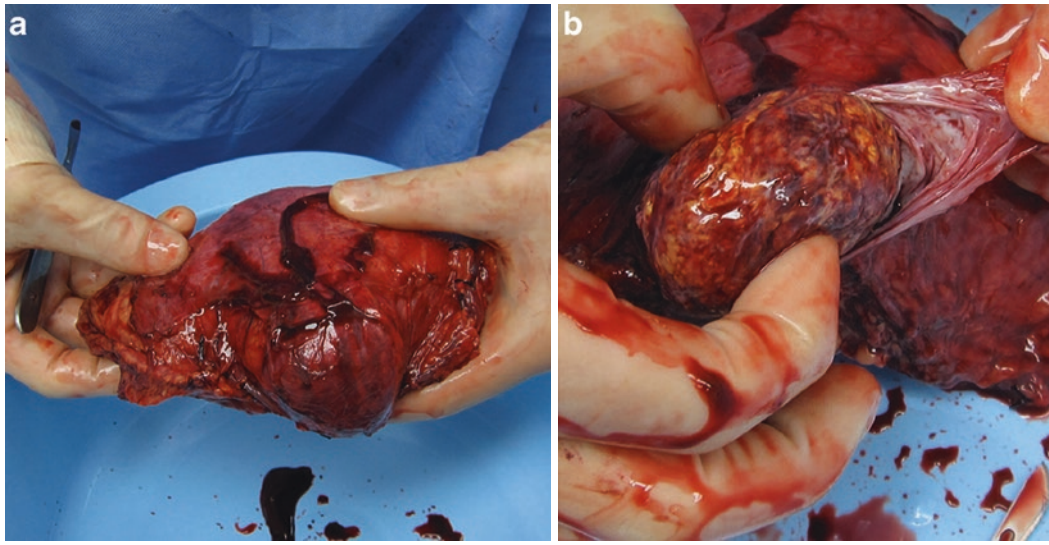
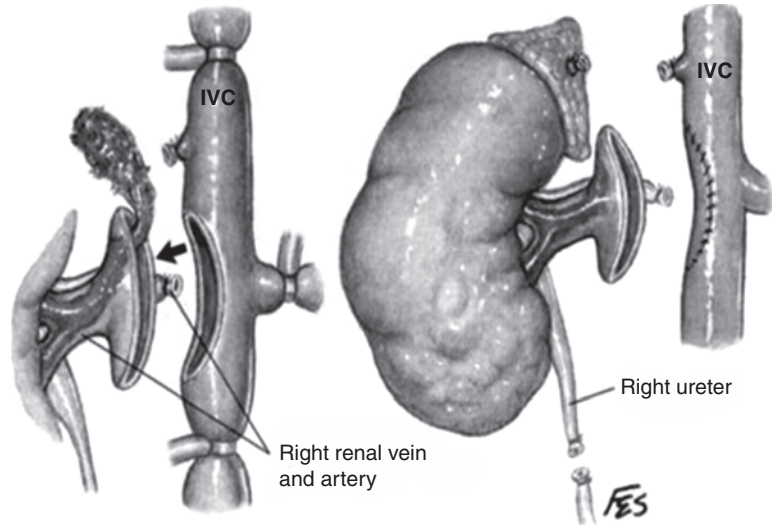


Fig. 15.9 Kidney specimen with thrombus in the renal vein

Fig. 15.10 Removal of infrahepatic tumor thrombus demonstrating placement of the Rummel tourniquets. Occasionally large lumbar veins will need to be dissected and treated with tourniquets as well



Tumor thrombectomy should only be started after the arterial supply has been addressed with ligation and division or successful embolization. Before making the cavatomy, we like to take a moment to reassess all our tourniquets and have the attention of operating room staff in case of unexpected blood loss. Once the tourniquets are tightened, we start with, a simple anterior longitudinal "hockey-stick" cavatomy with Potts scissors over the thrombus (Figs. 15.11, 15.12, 15.13, 15.14, 15.15, 15.16, and 15.17). Once there is adequate exposure, a small spatula or narrow 1/8-in malleable ribbon is used to free the thrombus from the caval wall. Significant back bleeding following cavotomy is almost always due to a missed lumbar vein. An Allis

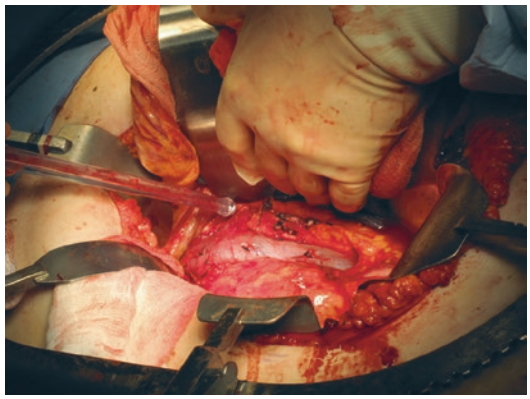


Fig. 15.11 Left renal cell carcinoma with tumor thrombus at the renal vein confluence. Patient had a previous caval filter placed precluding atraumatic placement of Satinsky clamps

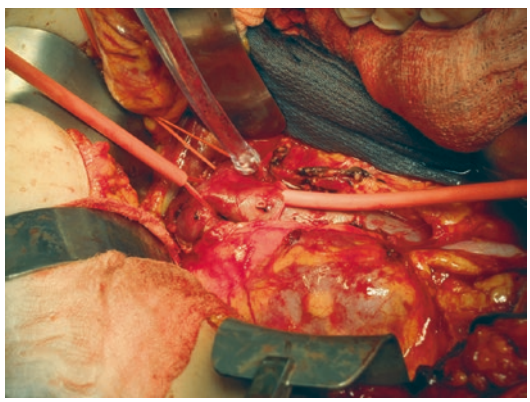


Fig. 15.12 Smaller *red* vessel loop in foreground isolated the contralateral retrocaval right renal artery. The caudal Rummel tourniquet is around the proximal portion of the inferior vena cava above the previous filter. Cephalad Rummel tourniquet encompasses the suprarenal IVC and contralateral right renal vein

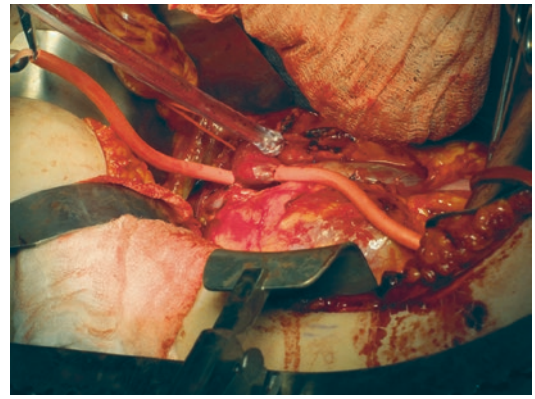


Fig. 15.13 Rummel tourniquets are cinched in place in preparation for anterior longitudinal cavatomy

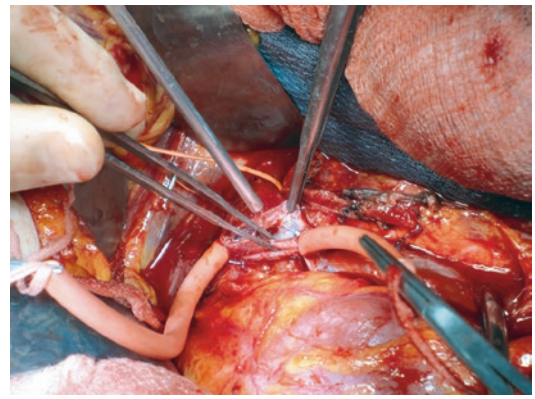


Fig. 15.14 Cavatomy demonstrates IVC filter

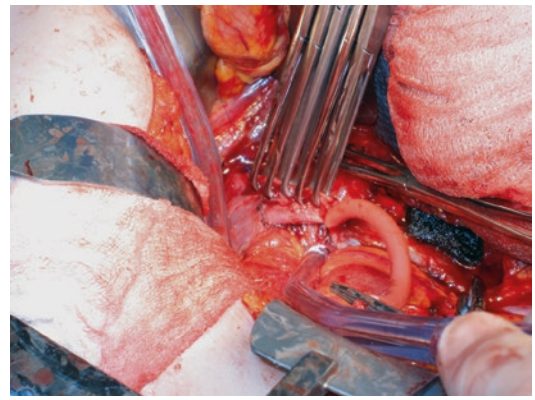


Fig. 15.15 After removal of thrombus and ligation of the left renal vein, Allis clamps are utilized to reapproximate IVC prior to reconstruction

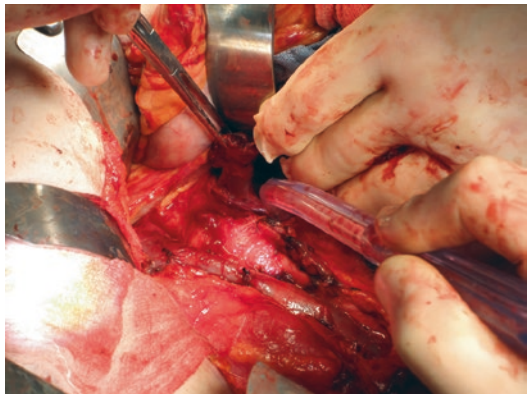


Fig. 15.16 Left renal vein with tumor thrombus noted in the lumen. Cavatomy has been closed with running 4-0 Prolene suture

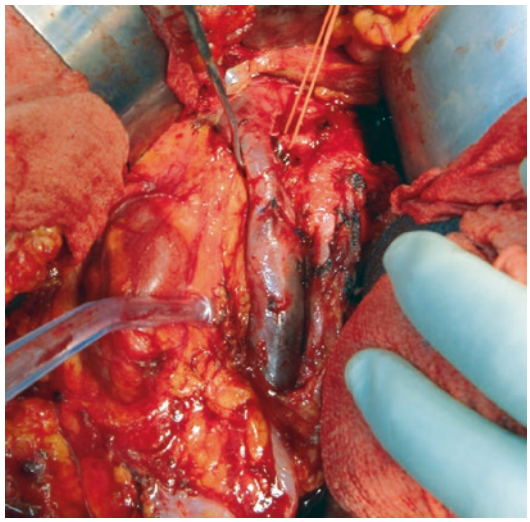


Fig. 15.17 Closed cavatomy

clamp can serve as a tag while placing figure-of-eight stitches, in some cases; however, if the vein retracts, one must be prepared to place large figure-of-eight sutures into the musculature.

After the tumor thrombus has been cleared the caval wall should be inspected for any evidence of invasion. Although the infrarenal and suprarenal IVC can be resected, in some cases, we do advocate primary repair with PTFE grafts or a pericardial patch. Prior to completing the primary caval closure the Rummel tourniquets are released sequentially starting at the infrarenal position to purge the system and minimize embolus risk. A running 4-0 polypropylene (Prolene) is our suture of choice. The inferior vena cava can be reapproximated primarily as long as the circumference is maintained at above 50% of its original size. Suture line bleeding can be managed with placement of Surgicel over the incision. After the cavatomy is closed, we then proceed with a standard radical nephrectomy.

Retrohepatic, Supradiaphragmatic, and Atrial Tumor Thrombus

Our experience with hypothermic circulatory cardiopulmonary bypass is one of the largest in the literature and remains our gold standard for resection of tumors at or above the major hepatic veins or within the right atrium [13, 14, 17]. In addition to describing our technique, we would also like to highlight other surgical techniques utilized by our contemporary colleagues in managing these complex cases via an intra-abdominal approach focusing on maximizing mobilization of the right lobe of the liver.

Venovenous Bypass (Caval-Atrial Shunt)

Our colleagues have reported their utilization of venovenous bypass for caval tumor thrombectomy in patients not able to tolerate the loss of cardiac output (hypotension) associated with cross clamping and whose tumor thrombus is nonadherent, and fails to extend into the right atrium [15]. The vena cava is mobilized and controlled at the infrarenal level, at the level of both renal veins and the intrapericardial portion. With adequate control a 20-F venous cannula may be placed in the IVC caudal to the tumor thrombus. An 8–14 F cannula is then inserted into the right brachial vein or right atrium for venous return. The cannulas are connected to an electromagnetic centrifugal pump, and bypass is initiated to maintain flow to the right side of the heart. Hepatic venous bleeding can be quite bothersome with this technique and may be addressed with a Pringle maneuver for a total of 45 min. Likewise the major hepatic veins can also be cross clamped if necessary. Additional bleeding

is sure to arise from the lumbar/azygous systems and can be difficult to control; however, it may be a necessary risk to take in those patients unable to tolerate cross clamping of' the caval system.

Liver Mobilization

We initially reported our technique and results of mobilizing the liver by dividing the triangular and coronary ligaments to facilitate exposure of the retrohepatic IVC in the 1980s [13, 14]. We have utilized this technique successfully in many patients with retrohepatic tumors extending to the level of the hepatic veins and the intrapericardial IVC. We are delighted that our colleagues at other major institutions have published equivalent results utilizing similar liver mobilization techniques that expose the retrohepatic IVC, allowing access to the IVC at the level of the hepatic veins or just above. Ciancio and colleagues at the University of Miami have utilized a technique similar to the one we originally described, dividing the ligaments (falciform, triangular, superior coronary, and ligamentum teres) and utilizing the Pringle maneuver via the foramen of Winslow [16] (Figs. 15.18 and 15.19). Following these steps, the major hepatics are the only structures in continuity with the IVC. Tumor thrombus can be gently milked below the hepatics in some instances without the need for bypass, unless there appears to be invasion of the hepatic venous system, the thrombus extends into the atrium, or there is concern that the thrombus has invaded the supradiaphragmatic wall of the IVC. The essential maneuver in this approach is to displace the tumor thrombus below the hepatic veins to avoid liver congestion.

Russo and colleagues at MSKCC have published their experience with off-bypass techniques for the removal of tumor thrombus in 78 patients between 1989 and 2009. Authors here also utilized venovenous bypass and liver mobilization techniques as previously described to remove suprarenal tumor thrombus, concluding that retrohepatic (n = 7) and suprahepatic (n = 3) tumor thrombus could be removed without the need for bypass.

Traditional Cardiopulmonary Bypass (Median Sternotomy)

At our institution [17] we utilize a chevron incision to evaluate tor any metastatic disease that may have been undetected by preoperative imag-

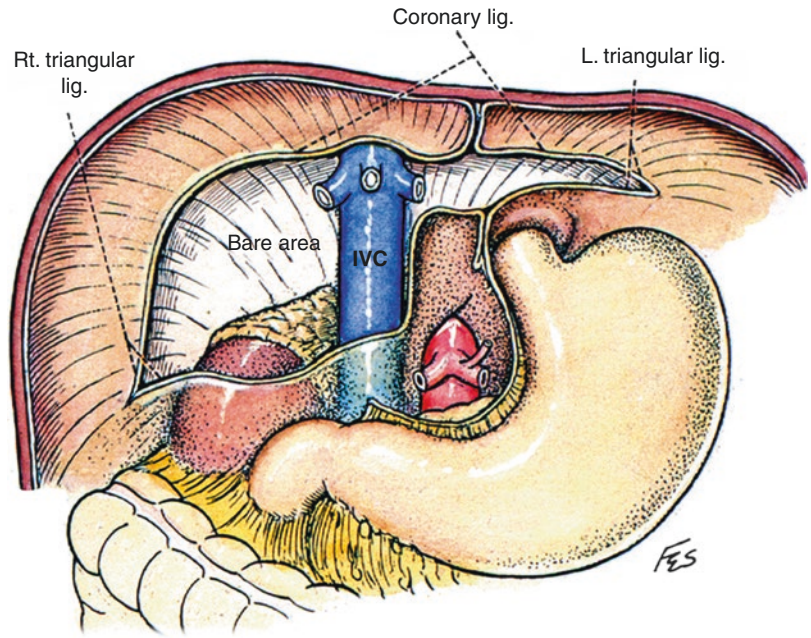


Fig. 15.18 Anterior schematic of the infrahepatic IVC demonstrating the relationship between the major hepatic veins and the diaphragm

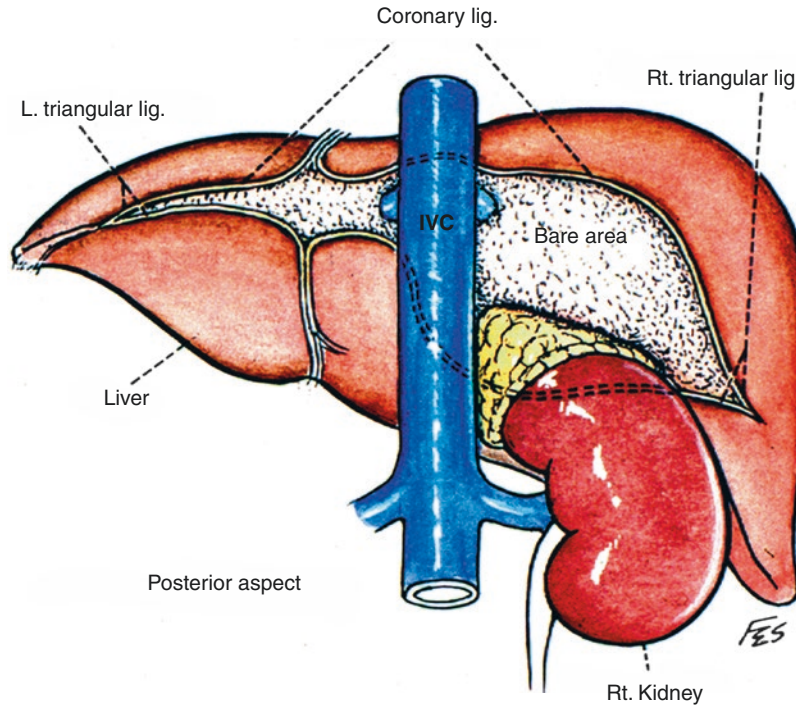


Fig. 15.19 Posterior view of the IVC

ing. A Kocher maneuver is performed to expose the infrarenal IVC and interaortocaval region. The retrohepatic IVC is exposed with a Langenbeck maneuver (liver mobilization cephalad and to the left by division of the right triangular and coronary ligaments) (Fig. 15.20). The kidney is mobilized with the exception of the renal vein and tumor thrombus paying close attention to hemostasis (Figs. 15.21 and 15.22). The renal artery is divided with a pair of Hem-O-Lok clips and a 0-silk suture leaving the renal vein as the sole attachment [17]. Any significant bleeding will be exposed and difficult to control following systemic heparinization for cardiopulmonary bypass. After the kidney has been mobilized, the entire inferior vena cava is exposed to the level of the diaphragm and distal to the common iliac bifurcation. The contralateral renal vein is also exposed to avoid damage during the cavatomy. Utilizing this approach mandates complete mobilization of the IVC in order to secure complete hemostasis, and avoid bleeding from anticoagulation necessary to initiate cardiopulmonary bypass. An undesirable consequence of this approach is that the complete mobilization of the IVC exposes the patient to a greater risk of a pulmonary embolus than the minimal access approach to be discussed in the next section.

At this time the patients are placed on systemic heparin and traditional bypass initiated with cannulation of the ascending aorta providing arterial return and venous drainage by means of the superior vena cava and right common femoral vein. Thiopental and methylprednisolone are administered as the core temperature is cooled to 18–20 C and the head and abdomen are packed with ice. Approximately 95% of the blood volume is removed providing an essentially bloodless operating field for at least 40 min before neurological sequelae can develop. Retrograde cerebral perfusion or utilization of trickle flow rates between 5 and 10 ml/kg per minute can exceed this length of time.

Next the right atrium is opened and distal control obtained, and any atrial thrombus may be removed to prevent any embolic events during the cavatomy and removal of the infradiaphragmatic tumor thrombus (Fig. 15.23). After distal control is obtained, an anterior cavatomy is made from the renal vein ostium to the level of the minor hepatic veins above the caudate lobe of the liver. The thrombus is removed with patient in

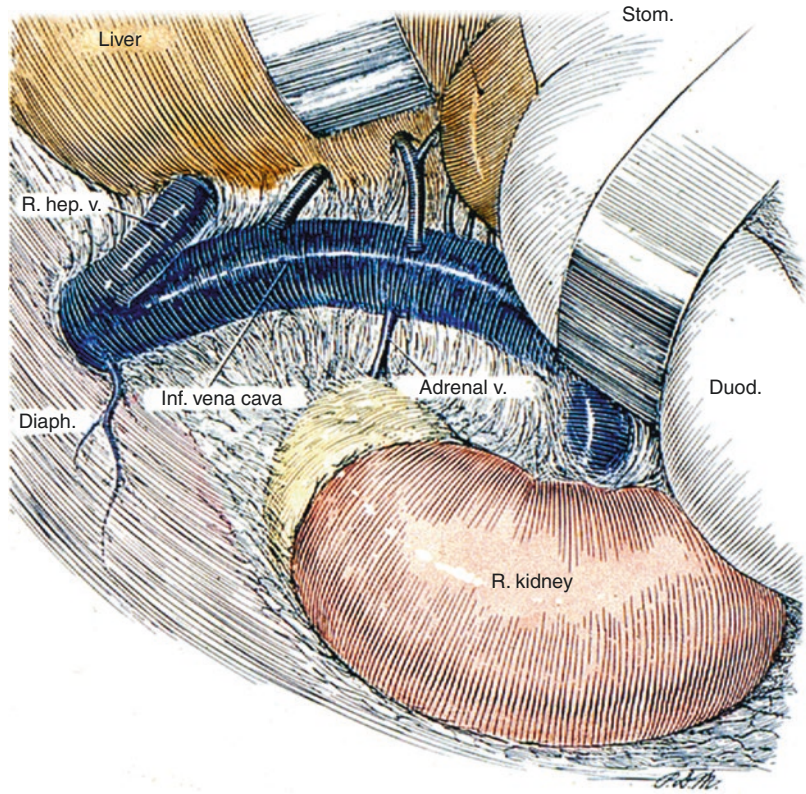


Fig. 15.20 Langenbeck

Trendelenburg's position and using positive pressure respirations. Ideally, the thrombus and the kidney are removed as one unit. Venacavascopy can be performed via the right atriotomy or the cavatomy from below to assure complete clearance of the thrombus, The cavatomy is closed with a running 4-0 Prolene suture (Figs. 15.24, 15.25, 15.26, and 15.27). This approach has been replaced, in our practice, completely by the minimal access approach discussed in the next section. If there is a need for coronary revascularization the traditional approach should be employed.

Cardiopulmonary Bypass (Minimally Access Approach)

First described at our institution in 1998 [18], we have adopted this technique in all patients requiring cardiopulmonary bypass in an effort to shorten the length of surgery and improve postoperative outcomes (decreased mechanical ventilation support and transfusion rates). Following a chevron incision, the IVC is only exposed along the anterior surface without mobilization of the IVC or the kidney; thus reducing the possibility of a pulmonary embolus. At this point, the CT surgeons begin with a 3-cm infraclavicular incision to mobilize and isolate the right subclavian artery. A right 3-cm transverse parasternal incision is made over ribs 3–5, and the respective cartilage is divided and the right internal thoracic artery may require ligation. A pericardial incision is made, and stay sutures are placed in the right atrium in anticipation for a formal atriotomy. An 8-mm synthetic graft is anastomosed to the right subclavian artery as systemic heparinization is instituted. A two-staged venous cannula is inserted into the right atrium and directed into the superior vena cava tor venous return.

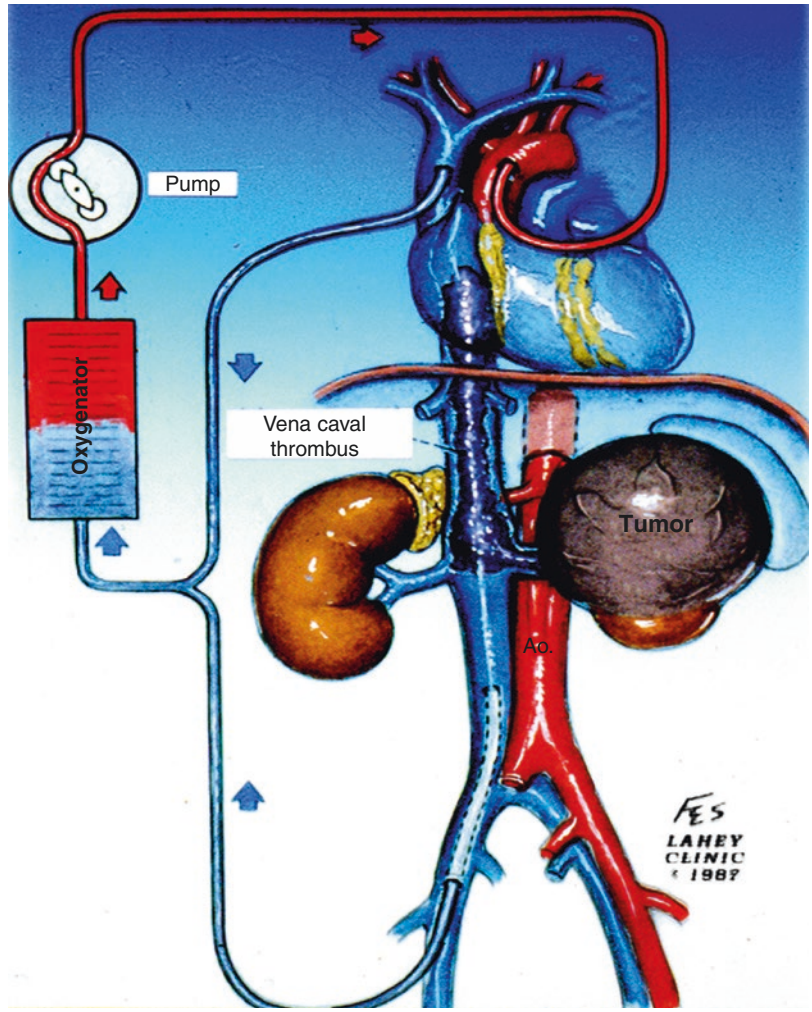


Fig. 15.21 Traditional cardiopulmonary bypass

Cardiopulmonary bypass and deep hypothermic circulatory arrest are initiated as discussed earlier (Fig. 15.28). After appropriate cooling, a formal atriotomy is made and any distal tumor thrombus is extracted. Complete mobilization of the IVC is performed again paying attention to potential bleeding that will resurface during rewarming while heparinized. A cavatomy is performed and the tumor thrombus removed as described in previous sections. Radical nephrectomy is performed, after the IVC is closed, while the patient is being rewarmed and protamine sulfate, fresh frozen plasma, platelets, and desmopressin are administered in order to offset coagulopathies.

Comparative Effectiveness of Median Sternotomy Versus Minimal Access Cardiopulmonary Bypass and Circulatory Arrest for Resection of Renal Cell Carcinoma with Inferior Vena Caval Extension

We recently published our outcomes of cardiopulmonary bypass using the traditional median sternotomy vs minimal access surgery for patients with RCC above the level of the hepatic veins [27, 28]. From 1986 to 2012, 70 radical nephrectomies with concomitant inferior vena cava (IVC) thrombectomies were performed at

our institution using median sternotomy (n = 23 patients) and minimal access (n = 47 patients) techniques. Preoperative patient characteristics, pathologic data, and organ-specific postoperative

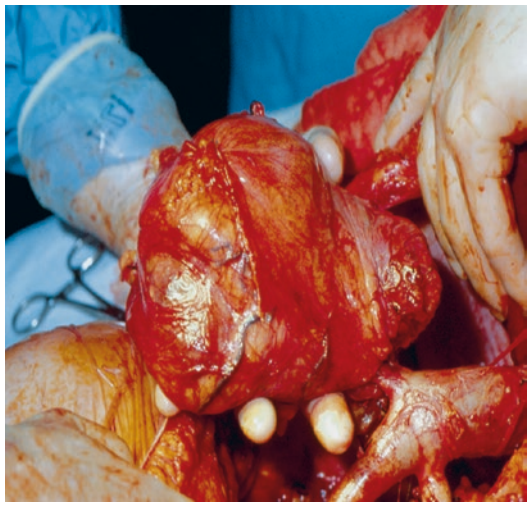


Fig. 15.22 Complete mobilization of the affected kidney with traditional cardiopulmonary bypass

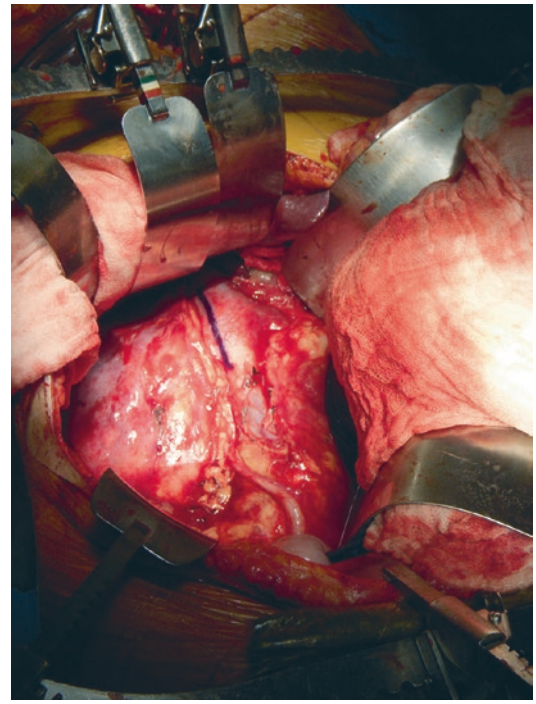
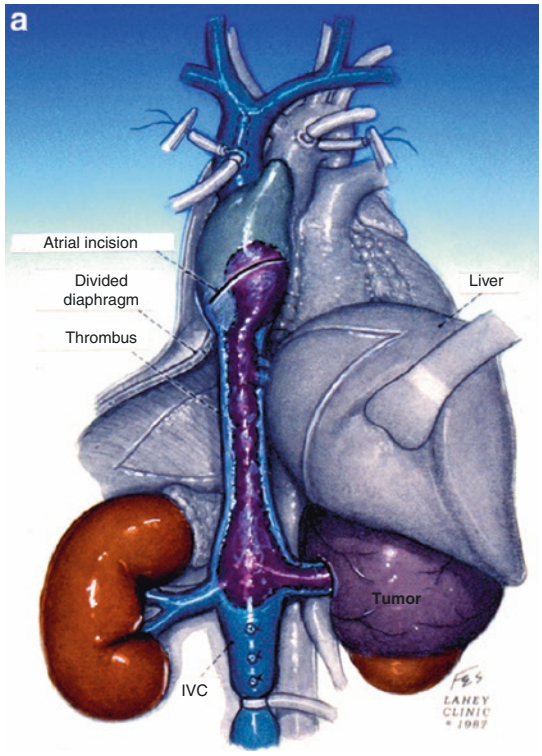


Fig. 15.24 Planned anterior longitudinal cavatomy for larger right renal cell carcinoma with caval tumor thrombus



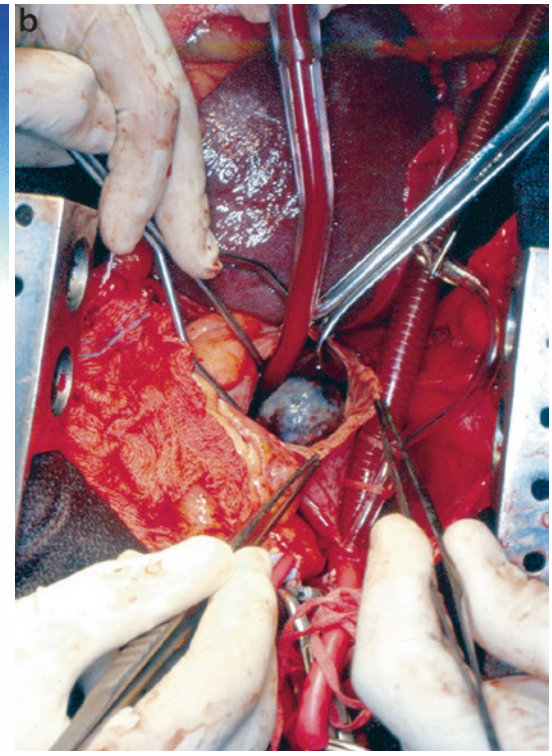


Fig. 15.23 Right atriotomy demonstrating tumor thrombus in the right atrium

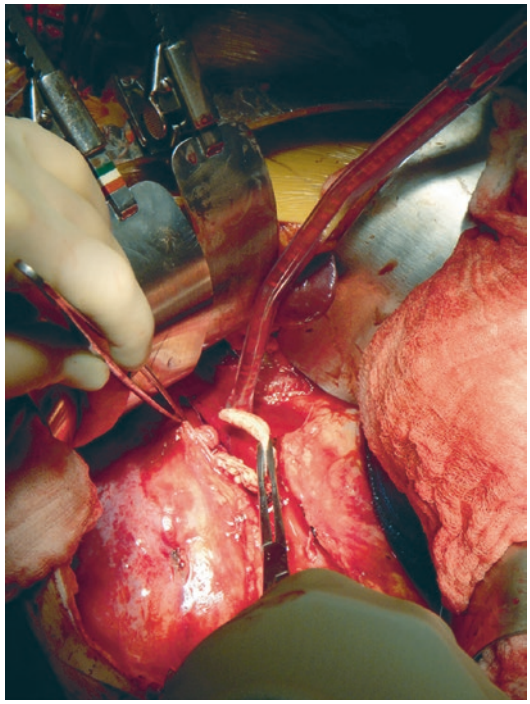


Fig. 15.25 Following cavatomy the thrombus is removed with a pair of forceps and the caval wall is inspected for invasion

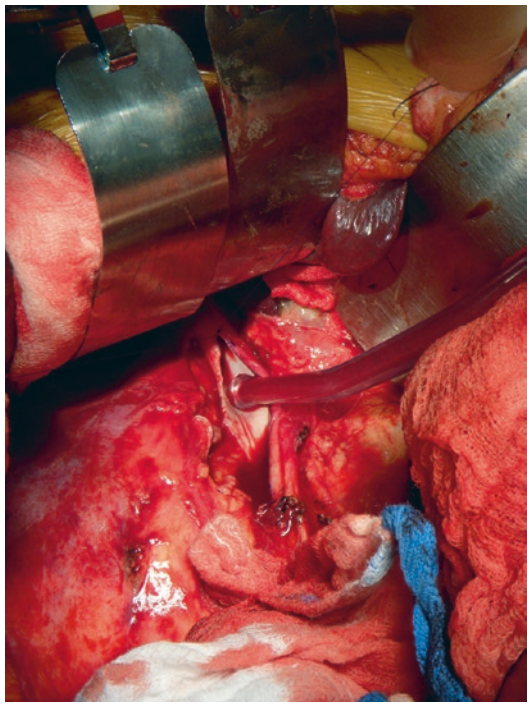


Fig. 15.26 The caval wall is inspected for any of caval wall invasion. A running 4–0 polypropylene suture is started at the cephalad portion of the cavatomy

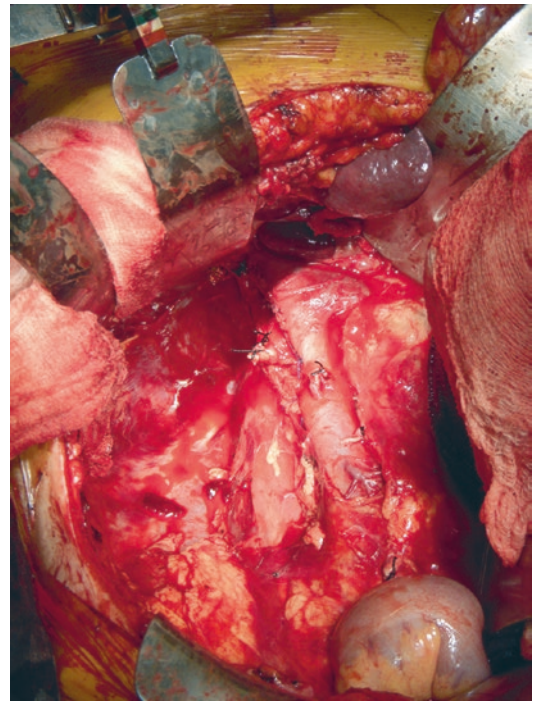


Fig. 15.27 The renal artery is double ligated with 0-silk suture and the cavatomy is closed without significant reduction in the lumen diameter. The gonadal vein has been sacrificed in the foreground

complications and follow-up data were compared between these groups. Estimates of overall and recurrence-free survival were constructed using Kaplan-Meier curves and compared using log-rank testing.

There were no significant differences with respect to patient demographics or preoperative comorbid conditions between the minimal access (MA) and median sternotomy (MS) groups. The MA group showed a significant reduction ($P < 0.05$) in the duration of postoperative mechanical ventilation, length of ICU and hospital stay, operative time, and number of blood transfusions compared to MS patients. Overall and organ-system-specific complications demonstrated a decreased incidence of wound infection (37.9% v. 12.5%, $P = 0.0135$) and sepsis (14.3% v. 0%, $P = 0.0137$) in patients undergoing the MA approach. Perioperative mortality was significantly reduced in the MA group (30.4% v. 8.5% $P = 0.0179$). Recurrence-free survival in the MS group was 0.59 years and 1.2 years in the MA group ($P = 0.06$).

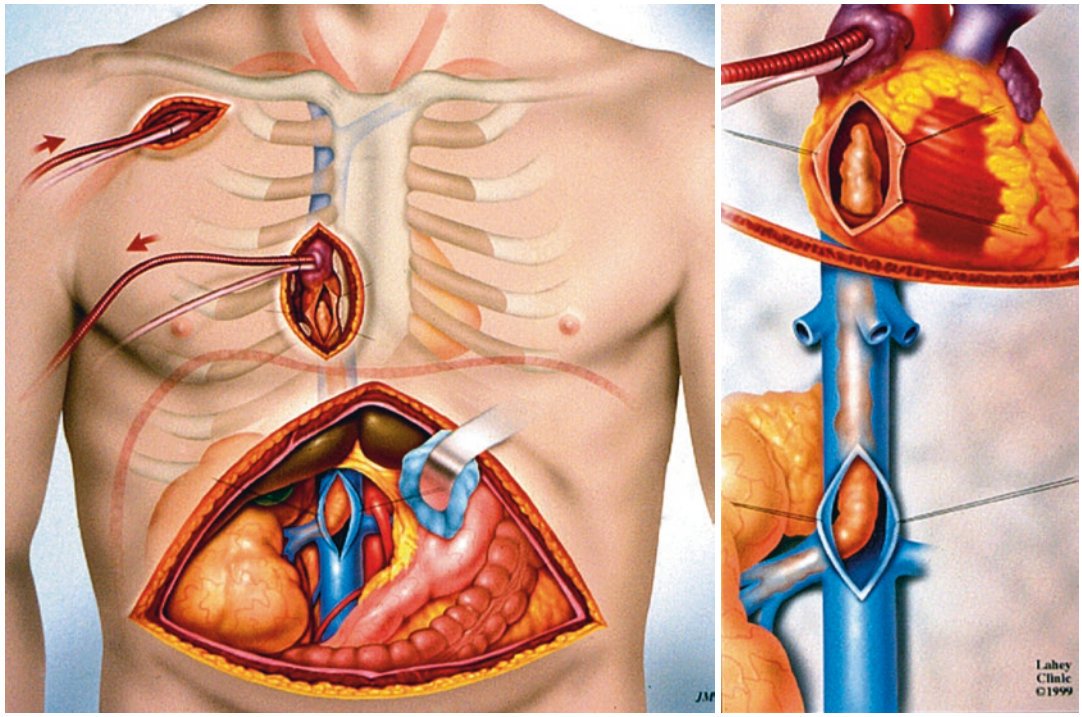


Fig. 15.28 Minimally invasive cardiopulmonary bypass for removal of a large right renal mass with tumor thrombus extending to the right atrium. Schematic demonstrates right subclavian artery graft and right atrial venous cannulation

For all of the abovementioned reasons, we no longer perform the traditional median sternotomy approach and clearly prefer the minimal access surgical approach for cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA) during the resection of RCC with extensive tumor thrombus, because it provides similar oncologic control with decreased duration of mechanical ventilation, length of stay, and infection-related complications. We believe that our findings suggest that MA techniques provide significant advantages over MS and suggest its use to our surgical colleagues as safe and effective.

Occluded Vasculature Management

In certain situations, there may be extensive tumor thrombus involving the contralateral renal vein, hepatic veins, or common iliac veins. In certain situations the thrombus may be of a bland vascular nature, secondary to venous stagnation, and is often easiest removed with gentle flushing. For adherent clot, we recommend using Fogarty balloon catheters for removal. In theory, one could also utilize endoscopy techniques with stone basket retrieval systems although we have yet to personally perform this procedure. Bland thrombus is often more difficult to remove from the venous System because of its gelatinous nature and adherence.

Caval Wall Resection and Caval Interruption

Regardless of the level of the tumor thrombus, one must inspect the caval wall for suspected invasion and perform a partial or complete resection. Studies suggest that invasion may be present in up to 23% of cases with the majority occurring at the renal vein ostium [13, 14, 19]. Caval reconstruction can be performed with synthetic patches (polytetrafluoroethylene) or biological substitutes (autologous saphenous vein or pericardial

patches). During a right radical nephrectomy, the IVC can be ligated or resected, provided the left renal vein is sacrificed distal to the gonadal, lumbar, and adrenal tributaries. Left renal masses with associated thrombus can undergo suprarenal IVC ligation following procedures to extend right venous outflow (autotransplantation or saphenous interposition vein graft to the splenic, portal, or inferior mesenteric vein).

Minimally Invasive Techniques and Tumor Thrombectomy

Renal cell carcinoma with tumor thrombi limited to the renal vein can be treated with pure laparoscopic approaches in many instances, if room is available to place Hem-O-Lok clips without compromising the vena cava or risking a thrombotic event [20]. Laparoscopy has been utilized in the past with hand-assist for removal of IVC tumor thrombi, utilizing intraoperative ultrasound to identify the extent of the tumor thrombus [21]. Hand-assist provides a tactile advantage over pure laparoscopy that is crucial in some cases to confirm ultrasound estimates of tumor thrombus and assist in placing clamps involving the inferior vena cava. The Ohio State University group has published their results utilizing the da Vinci robot to treat five patients with tumor involving the inferior vena cava [22]. While other reports in the literature have explored the possibility of robotic radical nephrectomy and IVC thrombectomy and reconstruction, in my opinion, the risks outweigh the benefits of this approach. In addition, in my experience, the very large size of most of the renal tumors, in general, obviates the benefits of the minimally invasive approach for this clinical problem.

A Novel Approach: Combination of Interventional Radiologic Tumor Extraction and Surgery

A 54-year-old male, with a right renal cell cancer and IVC thrombus at the cavoatrial junction, unfortunately developed a pulmonary embolus 2 weeks before being referred to us for surgery. Following our evaluation, the cardiothoracic surgeons were concerned about the possibility of a massive cytokine release from recently infarcted lung tissue resulting in death that might occur after cardiopulmonary bypass and circulatory arrest. The tumor was angioinfarcted and the patient heparinized, in an effort to delay the needed surgery for 3 months. In spite of angioinfarction the patient began having severe gross hematuria requiring transfusions. He was reevaluated, and we found that the IVC thrombus grew into the right ventricle. This critical situation demands a creative, novel approach. In conjunction with our interventional cardiologist, we were able to place the patient on an extracorporeal oxygen membrane (ECMO) device, whereupon the cardiologist extracted the tumor thrombus down to the level of the renal vein. We were then able to do a radical nephrectomy and IVC thrombectomy without the need to resort to cardiopulmonary bypass and circulatory arrest, thus avoiding the expected massive cytokine release. The patient did extremely well, and he is NED 3 years following surgery [29].

A link to the video of this procedure is listed below.

This novel approach, that of combining interventional removal of tumors above the diaphragm with radical nephrectomy and IVC thrombectomy, may create a new paradigm for the management of supradiaphragmatic tumors in properly selected patients.

Partial Nephrectomy and Tumor Thrombus

Radical nephrectomy (RN) with/without thrombus excision (ThE) is the undisputed standard treatment for kidney cancer (KC) with renal and/or caval thrombus (Th). However, partial nephrectomy (PN) ± ThE may be considered in rare cases when imperative indications exist.

The International RCC-IVC tumor thrombus consortium, founded in 2007, retrospectively reviewed our database of 3000 patients undergoing surgery for RCC with tumor thrombus at 23

institutions between 1971 and 2014. Primary outcomes analyzed were overall (OS) and cancer-specific survival (CSS), renal function variation after surgery, and complications. Secondary outcomes were predictors of OS and CSS for imperative partial nephrectomy cases (IPN). To reduce bias the IPN group was matched with the RN using a propensity score with greedy algorithm on the basis of age, gender, tumor size, TNM, and histology.

Forty-two patients, reported by Giancarlo Marra and associates, underwent imperative partial nephrectomy and tumor thrombectomy. All thrombi were ≥level I; five patients experienced Clavien ≥3 complications with two complication-related deaths. At 27.3 (IQR = 7.1–47.7) months OS and CSS were 54.8% and 78.6%, whereas at 9.7 (IQR = 1.4–43.7) months eGFR change was −17.3 ± 27.0 mL/min. On univariate analysis tumor size, preoperative eGFR, transfusions, hospital stay, high serum creatinine, operating time (OT), complications, lymphadenectomy, and metastases related to an increased risk of death. After matching (n = 38 per arm) no significant differences were present except for tumor necrosis (IPN 39.5%; 15.8%; $P = 0.01$), thrombus level ($P = 0.02$), so too for OT ($P = 0.27$), peri-operative transfusions ($P = 0.74$), and complications ($P = 0.35$). Five-year OS and CSS for imperative partial nephrectomy (IPN were 57.9% and 73.7% respectively with no significant differences with RN (OS 63.2 $P = 0.611$; CSS 68.4 $P > 0.99$). After 14.9 months creatinine and eGFR changes were (+0.4 ± 0.6 mg/dL and − 23.2 ± 37.3 ml/min; $P = 0.2879$). It would appear that in unusual, highly selected cases due to imperative indications, partial nephrectomy and tumor extraction may be an alternative to radical nephrectomy, and tumor extraction for RCC with tumor thrombus, yielding noninferior oncological outcomes, functional outcomes, and complications. Further studies are needed to determine the role of partial nephrectomy and thrombus extraction (PN ± ThE) for RCC patients with a tumor thrombus [30].

At our institution we have an extensive experience utilizing partial nephrectomy to preserve renal function, and have done several partial nephrectomies with renal vein involvement with good results; however, we would only advocate this approach with tumor thrombus in patients with imperative indications for partial nephrectomy, or with tumor involving the major branches of the renal vein with a patent main renal vein, or in a patient with a solitary kidney. However the work of the International consortium, as well as Kim and colleagues, who described two surgical cases with solitary kidneys and tumor thrombus in the renal vein that were spared hemodialysis and remained disease-free at 9 and 24 months, respectively, is noteworthy [23]. We applaud these outcomes; however, we recommend that surgeons undertaking this approach be familiar with extracorporeal bench surgery and renal autotransplantation.

Neoadjuvant Chemotherapy and Tumor Thrombus

As discussed earlier, on rare occasions thrombus in the renal vein or IVC has dramatically decreased in size with the neoadjuvant use of improved chemotherapeutic agents and has resulted in downgrading in some instances. The hypervascular nature or these tumors makes them ideal targets for vascular endothelial growth factor (VEGF) inhibitors. A report from Takeda and colleagues discusses a case in which Sorafenib was used presurgically resulting in a 43% regression in the size of the tumor thrombus, which retracted into the renal vein from the vena cava allowing nephrectomy to proceed [24]. Rini and colleagues recently published supportive phase II trial data in patients with renal vein or IVC extension with tumor shrinkage after neoadjuvant Sunitinib for locally advanced renal cell carcinoma [25]. Data from current investigational studies will help determine the appropriate timing of nephrectomy.

Tumor Thrombectomy and Metastectomy

Metastatic RCC has been shown in some patients to disappear following removal of the affected kidney, a concept known as the Lazarus

effect. At our institution, we advocate removal of accessible pulmonary metastatic disease when possible. In most instances a pulmonary metastectomy, first described by Barney and Churchill, for anterior lower lobe lesions is concomitantly performed with nephrectomy utilizing endovascular staplers and Doyen clamps [26]. We remain optimistic that nonpulmonary metastatic sites may become amenable to resection as we continue to see great strides in molecular targeted chemotherapeutic agents. Our colleagues at the European Organization for Research and Treatment of Cancer are randomizing patients with metastatic disease to neoadjuvant Sunitinib followed by nephrectomy and vice versa.

Personal Experience

The senior surgeon (JAL) of our group has treated 359 patients with renal cell carcinoma and renal vein or caval tumor thrombus. Tumor thrombus level of extension and survival outcomes data are illustrated in Figs. 15.29, 15.30, 15.31, 15.32, and 15.33. Our patient population includes a 2/3 male predominance with an average age of 62. Our complication and survival rates are well within the average of our contemporary colleagues at other major centers. One of our major contributions to managing these complex cases has been the implementation of a minimally invasive approach for cardiopulmonary bypass resulting in decreased blood loss, length of mechanical ventilation, analgesic requirements, duration of surgery, and hospital stay [28].

Another area of involvement in which we have personally participated in is the IRCC-IVC Tumor Thrombus Consortium. Dr. Juan I. Martinez-Salamanca and Dr. John A. Libertino formed the International RCC-IVC Thrombus Consortium in 2007. The consortium now maintains a database for over 3000 patients, from 23 institutions around the globe, suffering from this condition.

International Renal Cell Carcinoma: Venous Thrombus Consortium (IRCC-VTC)

Many lessons have been learned as a result of the collaborative efforts of this international consortium and are best summarized in a recent publication from the consortium [31]. On the basis of the analysis of a clinical, surgical, and pathologic data set from the largest cohort of patients with RCC and venous involvement to date, several issues concerning prognostic factors, operative procedures, and surgical outcomes in this setting have been addressed.

Lessons learned from the consortium include: the recognition of tumor thrombus anatomic level as an independent survival predictive factor, the confirmation of radical surgery

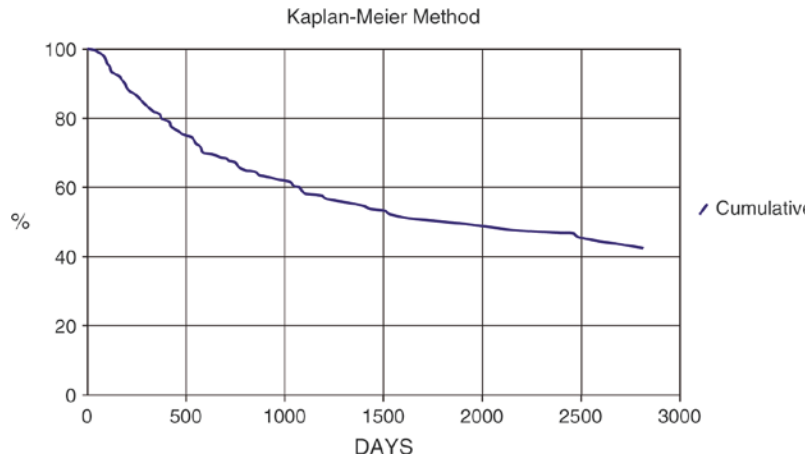


Fig. 15.29 Overall disease-specific survival (n = 300) median – 18 months, mean – 44 months

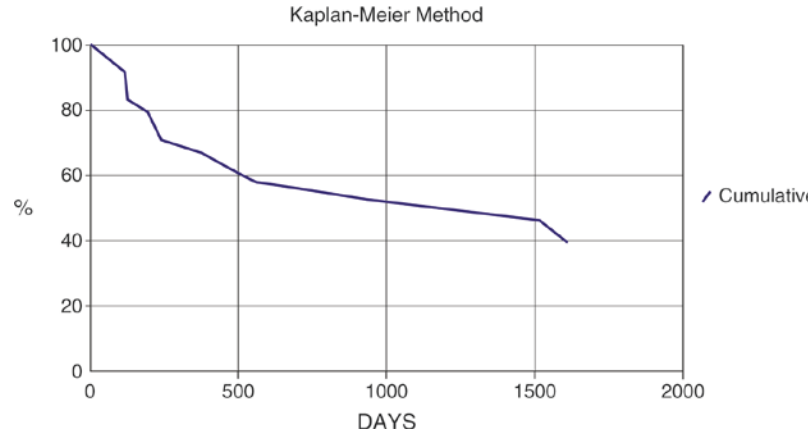


Fig. 15.30 Overall disease-specific survival – atrium ($n = 31$)

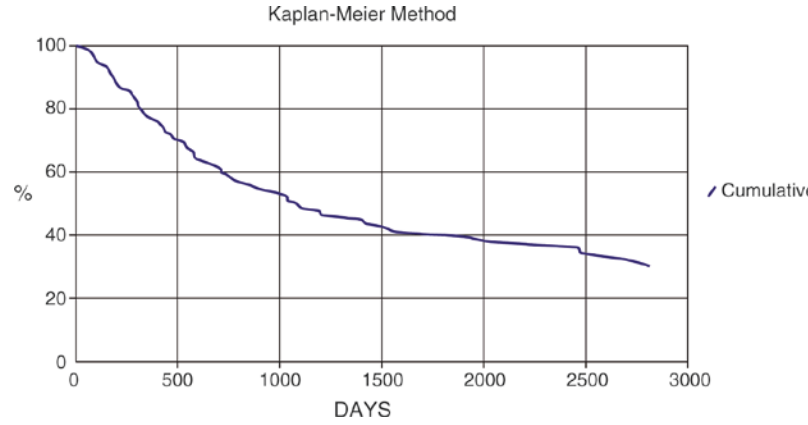


Fig. 15.31 Overall disease-specific survival – vena cava ($n = 146$)

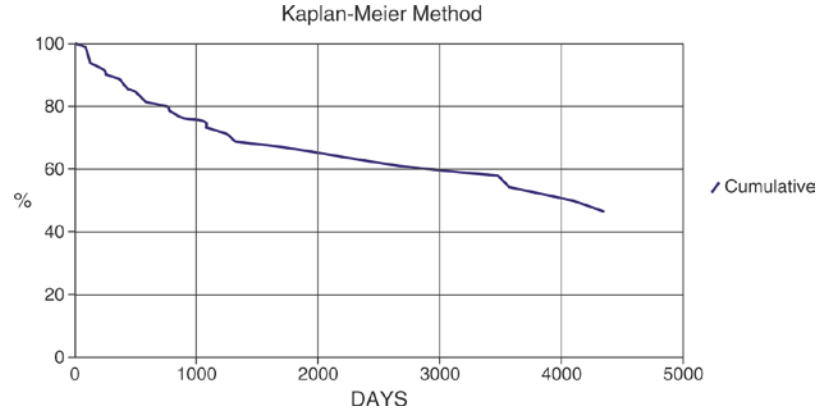


Fig. 15.32 Overall disease-specific survival – renal vein ($n = 123$)

as the mainstay of treatment for these patients even in the metastatic setting, the identification of papillary histological subtypes as a magnifier of oncologic risk when compared to other pathological subtypes, and the description of a direct relationship between the tumor thrombus level and severity of complications, making this a strong predictor of perioperative complications in patients with RCC and tumor thrombus.

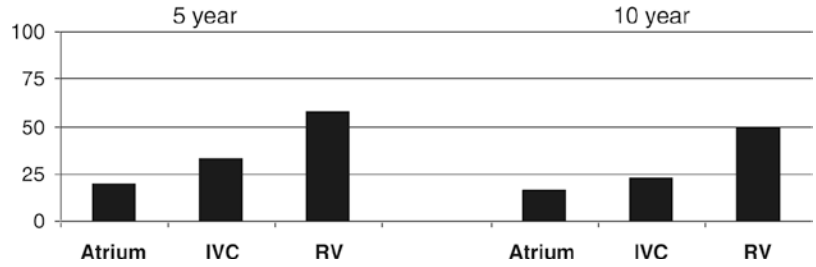


Fig. 15.33 Cancer-specific survival

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Role of Lymphadenectomy in Renal Cell Cancer

16

Mattias Willem van Hattem, Eduard Roussel, Hendrik Van Poppel, and Maarten Albersen

Introduction

After William S. Halsted demonstrated the efficacy of extensive surgical extirpation of regional lymph nodes (lymphadenectomy or lymph node dissection; LND) for breast cancer in 1894, radical excision and regional lymphadenectomy gradually evolved as the standard of care for most carcinomas. Although LND has become an integral part of management for most other genitourinary malignancies, this has to date not been standardized in the management of renal cell carcinoma (RCC). Indeed, no data have clearly demonstrated which patients should undergo LND in the treatment of RCC, and which can be spared this adjunct surgical procedure. Despite decades of evaluation—since Robson and colleagues first reported increased survival in a small cohort of patients who received LND in 1969 [1]—the therapeutic benefit of LND in the management of RCC remains controversial. The rising use of routine computerized tomography (CT), along with advanced imaging techniques, has made possible the early diagnosis of incidental renal masses. Contemporary series suggest that the incidence of isolated lymph node metastases (pN+) in clinically localized disease is small (1–6%) [2–6]. The 5-year overall survival (OS) in these patients is poor and ranges from 15% to 30% [3, 4, 7–9]. The anatomic localization of metastases is unpredictable due to the relatively heterogeneous metastatic spread of RCC through both hematogenous and lymphatic routes [10]. The absence of a demonstrated therapeutic benefit, as reported in the European Organization for Research and Treatment of Cancer (EORTC) trial number 30881 [2], has created controversy regarding the usefulness and extent of LND, formerly considered mandatory at the time of radical nephrectomy (RN) [1]. Patients in contemporary cohorts are more likely to undergo partial nephrectomy (PN) rather than RN and are less likely to undergo concomitant LND and adrenalectomy [11–13]. In this chapter, we assess the role of LND at the time of nephrectomy in patients with RCC. The controversy is whether the role of LND is limited to a staging procedure or whether LND may prevent local recurrence and improve OS.

Anatomy of Regional Lymph Nodes

Historically, RCC have been associated with early haematogenous dissemination rather than a predictable lymphatic spread [10, 14–16]. The patterns of renal lymphatic drainage were initially described by Parker in 1935 [17], during anatomical studies of the posterior lymphatic

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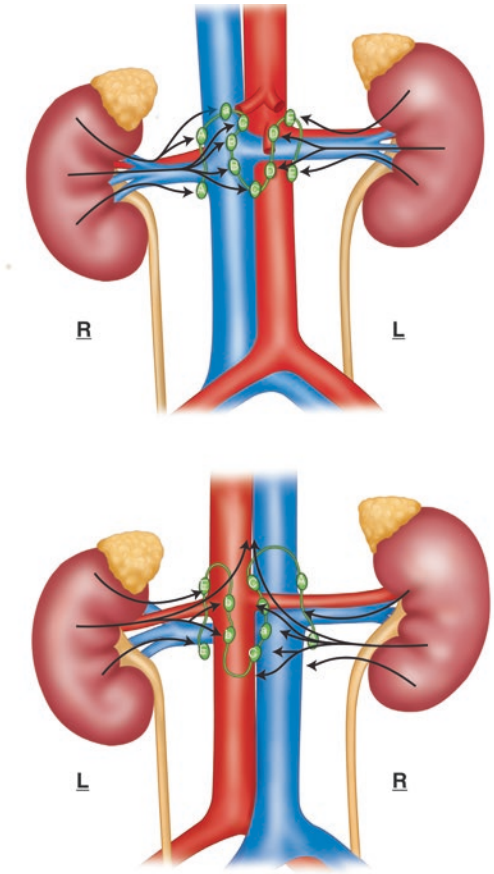
channels of the abdomen. He found that the pathways of retroperitoneal drainage could be quite variable [17]. Assouad et al. [16] confirmed the unpredictable anatomy of the renal lymphatic drainage. The most frequent lymphatic landing sites are paracaval and retrocaval nodes (right kidney), para-aortic and preaortic nodes (left kidney), and interaortocaval nodes (both right and left kidneys). Figure 16.1 shows a summary of the anatomical review of the lymphatic drainage of the kidney. However, in one-third of the patients, renal lymphatics have been found draining directly, without passing through any lymph nodes, into the thoracic duct [16]. Brouwer and colleagues confirmed this direct lymphatic drainage into the thoracic duct for the first time in vivo in humans [18]. They reported on four patients where early lymphatic drainage was visualized along the course of the thoracic duct using lymphoscintigraphy and single-proton emission CT SPECT/CT. In one patient, this was observed without any retroperitoneal lymph node interposition [18]. Saitoh, in an autopsy study of 1828 cases of renal cancer, observed extremely wide variation in the anatomic localization of lymph node metastases from RCC. There was a low incidence of metastases to the ipsilateral adrenal and renal hilar lymph nodes in nephrectomized cases [14]. In another autopsy study, analysing 554 patients with renal cancer, Johnsen and Hellsten [19] found lymph node metastases in 80 patients (14%), of which 75 had additional distant metastases. Exclusively paracaval or para-aortic positive lymph nodes were noted in only five patients (0.9%). Therefore, therapeutic benefit of extensive retroperitoneal LND in association with RN seems to be low. However, more limited LND may be useful, mainly as a staging procedure [19]. The predilection of RCC for early haematogenous dissemination without lymph node infiltration has been shown in different studies [16, 18, 20, 21]. Vasselli et al. [15] reported an incidence of 53% of distant metastasis without lymph node invasion (LNI). In a more recent study, of the 797 patients with metastatic RCC treated with cytoreductive nephrectomy and LND, 57% were found to have no lymph node metastases [22]. This haematogenous dissemination was confirmed by Capitanio et al. in 2016 [20]. A recent study by Kuusk et al. in 2018 observed lymphatic drainage to be outside the locoregional retroperitoneal templates in 35% [21]. One in five patients had supradiaphragmatic sentinel nodes [21].



	Anterior Efferent Lymphatic Vessels	Posterior Efferent Lymphatic Vessels
Right Kidney	A. Paracaval B. Precaval C. Interaortocaval a. Retrocaval	A. Paracaval a. Retrocaval C. Interaortocaval - Thoracic duct
Left Kidney	D. Preaortic E. Para-aortic	D. Para-aortic b. Retroaortic - Thoracic duct

Fig. 16.1 Summary of anatomical review of the lymphatic drainage of the kidney: anterior view (top) and posterior view (bottom). (Reprinted by permission from John Wiley and Sons: Karmali et al. [10], First published: 19 May 2014, doi: https://doi.org/10.1111/bju.12814).

Extent of LND for RCC and Templates

Currently, there is no consensus on the anatomic extent of LND for RCC management [23]. The majority of the studies available report only the presence or the absence of a non-standardized, surgeon-related LND.

The limits of the extended LND (eLND) during RN for RCC have changed over the years. In 1969, Robson and colleagues [1] included an eLND and demonstrated a 22.7% incidence of positive lymph nodes. They supported removal of the para-aortic and paracaval lymph nodes from the bifurcation of the aorta to the crus of the diaphragm as an essential element of RN. They suggested that the improved survival was due in part to this retroperitoneal LND [1]. It is reasonable that a template for LND should be based on the primary lymphatic drainage of the kidney and the location of metastatic disease observed in surgical series [24].

Templates proposed for eLND for tumours on the right kidney included the hilar, para-, pre-, retro-, and interaortocaval lymph nodes, whereas for left-sided tumours, inclusion of the hilar para-, pre- and retro-aortic, and interaortocaval lymph nodes was recommended [25]. Figure 16.2 shows an eLND after removal of the specimen (Fig. 16.2) and the specimen with RN and "en bloc" LND (Fig. 16.2). Crispin et al. [24] proposed a standard surgical template for LND based on locations of lymph node involvement. Of the 169 high-risk RCC patients who underwent LND in conjunction with nephrectomy, 64 patients (38%) had lymph node metastases. Of these 64 patients, 29 (45%) had no metastases in the perihilar lymph nodes, demonstrating the poor staging ability of a hilar-only node dissection. The authors recommend that when performing an LND the paracaval and interaortocaval lymph node is removed in patients with right-sided tumours, and the para-aortic and interaortocaval lymph node is removed from the crus of the diaphragm to the common iliac artery [24].

Although there are no rules regarding the extent and boundaries of LND at the time of RN, the staging accuracy of LND can be improved if extended template LND, rather than limited node sampling, is implemented [26–30]. Herrlinger et al. evaluated in a retrospective study—comparing outcomes of 320 patients who underwent eLND with data of 191 patients who underwent only "facultative" LND (removal of no or only a few nodes for staging purposes)—whether the extent of LND had any significant effect on patient survival. They concluded that eLND improves the prognosis of RCC patients without any additional morbidity and suggest that eLND is superior over facultative LND [26]. Terrone et al. [27] and Joslyn et al. [29] found a positive correlation between the increasing number of nodes

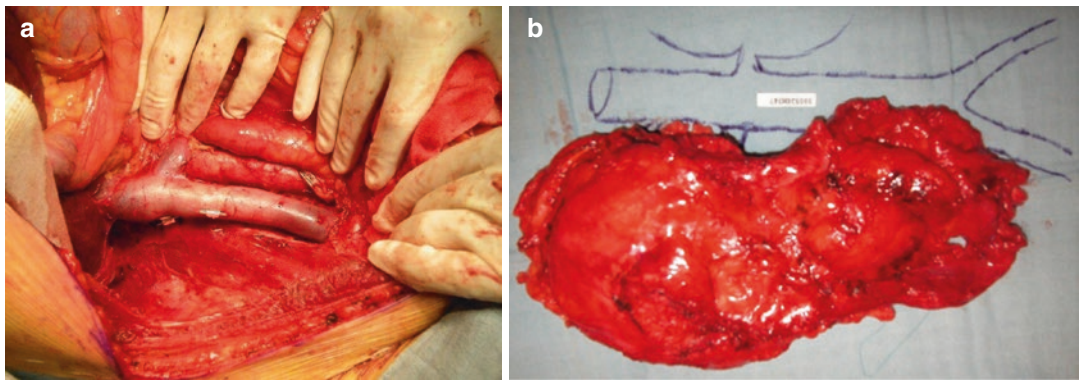


Fig. 16.2 (**a**) Extended lymph node dissection, view after removal of the specimen. (Reprinted by permission from Springer Nature: Van Poppel [70]. (**b**) Specimen with radical nephrectomy and "en bloc" lymph node dissection. (Reprinted by permission from Springer Nature: Van Poppel [70])

examined and the number of positive LNs detected. According to Terrone et al. [27] at least 13 nodes should be excised to provide adequate staging. They reviewed the reports of 725 patients with RCC submitted for RN. When ≥13 lymph nodes were removed the rate of pN+ increased from 10.2% to 20.8% ($P < 0.001$) [27]. Schafhauser et al. found a similar cut-off of 14 lymph nodes [28]. Capitanio et al. reported that when clinically indicated, staging LND in RCC should be extended. According to them the removal of 15 LNs represents the lowest threshold for considering a staging LND as adequate [30]. Moreover, they stated that the greatest accuracy in staging the disease is achieved when about 20 LNs are removed. Their study did not report on the impact on survival of (extended) LND [30].

The required number of lymph nodes examined to provide optimal nodal staging is not well defined by the American Joint Committee on Cancer (AJCC). The European Association of Urology (EAU) specifies that at least 15 LNs should be removed to obtain adequate staging information [31].

Disagreement continues about the ideal limits of LND. Whitson et al. (2011) analysed the Surveillance, Epidemiology, and End Results (SEER) database and found that increasing the number of lymph nodes removed significantly improved disease-specific survival in lymph node positive, nonmetastatic RCC patients. Increasing lymph node yield by 10 nodes resulted in a 10% absolute increase in CSS at 5 years in this subset of patients [32]. However, Sun et al. raised methodological concerns regarding the analysis by Whitson et al. [33]. In a recent study, Capitanio et al. reported improved CSS with a greater extent of LND among patients with pT2, pT3c-pT4 tumours, or tumours with sarcomatoid features [5]. Conversely, Gershman et al. recently reported no association of extent of LND with oncologic outcomes [34].

Nevertheless, selection bias in these reports cannot be excluded and any recommendation regarding the optimal extent of LND in RCC treatment is based on a low level of evidence.

Morbidity of LND

Several studies evaluated peri-operative morbidity of LND [2, 7, 35–37]; none of these studies reported an increased peri-operative morbidity for LND. However, unmeasured confounding may impact the observed results since none provided adjusted effect estimates. The EORTC 30881 trial reported an overall complication rate of 22% and 26% for surgery without or with LND, respectively [2]. The most common complications associated with the surgical treatment of RCC are lymphocele, chylous ascites, bleeding from lumbar or major vessels, and damage to adjacent organs [2]. However, it is difficult to determine a direct correlation of these surgical complications with the LND procedure. Compared to nephrectomy alone, nephrectomy associated with LND did not increase morbidity. Only a slightly higher risk of bleeding was observed among those undergoing LND [2]. LND is still a highly complex procedure and should be performed by well-trained surgeons. A recent study by Gershman et al. [37] reported that LND at the time of RN was associated with an overall complication rate of 9% and a 4% rate for Clavien grade ≥3 complications. In this study, LND was not associated with 30-day complications or prolonged hospitalization on univariable analysis [37]. Likewise, in another recent study (a secondary analysis of the ECOG-ACRIN 2805 trial) there was no difference in complication rates between patients who did and did not undergo LND [36].

With the increased use of laparoscopic techniques in the recent era, there has been some concern about the limited use of LND and about difficulties in performing an adequate laparoscopic LND that may negatively impact treatment outcome. However, a report by Chapman et al. [35] showed that laparoscopic LND in clinically node-negative patients undergoing nephrectomy for RCC is feasible and safe, and may improve staging accuracy. A mean of 12.1 nodes was recovered using an eLND. The overall risk of intraoperative and postoperative complications was similar between the group undergoing laparoscopic RN with LND and the group without LND [35].

False-Positive and False-Negative CT Findings

Today, those patients with micrometastases in normal-sized lymph nodes who might indeed benefit from LND [38] cannot be visualized by the currently available imaging techniques [39]. Therefore, the absence of any evident lymph node metastasis with modern imaging technology should not rule out a regional LND. Figure 16.3a, b show an LND for CT-scan suspicious nodes, in conjunction with PN.

In the detection of microscopic LNI, CT scan can give both false-positive and false-negative images [20, 40]. Studer et al. reviewed CT scans of 163 patients with RCC to evaluate the predictive value for the diagnosis of regional lymph node metastases. False-negative CT scans were found in five patients: two had metastatic nodes in the renal hilus and three had micrometastases in nodes <1 cm. In 43 CT scans, enlarged lymph nodes with a diameter of 1–2.2 cm (median 1.4 cm) were observed. Only 18 of the 43 patients (42%) had lymph node metastases. In 58% the enlarged lymph nodes showed only inflammatory changes and/or follicular hyperplasia (false positivity). This finding was significantly more frequent in patients with renal vein invasion and tumour necrosis (P = 0.0044) [40]. Capitanio et al. performed a systematic analysis of 2954 patients who underwent RN of PN for RCC. Preoperative axial CT scans revealed 424 patients showing at least one enlarged lymph node, cN1. Of those, LNI (pN1) was pathologically confirmed in only 122 patients (28.8%) [20]. However, a recent study by Connolly et al. suggested a sufficient accuracy of modern CT scan predicting metastasis within regional lymph nodes. They reported sensitivity, specificity, positive, and negative predictive values of 82, 71, 56, and 90%, respectively [41]. Despite these findings, the overall consensus remains that nowadays it is not possible to preoperatively differentiate LNI from enlarged inflammatory nodes by using the existing imaging techniques [20, 23, 42].

These studies support the need for eLND in patients where accurate staging is important.

Prevalence of Lymph Node metastases

The incidence of lymph node metastasis has decreased over time. The early study of Robson et al. (1969) and the more recent EORTC 30881 study of Blom et al. (2009) reported an incidence of positive lymph nodes of 22.7% and 4%, respectively [1, 2]. However the EORTC study was limited by patient selection, as most patients included had localized or low-grade RCC [2]. In most historical series, incidence of

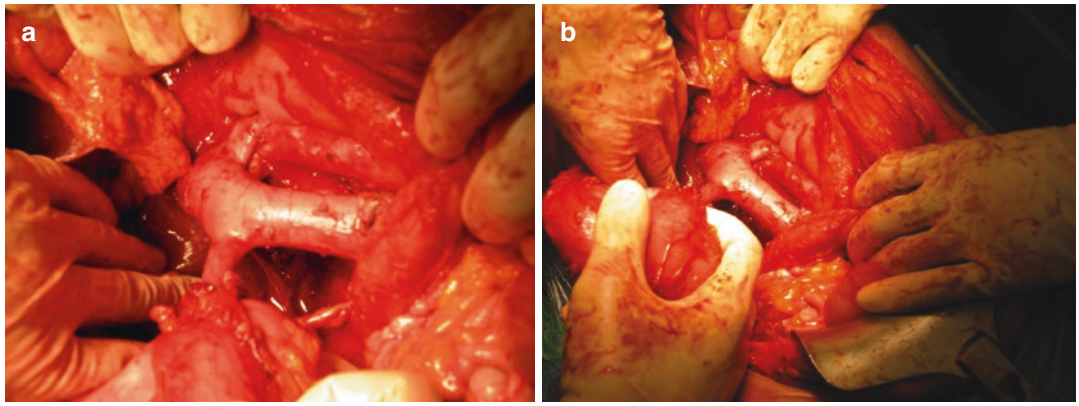


Fig. 16.3 (**a**) Lymph node dissection for CT-scan suspicious nodes, in conjunction with partial nephrectomy. (Reprinted by permission from Springer Nature: Van Poppel [70]). (**b**) Lymph node dissection for CT-scan suspicious nodes, in conjunction with partial nephrectomy. (Reprinted by permission from Springer Nature: Van Poppel [70])

positive lymph nodes among patients undergoing RN and LND ranges from 23% to 35% [1, 43]. In contemporary series, smaller asymptomatic lesions are diagnosed with rising frequency, and the prevalence of LNI has decreased significantly [13]. Nowadays, the incidence of pN+ in a low-risk population of clinically node and metastasis negative (cN0 M0) patients ranges from 1% to 5% [2–4, 42].

Higher clinical stage and higher pathological tumour grade are associated with higher rates of positive nodes. Giuliani et al. reported 13.2% and 36.1% positive nodes in stage pT1–2 and pT3–4, respectively [44]. Pantuck et al. observed 5.2% and 23.4% positive nodes for T1–2 and T3–4, respectively. They reported nodal metastasis in 32% of Fuhrman grade 1–2 tumours and in 68% of grade 3–4 tumours [7]. Sun et al. and Capitanio et al. reported similar findings of increasing prevalence of LNI with increasing tumour stage and grade [4, 5]. In another study, Capitanio et al. reported that the percentage of LNI remained stable over time for locally advanced disease, 12% against 12% in 1988–1996 and 2008–2014, respectively [13]. Blute et al. noted on a multivariate analysis that the risk of dying from RCC was 7.87-fold higher with LNI at nephrectomy than without [3]. Tilki et al. confirmed this worse CSS for LNI at nephrectomy in a cohort of patients with RCC and tumour thrombus. They showed a significantly worse 5-year CSS for pN1 patients compared to pN0- and pNx patients, 22.6%, 68.3%, and 62.5%, respectively [45]. Finally, Pantuck et al. reported that patients who did not undergo LND were 3 times more likely to die than those who underwent the procedure. Recurrence rates were similar regardless of the extent of LND ($P = 0.57$) [7].

Predicting Lymph Node Involvement

Several series indicate that lymph node metastasis is one of the most significant prognostic factors for survival in patients with RCC [1, 7, 8, 29, 45, 46]. The great challenge is to accurately identify those patients that would most benefit from LND.

Protocols and Nomograms

Different clinical predictive tools have been proposed in RCC to identify those patients at risk of harbouring LNI. Blute et al. retrospectively reviewed an institutional cohort of 1652 patients from the Mayo Clinic surgically treated for clinically nonmetastatic (M0) clear cell RCC (68/1652 or 4.1% were pN+). They developed an intraoperative risk factor protocol to predict the probability of regional LNI based on metastatic risk. On multivariate analysis, the primary tumour pathological features of nuclear grade (Fuhrman 3 or 4), tumour size ≥10 cm, pathological stage pT3 or pT4, sarcomatoid differentiation, and the presence of coagulative tumour necrosis can be used to predict patients at the greatest risk for regional LNI at RN [3]. If two or more of these five features are present in the primary tumour there is a 15-fold higher incidence of N+. Moreover, the same authors recently confirmed their results in an updated series of 169 patients who received LND in conjunction with nephrectomy for high-risk RCC. Lymph node metastases were identified in 64 (38%) patients. When two or more of the five primary tumour pathological features were identified during surgery, patients were considered high risk for nodal metastasis and LND was performed at the time of nephrectomy [24]. The difficulty with the application of the protocol is that in routine clinical practice the utility of this protocol is limited as frozen section analysis to determine the risk features is not available at all institutions [38]. Hutterer et al. [47] developed a preoperative nomogram based on patient age, symptom classification, and tumour size to predict the probability of LNI. On multivariate analysis, only tumour size and symptom classification were independent predictors of nodal metastases. External validation demonstrated 78.4% accuracy [47]. However, the nomogram was based on only hilar node dissection, which does not represent the exclusive landing zone for RCC. This may result in remarkable underestimation of the exact number of pN+ patients. Another limitation of the study is that the clinical node status of these patients was not reported.

Capitanio et al. developed a preoperative nomogram to estimate the risk of LN involvement and/or LN progression during follow-up, based

on clinical TNM stage and tumour size [48]. This predictive model had a discrimination of 86.9%. External validation of the nomogram is needed to confirm these findings. Babaian et al. [49] also developed a nomogram based on ECOG performance status, cN stage, lactate dehydrogenase, and local symptoms to estimate the probability of LN involvement with an 89% discrimination after internal validation. In this study, patients with distant metastasis were excluded [49]. Recently, Gershman et al. developed two predictive models based on maximum LN short-axis diameter and presence of radiographic perinephric/sinus fat invasion [50]. These radiographic features outperformed, in their models, traditional clinical variables—as used in the abovementioned protocols and nomograms [3, 24, 47–49]—in predicting pN1 risk [50].

Intra-Operative Lymph Node Assessment

In EORTC study 30,881, 84 patients had palpably enlarged lymph nodes at nephrectomy. In only 14 of these 84 patients (17%), the palpably enlarged lymph nodes were positive for RCC metastases at the time of surgery. That means that in many patients the enlargement of the nodes was not due to metastasis [2]. Intra-operative frozen section has been assessed to guide the decision to perform a full LND. In a recent study, 114 patients with RCC underwent frozen section examination of retroperitoneal enlarged lymph nodes and concurrent regional LND. The final histopathologic results indicated that only 36 patients (31.6%) had nodal metastases at LND. The frozen section examination revealed positive findings in 32 patients and negative findings in four patients [51].

Sentinel Lymph Nodes

Sentinel node biopsy is widely used for nodal staging of melanoma and breast cancer.

Intra-operative sentinel lymph node mapping in the kidney was first described in a live porcine model by Bernie et al. in 2003 [52]. Since then several other groups successfully applied sentinel lymph node mapping techniques to study lymphatic drainage in RCC [18, 53–55]. Bex et al. were the first to explore the sentinel node technique for RCC in humans. They prospectively evaluated the feasibility of intratumoural injection of radiolabelled technetium-99 m (^{99m}Tc) nanocolloid under ultrasound guidance followed by lymphoscintigraphy and hybrid SPECT/CT to image and sample the draining lymph nodes in eight patients with clinical T1-T2N0M0 RCC. Surgery with sampling was performed the following day using a gamma probe and a portable mini gamma camera. Lymphatic mapping was successful in identifying lymphatic drainage in 75% (6 of 8) of patients with visualization of one or more nodes [53]. In a study, performed by the same group, of 20 patients with pT1-2pN0cM0 RCC, visualization of at least one sentinel node in 14/20 (60%) patients was reported [54]. Most of the nodes were within the template as described by Crispen et al. [24]. A Swedish group evaluated the feasibility of performing SN detection in patients with T1b-T3b RCC by preoperative injection of radiolabelled ^{99m}Tc nanocolloid and preoperative lymphoscintigraphy followed by SPEC/CT. They reported SN detection in 10/11 patients with a total of 32 SN identified [55]. Recently, Kuusk et al. performed a phase II, prospective single-arm study investigating the distribution of sentinel nodes from renal tumours on SPECT/CT in 68 patients. They observed lymphatic drainage outside the locoregional retroperitoneal templates in 14 patients (35%). Further, they reported a non-visualization of SN on preoperative imaging in more than a third of patients [21]. The different authors all conclude that sentinel lymph node sampling is feasible and safe, and its use may improve the insight in renal lymphatic drainage. Further studies are needed to demonstrate if identification of lymphatic landing sites may have diagnostic and/or therapeutic significance [21, 53–55].

Future Options

New approaches, such as positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG) or detecting labelled antibodies

against carbonic anhydrase IX (CAIX) [56], have been proposed to improve preoperative staging of RCC patients. However, future studies are needed to confirm these promising findings [23, 42].

When to Perform a LND?

Localized Disease (cT1abN0M0)

Prospective data regarding LND in the treatment of RCC is limited to the EORTC 30881 study that evaluates the outcome in patients with clinically node-negative (cN0) RCC. In this study, 732 patients with clinically node-negative (cN0) RCC without evidence of metastases (M0) were randomized to undergo RN plus eLND ($n = 362$) or RN alone ($n = 370$). LND in conjunction with RN could be performed with no additional morbidity but conferred no survival advantage. The study revealed no significant differences in OS, time to progression of disease, or progression-free survival between the two treatment groups. This is mainly due to the low incidence of unexpected lymph node metastases (4.0%) detected by LND [2]. In patients with low-stage (T1-T2) RCC and clinically negative (cN0) lymph nodes, LND offers no benefit in terms of decreasing disease recurrence or improving survival (level 1 evidence) [2]. An older study presented by Pantuck et al. studying retrospectively 900 patients who underwent nephrectomy for RCC. LND did not offer a survival benefit in patients without enlarged lymph nodes at diagnosis [7]. They reported that in the setting of patients with clinically localized, clinically node-negative RCC (cT1-2N0M0), LND would only be "useful" for staging and not for a proposed therapeutic benefit [7]. Currently the EAU guidelines state that in patients with localized disease and clinically negative (cN0) lymph nodes, LND is not recommended (level 1 evidence) [57].

Localized Disease: Larger Tumours (cT2abN0M0)

Capitanio et al. reported an independent protective effect on survival for LND and its extent in patients with pT2a-pT2b RCC (hazard ratio (HR) 0.91, $P = 0.0008$) and large tumours (tumour size >10 cm) [5]. Conversely, Feuerstein et al. did not find a difference in recurrence-free survival in patients with ≥7-cm tumours whether or not they underwent LND [58]. The authors suggest however a role for LND to acquire important staging information [58]. As mentioned above, Blute et al. and Crispen et al. presented data indicating that patients with larger tumour masses may benefit from LND, at least for staging purposes due to the higher risk of LNI [3, 24]. Recently, Dell'Oglio et al. reported that patients with RCC larger than 7 cm (cT2a or higher) might still benefit from LND because of a non-negligible risk of LNI and/or LN progression [42]. However, as well as Blute et al., Crispen et al. as Dell'Oglio et al. did not evaluate the impact of LND on survival [3, 24, 42].

Locally Advanced Disease (cT3-T4N0M0)

The value of LND in patients with locally advanced disease (cT3–4N0M0) has not been adequately assessed in a prospective randomized study. The EORTC trial has been criticized because most of the patients included in it were at low risk of developing lymph node metastases, suggesting that the study is underpowered to conclude that the outcome in both arms is equivalent for all tumour stages [5, 23, 39, 59]. However, Bekema et al. recently presented a subanalysis of the prospective EORTC trial focusing on cT3 tumours [59]. They showed a not statistically significant improved survival at 5 years for the RN + LND group compared with the no-LND group [59]. This not statistically significant result might reflect the EORTC trial being underpowered to evaluate the impact of LND in this subgroup [23]. Older retrospective studies by Herrlinger et al. and Schafhauser et al. reported improved 5- and 10-year survival rates for patients that underwent RN + eLND compared to patients that underwent RN + LND or simple RN [26, 28]. However, in both studies selection biases cannot be excluded. Blute et al. and Crispen et al. showed that patients with high

stage (pT3-pT4) were twice as likely to have regional LNI compared with low stage RCC (P = 0.017) [3]. Tilki et al. studied the effect of LND on oncological outcome in a specific subset of 1978 patients with RCC and tumour thrombus in the absence of metastatic diseases, using data from the International Renal Cell Carcinoma-Venous Thrombus Consortium (IRCC-VTC). They showed that the number of positive nodes harvested during LND and LN density was strong prognostic indicators of cancer-specific survival. The rate of pN1 patients among clinically node-negative patients was relatively high (9.6%); since the removal of positive nodal disease appears to provide survival benefit, the authors conclude that LND may be warranted in this patient population [45]. In the setting of patients with locally advanced clinically node-negative RCC (cT3–4 N0 M0), LND has a staging as well as a possible therapeutic benefit. Routine LND should at least be offered to these very high-risk patients.

Clinical Node-Positive (cT1-4, N+M0) RCC

Several older retrospective reports have suggested a role of LND in the presence of clinical positive lymph nodes and no distant metastases [26, 60–63]. Already in 1980, Peters and Brown demonstrated an improved survival associated with LND, with an increase in the 5-year survival from 25.8% to 43.5% [60]. Similar findings, of a survival benefit attributed to LND, were reported by Herrlinger et al. [26], Giberti et al. [61], and Canfield et al. [62]. Another retrospective analysis of pooled data of 171 RCC patients with positive nodal metastases and absence of distant metastases showed a 10- to 15-year CSS of approximately 30%, suggesting that LND of positive nodal metastases in patients undergoing RN for RCC may be beneficial for some patients [63]. However, these historical series comprise small cohorts and biases such as selection bias must be considered.

Among contemporary studies, the Mayo Clinic reported on a large RN cohort: 1797 patients of whom 606 underwent an LND. Here, no survival benefit was associated with LND at RN [34]. Recently, the same group presented an extended RN cohort of 2722 patients of whom 1215 underwent LND. Overall 171 patients (6.3%) had pN1 disease. Median follow-up was 9.6 years [6]. This analysis confirmed their previous findings that LND is not associated with improved oncological outcomes among patients at high risk who undergo radical nephrectomy for M0 RCC. This included patients with radiographic lymphadenopathy and across increasing probability thresholds of pN1 disease [6]. However, a methodological issue was reported by Porter since 153 high-risk patients were excluded from the propensity matching analysis because there were no suitable matches in the non-LND group [64]. A recent secondary analysis of the ASSURE (ECOG-ACRIN 2805) adjuvant trial by Ristau et al. reported no improvement in survival, for adjuvant therapy relative to placebo, in patients with pN+ who underwent LND [36]. Gershman et al. report a poor prognosis for isolated pN1 disease with a 5-year probability of metastasis-free survival of only 16%. Nevertheless, they state that a subset of patients experience durable long-term survival to 10 years after surgical resection of isolated lymphatic metastases, suggesting a potential therapeutic role of LND for a small subset of patients [8].

Current EAU guidelines state that in patients with localized disease and clinically enlarged lymph nodes, use of LND can provide staging information and thus is always justified (level 3 evidence) [31, 57].

Regional Lymph Node Recurrence

Therapeutically, LND might help reduce the incidence of local recurrences. Kwon et al. followed 1503 patients who had undergone nephrectomy for RCC and found that 2.4% (36/1503) had a local recurrence with the most common site being regional lymph nodes (30/36) [65]. A recent series of the Mayo Clinic examined the outcomes of 15 patients who underwent salvage retroperitoneal LND for isolated lymph node recurrence after RN. Median time from nephrectomy to resection was 10.3 months (3–159).

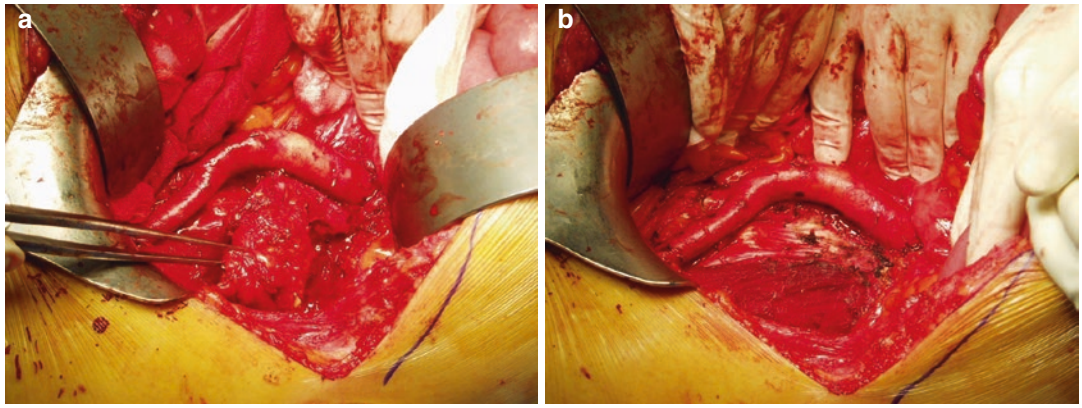


Fig. 16.4 (**a**) Salvage LND for recurrence after radical nephrectomy. (Reprinted by permission from Springer Nature: Van Poppel [70]). (**b**) After removal of lymph node recurrence. (Reprinted by permission from Springer Nature: Van Poppel [70])

Approximately two thirds (66.7%) of patients progressed after salvage retroperitoneal LND at a median of 6 months [3–27] after RN. Median progression-free survival (9.1 months) was comparable to that of patients who had lymph node-positive RCC (8.7 months) at the time of RN. The authors concluded that a proportion of patients with isolated lymph node recurrence would benefit from salvage surgery [66]. More recently a multi-institutional study by Russell et al. reported the largest cohort of patients ($n = 50$) after surgical resection of isolated retroperitoneal lymph node recurrence of RCC after nephrectomy and no evidence of distal metastases [67]. These reports indicate the potential benefit of resection of isolated nodal recurrence in highly selected patients. Furthermore, they highlight the potential for undertreatment that may occur when LND is not incorporated into the initial resection for some patients. Figure 16.4 shows salvage LND for recurrence after RN (Fig. 16.4a) and a view after removal of lymph node recurrence (Fig. 16.4b).

Distant Metastasis and Cytoreduction (cTanyNanyM1)

The value of LND in patients with metastatic disease during cytoreductive nephrectomy has been assessed by several older and recent retrospective studies in the era of immunotherapy [7, 15, 22, 46, 68, 69]. These studies have shown conflicting results. Older studies have suggested a potential role for LND in patients in the metastatic RCC setting. Vasselli et al. evaluated the presence of lymphadenopathy (radiographic cN+) in 154 patients with metastatic RCC undergoing cytoreductive nephrectomy prior to treatment with interleukin-2 (Il-2). No significant difference in survival was observed between patients with preoperative positive lymph nodes who had a complete regional LND and those with preoperative negative lymph nodes, suggesting a possible benefit of LND. No significant differences in response rate for IL-2 were detected with respect to the absence or presence of lymphadenopathy [15]. Similarly, Pantuck et al. reported a significant survival advantage (approximately 5 months) in 112 node-positive patients who underwent LND at the time of cytoreductive nephrectomy prior to immunotherapy, compared with 17 node-positive patients who did not undergo LND ($P = 0.0002$) [7].

Contemporary studies have not demonstrated a survival benefit between patients with metastases at diagnosis that did or did not underwent LND. Capitanio et al. observed in a cohort of 1938 patients (M0 and M+) no effect of LND and its extent in the group of M+ patients; they state that an effect of LND may be expected in a proportion of those patients, e.g. when the patient

shows a bulky mass or a tumour with sarcomatoid features [5]. Feuerstein et al. reported on a cohort of 256 patients who underwent cytoreductive no significant difference in 5-year survival between patients who did and did not underwent LND, 21% against 31%, respectively [68]. The 5-year overall survival was 27% and 9% for negative and positive nodal status, respectively ($P < 0.0005$) [68]. Similarly, Gershman et al. presented data using propensity score techniques, on 305 patients undergoing cytoreductive nephrectomy, not supporting an oncological benefit of LND [69].

Notwithstanding the discordance concerning the therapeutic benefit of LND in M+ RCC, all authors report the presence of lymphatic involvement as an independent worse predictor of survival in patients with distant metastases [5, 7, 22, 46, 68, 69]. Indicating that LND may still serve as an important tool for staging purposes.

In summary, in patients with T1-T2 N0 RCC and an absence of unfavourable characteristics, regional LND offers limited staging information and no benefit in terms of decreasing disease recurrence or improving survival (level 1 evidence). However, it cannot be concluded that LND is of no benefit in CT-negative patients. Removal of LNs containing microscopic metastases may be beneficial to some patients [8, 9, 38].

In high-risk patients (cT3-T4N0M0 or cTanyN+M0), discordance exists with some of the retrospective nonrandomized studies suggesting a possible benefit of regional LND on CSS. In the setting of patients with clinical node-positive RCC (cTanyN+M0), LND has a staging as well as a possible therapeutic benefit. If RN or PN is planned, enlarged lymph nodes either at imaging or palpation during surgery should be resected when technically feasible (level 3 evidence).

A recent systematic review and meta-analysis by Bhindi et al. reported that the existing literature does not support a survival benefit with LND in either M0 or M1 RCC [9]. However, a small subset of patients with isolated nodal metastases experience long-term survival after surgical resection [9]. They conclude that LND may play an important staging role in the contemporary management of RCC [9].

Conclusion and Future Research

Patients with low-grade RCC (cT1-2N0M0) without lymphadenopathy are considered at low risk for LNI, and therefore many urologists find that omitting LND is acceptable. In high-grade RCC, most historic studies report a benefit of LND on survival, whereas more recent studies do not demonstrate a survival benefit for LND. Notwithstanding the discordance over the therapeutic benefit of LND, most studies support a staging role for LND as pN1 status is independently associated with worse survival in both M0 and M1 RCC. For now, it would be prudent to continue performing LND in carefully selected patients with a high risk of nodal metastasis based on preoperative clinical features, being TNM stage and tumour size.

Definition of template and techniques require standardization and in view of directing patients to adjuvant therapies; further prospective studies will be warranted to redefine the prognostic and therapeutic value of LND in the management of renal tumours. Future research should focus on improved imaging techniques to detect nodal and distant metastases, validation of LND templates, and the development of prediction tools which use clinical variables to suggest who is likely to benefit from LND. The introduction of informative biomarkers capable of identifying the risk of LNI might help clinicians in decision making. Advancements in tumour molecular profiling will also be important aspects for determining the most favourable treatment strategy. Ultimately, the hope is to build an evidence-based consensus on the role and extent of LND in patients with RCC.

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17 Role of Surgery in Locally Recurrent and Metastatic Renal Cancer

Andrew G. McIntosh, Eric C. Umbreit, and Christopher G. Wood

Kidney Cancer and Recurrence

Approximately 63,990 new kidney cancer cases and 14,400 kidney cancer deaths occurred in the United States in 2017 [1]. Most cases are not metastatic at presentation; however, between 30% and 40% of kidney cancer patients will either present with or later develop metastatic disease [2, 3]. Most patients with localized disease at presentation will be managed with surgical therapy. Recurrent disease has been reported in approximately 11% of patients treated with surgical resection of non-metastatic kidney tumors, with local recurrences occurring in 1–5% of patients following partial nephrectomy (PN) and 1–3% of patients following radical nephrectomy (RN) [4–11].

Locally recurrent disease often presents clinicians with surgically challenging and therapeutically complex disease. Repeat surgery in the ipsilateral retroperitoneum either following prior RN, PN, or ablative procedures has been associated with increased morbidity and may lead to worse renal functional outcomes [12–15]. However, aggressive surgical resection is justified if technically feasible as long-term survival can be achieved. As targeted systemic agents for advanced and metastatic renal cell carcinoma (RCC) revolutionize the treatment landscape, clinicians are beginning to implement these therapies in both neoadjuvant and adjuvant settings surrounding recurrent disease [16, 17]. By extension, appropriate patient selection becomes paramount in triaging patients to appropriate treatment plans.

Metastatic disease presents its own diverse set of challenges. With targeted therapies showing promise, the application of surgical intervention is evolving, but a significant proportion of patients will not demonstrate adequate response rates [18]. Surgical resection remains an important modality in the treatment of metastatic patients with 5-year survival rates as high as 50% in several retrospective series [19–21].

Recurrence After RN

In the absence of distant metastatic disease, localized retroperitoneal recurrence (RPR)—disease recurrence in these perinephric soft tissues/renal fossa, psoas muscle, ipsilateral adrenal gland, or ipsilateral lymph nodes—following curative RN for RCC is rare (Fig. 17.1) [15]. While modern imaging modalities have enhanced surveillance)strategies following RN, the incidence of isolated RPR from cancer centers with extensive nephrectomy cohorts is low, ranging from 1% to 3%, rarely occurring in the absence of distant metastatic disease [9–11]. As no prospective, randomized clinical trials exist involving

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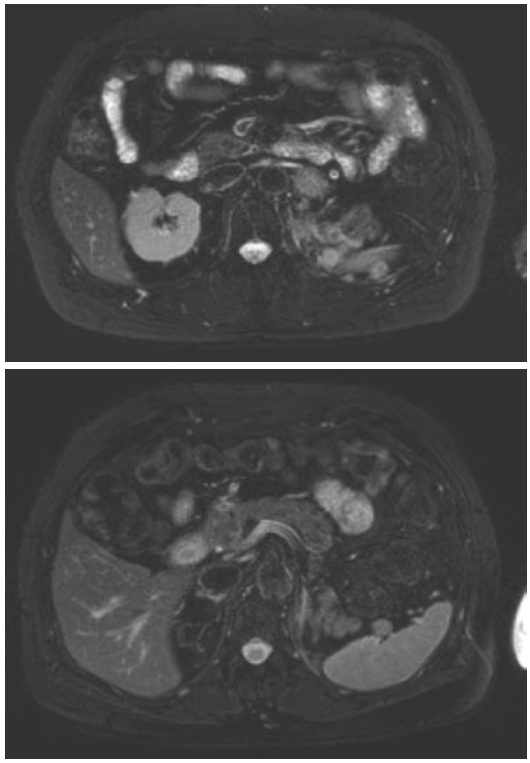

Fig. 17.1 MRI of the abdomen revealing a local recurrence in the left renal fossa following a prior left radical nephrectomy. The patient underwent RPR resection with resection of renal artery and venous stump. Additionally, a distal pancreatectomy, splenectomy, left hemicolectomy, left adrenalectomy, omentectomy, partial diaphragm resection, and retroperitoneal lymph node dissection were performed. The patient was disease free 21 months postoperatively

RPR, clinicians must rely on retrospective series to elucidate optimized management strategies.

RPR likely evolves secondary to the presence of micrometastatic disease in the nephrectomy bed, regional lymph nodes (LN), or microscopic invasion of adjacent organs (e.g., pancreas, spleen, stomach, duodenum, etc.) not recognized at the time of extirpative RN [22]. Indeed, positive surgical margins have been noted to be a risk factor for RPR [23]. Although most reported experience with RPR involves open surgical resection, laparoscopic approaches have been described in small case-series [24, 25]. Additionally, a small series of three patients undergoing percutaneous cryoablation for RPR has been described, with two patients remaining disease free at 43 months [26].

Patients with RPR have historically had a poor prognosis and are at high risk of developing clinically apparent distant metastatic disease over short periods, thus representing a complex therapeutic challenge [27, 28]. Autopsies of patients deceased due to metastatic RCC have revealed subclinical disease in nephrectomy beds, suggesting a close relationship between RPR and distant disease [29]. Moreover, patients with isolated RPR represent a significant surgical dilemma, as early reports on outcomes of patients with RPR are notable for significant surgical morbidity [9, 10, 22, 30–32]. Long-term survival, however, was achieved in significant proportions of patients, suggesting an aggressive surgical resection can be prudent. As such, aggressive operative interventions for RPR have been reported, often requiring the resection of organs adjacent to the tumor [28]. These series represent efforts to address RPR prior to the era of targeted therapy for locally advanced/recurrent and metastatic RCC, which have improved survival and response rates [17]. As such, treatment paradigms are shifting to involve a multidisciplinary approach, combining medical and surgical interventions in patients with RRP, which is critical to optimize oncologic outcomes while minimizing patient morbidity [9].

Further complicating the diagnosis and surgical evaluation of RPR may be the appearance of inferior vena cava tumor thrombus, sometimes extending into the right atrium. This scenario often requires collaboration with one or more additional surgical teams such as vascular surgery for possible vena caval reconstruction/grafting and cardiac surgery for utilization of cardiac bypass, if needed, for tumors extending into the heart. Despite the technical difficulties, surgical resection can be successful and is advisable in selected patients [33–36].

The largest series of patients with RPR comes from MD Anderson Cancer Center (102 patients; 32-month median follow-up) where Thomas et al. note an encouraging CSS of 92%, 71%, and 52% at 1, 3, and 5 years, respectively [15]. In addition, over 60% of patients with no evidence of disease (NED) or alive with disease at last follow-up. This is somewhat in contrast with a

multi-institutional French cohort reported by Paparel et al. (72 patients; 26-month median follow-up) where more modest CSS rates of 74%, 55%, and 46% are reported at 1, 3, and 5 years, respectively, and a meager 17% of patients NED at last follow-up [37]. This is likely accounted for by the fact that in the latter series a larger proportion of patients (30%) had distant metastatic disease at presentation with RPR while in the MD Anderson series 100% of patients had localized RPR undergoing surgery. Encouraging survival outcomes in a larger cohort all treated with surgery advocates for an aggressive surgical approach in well-selected patients. More recently, Herout et al. (54 patients; 48-month median follow-up) reported further favorable results in a cohort of patients undergoing surgery for RPR with a 5-year overall survival (OS) of 60% (median OS 6.6 years) and 48% of patients either NED or alive with disease at last follow-up.

Improvements in outcomes for recently published series of patients with RPR also likely reflects the revolutionary impact of the targeted systemic therapy era in managing locally advanced and metastatic disease [16]. In recent series, >50% of patients received targeted therapy for RPR in either the neoadjuvant or salvage settings [15, 37]. Despite significant improvements in the application of targeted therapy in these patients, no prospective trials exist directly comparing systemic targeted therapy to surgical extirpation in patients with RPR.

Given the high surgical morbidity reported in early series [38], Margulis et al. identified prognostic features for cancer-specific survival (CSS) at RPR extirpation that can be used to help appropriately select patients for surgery. On multivariate analysis (MVA), these included a positive surgical margin after RPR resection (RR 3.34, 95% CI 1.01–13.03, $P = 0.04$), recurrent tumor size (RR 1.16, 95% CI 1.08–1.48, $P = 0.004$), and sarcomatoid features in the RPR (RR 4.68, 95% CI 1.08–20.36, $P = 0.04$). Abnormal serum alkaline phosphatase and lactate dehydrogenase also had a strong association with poor CSS on univariate analysis, but this was not statistically significant on multivariate analysis. An updated report reveals that pN1 patients (HR 4.08, 95% CI 1.89–8.83, $P = 0.001$) at index nephrectomy had a significantly worse CSS at RPR surgery while RPR size remained a significant predictor of cancer-specific mortality on MVA [15]. Sarcomatoid features in RPR specimen, positive surgical margins in the RPR specimen, Charlson score ≥2 [39], along with time to recurrence and surgical intervention [37] have also been reported to be predictive of OS in larger series. Recently, complication rates of 29–45% have been reported; however, the majority of these patients had Clavien 1–2 complications, representing a significant improvement from early cohorts [15, 37, 39]. Nevertheless, high complication rates are observed emphasizing the importance of referral of patients with RPR to high-volume centers.

RPR following RN is a complex therapeutic problem with a historically poor prognosis. In experienced centers, long-term survival with limited morbidity can be achieved with aggressive surgical resection. The targeted therapy era for advanced and metastatic RCC provokes elusive questions about the appropriate balance of systemic therapy and aggressive surgical intervention that can only be appropriately answered with prospective trials of these approaches.

Recurrence After PN

In the past two decades, the use of PN has evolved to replace RN as the standard of care for the surgical management of localized cT1 renal masses (<7 cm). Further, PN is being expanded to include tumors of any size assuming optimal oncologic control is feasible [40–42]. By extension, a proportion of patients (approximately 1–5% [4–8]) will develop ipsilateral recurrent (IR) disease following PN (Fig. 17.2). The majority of these recurrences are likely sporadic and metachronous ipsilateral tumors, with bonified recurrence in the previous PN surgical bed likely quite rare [4, 43]. The literature on local recurrence following PN is sparse, and reliant on small, retrospective cohorts of patients. Additionally, authors employ varied and broad definitions of local recurrence, leading to difficult to interpret data across the available literature. No doubt, it is often not possible for

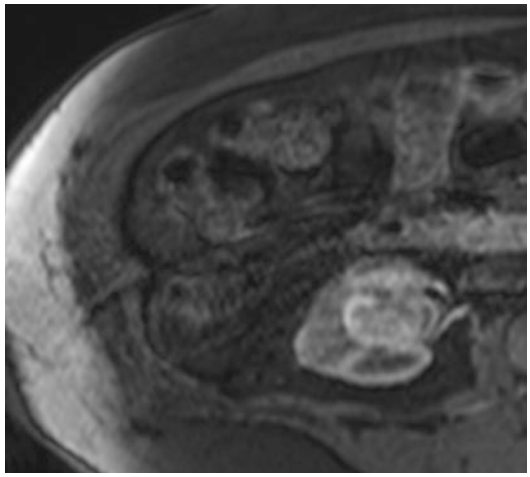

Fig. 17.2 MRI of the abdomen revealing a 5.5-cm right local recurrence following a prior right partial nephrectomy. The patient underwent a successful laparoscopic right radical nephrectomy revealing pT3a clear cell RCC with negative margins. The patient is without evidence of disease 30 months postoperatively

clinicians to determine whether an IR represents an incomplete index resection or a new tumor. The role of surgery is, as a result, not well defined.

Patients with a positive surgical margin (PSM) at PN are more likely to develop a local recurrence [44, 45] and time-to-recurrence has been shown to be shorter in patients with a PSM [4]. It is less clear, however, what impact a PSM has on oncologic outcomes. Yossepovich et al. investigated 1344 patients undergoing PN over more than three decades at Memorial Sloan Kettering and the Mayo Clinic and found the PSM rate to be 5.5%. No difference was noted in local or metastatic recurrence rates between patients with PSM or negative surgical margins (NSM) [46]. This finding is further supported by Bensalah et al. who found in a multi-institutional cohort of 111 patients with PSM compared to a matched cohort of 664 patients with NSM that there was no difference in recurrence-free survival (RFS), CSS, or OS between the groups [45]. Conversely, in a recent analysis of a large multi-institutional prospectively maintained a cohort of 943 patients undergoing robotic PN, Khalifeh et al. demonstrated a PSM rate of 2.2% and a markedly increased risk of recurrence (HR 18.4) in the PSM group in addition to lower RFS and CSS [44]. This study, however, may exhibit some statistical flaws related to a low number of events [47]. In general, experts advocate observation in the setting of a positive margin until visible disease is apparent [5].

Re-do surgery for ipsilateral recurrence (IR) following PN presents a difficult challenge. Planes may be obliterated and scarred, leading to a tedious and vexing operation, complicated by altered anatomical relationships and surgical landmarks replaced with fibrosis. Again, the literature on this topic is limited to a few heterogeneous cohorts, and most studies do not define local recurrence or differentiate between metachronous separate tumors and true tumor-bed recurrence. Furthermore, much of the available literature is based on patients with hereditary RCC and therefore likely represents mostly metachronous ipsilateral tumors. The group at the National Cancer Institute (NCI) reported their experience with repeat PN in patients with hereditary RCC, citing a 19.6% major complication rate and significant renal functional decline. The same group reported acceptable oncologic outcomes (95% MFS at 57 months) for repeat PN in a solitary kidney [12]. The NCI group subsequently published perioperative outcomes in patients who underwent repeat ipsilateral robotic PN, including patients with both hereditary and sporadic RCC. They found that operative time, renal functional outcomes, and most complications (urine leak was higher in the repeat group) were similar compared to patients undergoing initial robotic PN. Oncologic outcomes were not analyzed [48]. In a separate report on 25 patients undergoing repeat partial nephrectomy in a solitary kidney, they reported a complication rate of 52%, including 4 patients rendered anephric and one perioperative death. However, MFS at 57 months was 95%. As such, although high risk, nephron-sparing surgery can be justified to save patients being burdened by definitive dialysis.

Finally, the group at MD Anderson recently published their analysis of a cohort of 44 patients (1.9%) with IR following PN matched with 163 controls (underwent PN without recurrence). This study was unique in that it employed a strict definition of IR in order to isolate those patients

with true tumor-bed recurrence; limiting the inclusion criteria to those with a new enhancing lesion in the surgical bed or in the same region as the original PN site and excluding hereditary RCC. Patients with IR had more complex operations (longer operative times, higher EBL, and longer clamp time) and were more likely to have pT3 pathology and positive margins. Of the patients with IR, 55% underwent salvage surgery, with the remainder have alternate therapy (e.g., ablation, systemic therapy). No significant difference in OS was noted with a mean (+/− SD) 5-year OS was 77.5% (+/− 6.5%) in the IR group vs. 83.2% (+/− 3.4%) in the control group ($P = 0.22$). However, the IR group experienced significantly worse 5-year CSS (86.4% [+/− 5.5%] vs. 99% [+/− 1%], $P < 0.001$). Surgical outcomes and comparisons to non-surgical groups were not evaluated [4].

Certainly, as targeted systemic therapy has revolutionized the treatment of advanced and metastatic RCC, many patients with ipsilateral local recurrence after PN may benefit from such treatments. Given the high surgical risk of re-do renal surgery, there is sure to be a population of patients with significant competing risks (age, comorbidity, etc.) in whom targeted therapy may be felt to be a more appropriate treatment than major surgery. Future trials comparing targeted therapy to surgical extirpation would be informative.

Local Recurrence Following Primary Ablative Therapy

Amplified use of imaging in modern medicine has corresponded with an increased rate in the diagnosis of renal tumors, especially small renal masses of low stage [49]. In poor surgical candidates, energy ablation using radiofrequency ablation (RFA) or cryoablation has become a popular treatment option with acceptable oncologic outcomes [41, 50, 51]. However, ablation techniques may be unsuccessful or local recurrence may be demonstrated on subsequent post-ablation imaging (Fig. 17.3) [7, 52]. In these cases, therapy options include expectant management, active surveillance, tissue biopsy, repeat energy ablation with tissue biopsy, or surgical salvage therapy. Most patients were poor surgical candidates at presentation; thus, repeat ablation is commonly deployed for local recurrence. However, surgical salvage has been reported in surgical candidates [14, 53–55].

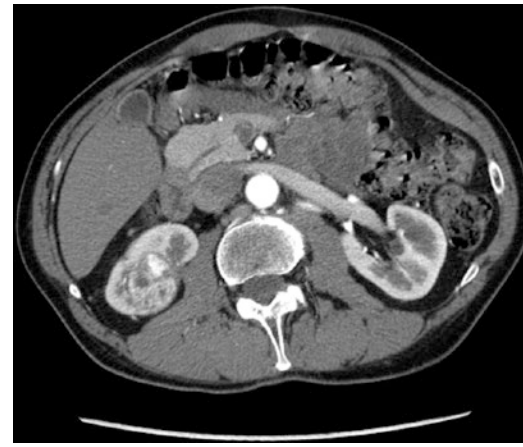

Fig. 17.3 Computed tomography of the abdomen revealing a recurrence in the right kidney following prior ablative therapy. This patient underwent a right open partial nephrectomy revealing a 3.8-cm pT1a clear cell RCC with negative margins. The patient was without evidence of disease 38 months postoperatively

Local recurrence rates following thermal ablation have been reported in 3–9% of patients [7, 52]. However, many CT findings following the ablation are non-specific for recurrence, including enhancement secondary to neoplastic activity or inflammation. Early study of CT enhancement and MRI signaling after ablation demonstrated enhancement even 9 months after ablation does not necessarily correlate with treatment failure [56, 57]. Weight et al. evaluated 6-month post-ablation percutaneous biopsy of treated masses and found 6 of 13 positive biopsies after radiofrequency ablation without contrast enhancement on CT or MR imaging [58]. In addition, Kowalczyk et al. noted 7 of 13 patients had no viable tumor following partial nephrectomy for presumed ablation failure and recurrence based on imaging characteristics [54]. Clearly, imaging alone is not as accurate as desired. While complete verification of ablation success may not be possible with current imaging and biopsy

techniques, biopsy-proven malignant recurrence should be a goal prior to considering surgical salvage therapy.

Early experience with salvage surgery typically entailed radical nephrectomy, although more recent series have demonstrated the feasibility of partial nephrectomy. Nyugen et al. [53] described renal surgery following post-ablation local failure in ten patients, who were not deemed candidates for repeat ablation, leading to seven patients undergoing radical nephrectomies, two patients undergoing partial nephrectomy, and one aborted surgery. Most patients in this series were preoperatively prepared for radical nephrectomy, as only two patients were unable to receive a planned partial nephrectomy, resulting in a radical nephrectomy and an aborted surgery secondary to patient preference. Three subsequent series demonstrated successful partial nephrectomy in nearly all selected patients, resulting in 39 of 45 (87%) patients receiving partial nephrectomy [14, 54, 55].

The published series to date include a very heterogeneous patient and tumor population, made up of small numbers and inconsistent intraoperative and postoperative reporting. However, they find common ground describing these cases as technically challenging, requiring more operative time and, consequentially, higher risk of complications and blood loss. In total, 9 of 37 (24%) patients experienced intraoperative complication, 19 of 37 (51%) patients experienced postoperative complications prolonging recovery, and 15 of 37 (41%) required a perioperative blood transfusion. Intraoperatively, there were 7 (19%) pleural injuries. Postoperatively, there were 2 (5%) reoperations, 5 (14%) urine leaks, and 3 (8%) pleural effusions [14, 53, 54].

In addition, there appears to be significantly more surgical complexity for patients following cryoablation versus RFA. Both Nyugen et al. and Karam et al. noted extensive desmoplastic reaction frequently in patients with prior cryoablation [14, 53]. In fact, Nyugen et al. demonstrated significant scarring in all six patients treated with previous cryoablation, leading to a renal artery injury, a diaphragmatic injury, a pleurotomy, a urine leak, and one conversion from partial to radical nephrectomy. In contrast, there were no reported intraoperative complications in the four patients previously treated with RFA [53].

Post-ablation local recurrence treated with surgical salvage is a technically demanding approach, possibly leading to radical nephrectomy in prior partial nephrectomy candidates. This approach is associated with significantly increased morbidity over primary kidney surgery; therefore, it is imperative to properly select excellent ablation candidates at initial diagnosis and verify local recurrence prior to considering salvage surgery. Taken together, the current studies suggest that in properly selected patients, surgical salvage for post-ablation local recurrence, including partial nephrectomy, is feasible albeit demanding.

Renal Cell Carcinoma Metastasectomy

Approximately 20–30% of patients present with metastatic RCC and 20–30% will develop metastases despite surgical therapy for localized RCC [59–61]. Recent advances in targeted therapies and immune checkpoint inhibitors have been encouraging, but few patients with metastatic disease will demonstrate a complete response to these therapies [18]. High-dose interleukin-2 can rarely achieve durable complete response but is rarely selected secondary to dreary morbidities [62, 63]. However, surgical resection of metastatic disease, when technically feasible, is a potentially curative treatment option in properly selected patients. There is no Level 1 evidence demonstrating metastasectomy is more beneficial than systemic therapy, but retrospective and observational studies have recognized a 5-year survival rate approaching 50% following metastasectomy for metastatic RCC [19–21]. As early as 1939, promising accounts following resection of solitary metastases started to be reported [64–66] RCC most often metastasizes to the lung, bone, lymph nodes, liver, brain, adrenal, pancreas, and thyroid [67, 68].

The most common location of metastatic RCC is the lungs [20, 67]. Following pulmonary

metastasectomy in the absence of mediastinal lymph node involvement, the 5-year survival rates have been reported between 36.9% and 54% [69–72]. Studies have shown consistent risk factors associated with death in this group of patients: pulmonary nodules >3 cm, hilar/mediastinal lymph node involvement, decreased pulmonary reserve, increased disease-free interval between definitive kidney therapy and development of pulmonary metastases, and incomplete metastasectomy [69, 71–73].

Meimarakis et al. [74] proposed a risk stratification score, the Munich score, to help long-term prognostication following pulmonary metastasectomy. The significant risk factors following resection were pleural infiltration, synchronous metastases, nodal status of primary tumor (pN), metastatic disease <3 cm, and hilar/mediastinal lymph node metastases. Munich I (complete metastasectomy with no risk factor), Munich II (complete metastasectomy with ≥1 risk factor), and Munich III (incomplete metastasectomy) had a median survival of 90.1, 31.4, and 14.2 months, respectively.

In addition to pulmonary metastases, there are reports of successful metastasectomy for disease in the bone, lymph nodes, liver, pancreas, and thyroid [75–80]. One study comparing five organ sites demonstrated no difference in recurrence-free survival for patients that undergo complete metastatectomy in either adrenal, liver, lung, or pancreas lesions [81]. There has been significantly less success with brain metastases from RCC.

Brain metastases are reported in up to 17% of patients with metastatic RCC, with a median OS of 10.7 months and 5-year survival rates of only 12% [82]. For patients undergoing local therapy for brain metastases, Ikushima et al. [83] demonstrated median survival of 25.6 months with fractionated stereotactic radiotherapy, 18.7 months with surgical resection plus conventional radiotherapy and 4.3 months with conventional radiotherapy alone. Furthermore, Ippen et al. [84] compared sterotactic radiosurgery with surgical resection, sterotactic radiosurgery alone and whole brain radiotherapy, demonstrating median survival of 21.9 months, 13.9 months, and 5.9 months, respectively. Overall, the data for local treatment of brain metastases from RCC are sparse, suggesting the need for a multimodality approach and further research.

In addition to the resection of single site and single organ metastatic disease, the role of metastasectomy involving multiple sites has been gaining traction as well. In retrospective analyses, mostly predating the use of targeted therapy, the resection of metastatic disease in multiple locations was associated with improved CSS [19, 20]. Kavolius et al. [19], describing a single institution experience, demonstrated a 5-year OS rate of 44% for patients that underwent complete metastatic resection versus 11% without resection or systemic therapy. As expected, however, for patients with multiple sites of metastatic disease, the authors found a significantly lower 5-year OS compared to patients with a single site resected (29% vs. 54%, $P < 0.001$) [19].

Alt et al. [20], reporting another single institution experience, found a 5-year CSS rate of 49.4% for patients who underwent complete metastasectomy at multiple sites compared with 13.9% for patients without complete resection ($P < 0.001$). Complete resection for patients with three or more metastases continued to demonstrate this survival advantage over patients with incomplete resection [20]. Controlling for number of lesions, location, timing of metastases, and ECOG performance status, patients undergoing complete resection of all metastatic disease had a threefold decreased risk of cancer-specific death (HR 2.91; 95% confidence interval, 2.17–3.90; $P < 0.001$). Naito et al. [85] evaluated 556 patients with metastatic RCC who underwent complete metastasectomy versus incomplete metastasectomy and demonstrated a significant survival advantage for patients with complete resection (109.8 vs. 31.9 months, $P < 0.001$). It appears that despite disease burden, the value of complete metastasectomy, if feasible, has been recognized.

Retrospective studies of this nature have obvious biases toward healthier patients with less disease burden, with many incomplete resections accomplished for palliative care. Selection bias skews results remarkably. A meta-analysis completed by Zaid et al. [86] made a concerted effort

to control for these concerns. When comparing complete metastasectomy patients by performance status, they found no significance in OS [86]. In addition, the pooled data from eight studies reveal an HR of 2.37 (95% CI, 2.10–2.87; $P < 0.001$) for complete metastasectomy, further reiterating the benefit of complete metastasectomy when achievable [86].

While complete metastasectomy has gained more extensive acceptance, the role, if any, of incomplete resection of metastatic disease continues to be debated. It has been demonstrated by multiple studies that incomplete metastasectomy is a powerful negative prognostic factor for survival [19, 20, 85–87]. Median survival time reported for patients with complete resection versus incomplete resection were 4.8–9.1 years and 1.3–2.7 years, respectively [20, 85, 87]. However, some studies have attempted to compare patients who underwent incomplete metastasectomy with patients who had no resection at all. In the previously discussed Alt et al. [20] study, not only did complete metastasectomy convey a 5-year CSS advantage (49.4%), but so did incomplete resection in comparison to no resection at all (23.7% vs 8.9%, $P < 0.001$). The patients that may benefit from incomplete resection and how to utilize targeted therapy and immune checkpoint inhibitors will require further dedicated research.

With the advances in systemic modalities for the treatment of the metastatic RCC, targeted therapies and immune checkpoint inhibitors are inevitably used in combination with surgical resection and will continue to be for the foreseeable future. Metastasectomy following target therapies has been reported in a limited number of patients [88–90]. Karam et al. [88] evaluated 22 patients treated with targeted therapy and complete metastasectomy at multiple sites, demonstrating 50% tumor recurrence and all but one patient was alive at median follow-up on 109 weeks. The one reported death was approximately 2 years after metastasectomy. Patients undergoing retroperitoneal resections had the highest risk of perioperative complication, including chylous ascites, atrial fibrillation, and prolonged ileus. In total, 9 of 22 patients received adjuvant targeted therapy. The role of adjuvant systemic therapy following metastasectomy is being further evaluated by EGOG 2810 (NCT01575548), which has completed accrual and randomized patients following complete metastasectomy to receive pazopanib or placebo.

Conclusion

Careful patient selection in the surgical management of local recurrent and metastatic RCC is vital to apply the proper therapy at the appropriate time. Isolated local recurrence following optimally performed radical nephrectomy, partial nephrectomy, and tumor ablation is an infrequent outcome.

Surgical resection following both radical and partial nephrectomy is technically challenging and risks significant morbidity. However, excellent oncologic outcomes are possible in well-selected patients. Critical to successful management of these patients is the integration of a multidisciplinary approach at a high-volume referral center.

In the case of post-ablation local recurrences, it is vital to identify biopsy-proven recurrence prior to undertaking a formidable resection in comparison to primary renal surgery. Proper surgical planning and expectation are crucial. Metastasectomy in properly selected patients appears to be associated with prolonged disease-free survival. Presently, candidates for metastatectomy should have good performance status and completely resectable disease. In the future, determining the therapeutic benefit of this approach will need to be interwoven with expanding evaluation of targeted systemic therapies.

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Management of Non-Clear Cell Renal Cell Carcinoma

18

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Introduction

In 2018, over 65,000 Americans are expected to be diagnosed with cancer of the kidney and renal pelvis, and over 14,500 will die of their disease [1]. Over the last 35 years, the incidence of kidney cancer has steadily increased, and there has been an increasing trend in years of life lost due to renal cancer [2]. This translates to a lifetime cumulative mortality risk of 0.5% and 0.2% for men and women, respectively, in the developed world [3].

Surgical resection remains the primary treatment modality in early-stage renal cell carcinoma (RCC), irrespective of histological subtype. When technically feasible, partial nephrectomy is the preferred surgical treatment as it has been shown in most studies to be associated with improved overall mortality and preserved renal function when compared with radical nephrectomy [4–6]. The role of routine lymphadenectomy is less clear. Patients with T1–T2 tumors without clinically apparent nodal metastases and in the absence of unfavorable features may be spared lymphadenectomy [7, 8].

Unfortunately, up to 30% of patients with apparently local disease will ultimately develop recurrence, and once renal cancer metastasizes to distant organs, patient prognosis is universally poor [9]. Spontaneous responses of metastatic RCC can occur but are seen in less than 2% of patients treated with cytoreductive surgery [10, 11]. Comparatively, at experienced centers, the mortality of cytoreductive surgery may be lower than 0.1% [12]. The role of cytoreductive surgery in non-clear cell RCC has not been studied explicitly and management should be considered in that context. In patients with clear cell RCC, cytoreductive nephrectomy prior to interferon-alpha-2b conferred a survival advantage over interferon-alpha-2b, alone [13], but without a full understanding of why cytoreductive surgery benefited patients; extrapolating this evidence to patients with non-clear cell RCC should only done with caution. For example, in very aggressive RCC, such as collecting duct carcinoma (CDC), renal medullary carcinoma (RMC), or RCC with sarcomatoid dedifferentiation, nephrectomy may only delay systemic therapy [14]. Conversely, in more indolent RCC, cytoreductive surgery or metastasectomy may offer clinical benefit.

Renal cell cancers have historically been considered radio-resistant [15], although this may no longer be the case with the ablative radiation doses currently achievable [16]. A dose-response

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relationship has been noted from experience with radiation treatment in the palliative setting [17]. To date, there is no established role for radiation therapy in locally advanced or regional disease in the adjuvant or neoadjuvant setting [18]. The role of radiation treatment in non-clear cell carcinomas should be confined to palliative therapy for specific lesions, such as brain or symptomatic tumors (e.g., bone lesions), or in a clinical trial.

Still grouped epidemiologically as one entity, RCC encompasses a pathologically diverse group of malignancies including clear cell renal cell carcinoma (ccRCC, 70–80%), papillary renal cell carcinoma (pRCC, 10–15%), chromophobe renal cell carcinoma (chRCC, 5%), unclassified renal cell carcinoma (uRCC, 5%), collecting duct carcinoma (CDC, <1%), translocation RCC (<1%), and renal medullary carcinoma (RMC, <1%) [19, 20]. Each subtype has its own unique histologic, cytogenetic, molecular, and clinical characteristics. Sarcomatoid RCC, an aggressive variant of renal cancer once believed to be a separate histologic entity, can arise from any histologic subtype and should be considered in that context [21]. Sarcomatoid dedifferentiation is found in approximately 5% of all RCC tumors but is present in up to 20% of patients with advanced disease [22]. Though the presence of sarcomatoid features seems to portend a poorer prognosis independent of tumor, node, metastasis (TNM) staging [23], the effect of histologic subtype of RCC on prognosis remains unclear. In univariable analysis, histologic subtype seems to be a prognostic indicator, but may or may not be preserved in multivariable analysis [24, 25]. chRCC, however, is biologically a tumor of low malignant potential (particularly in the absence of sarcomatoid dedifferentiation) and is significantly associated with a better prognosis than other RCC subtypes, with 10-year survival reported as high as 90% [26]. Non-clear cell histologies of RCC may have diminished metastatic potential compared to ccRCC, but once metastatic, prognosis between the two groups becomes similar [27, 28]. Histologic subtype may be predictive of response to immunotherapy, with non-clear cell variants showing increased resistance compared with ccRCC [29, 30]. Potential treatment options for non-clear cell renal cancers are subtype specific. Anti-vascular endothelial growth factor (VEGF) agents and mammalian target of rapamycin (mTOR) inhibitors may be efficacious in some non-clear cell variants although it can be difficult to perform subtype-specific comparisons because the number of patients with non-clear cell renal cell carcinomas included in most clinical trials has been relatively small [24, 31].

Papillary Renal Cell Carcinoma

Unlike ccRCC, non-clear cell histologies do not result from von Hippel-Lindau (VHL) inactivation, a gene that resides on chromosome 3p25. The loss of VHL function, either through mutation or inactivation by methylation, results in increased concentrations of hypoxia-inducible factor (HIF) within the affected cells [32, 33]. The over-expression of HIF then leads to increased production of VEGF and erythropoietin, and impairs glucose metabolism, which leads to the clear cell appearance. Conversely, pRCC type I may be characterized by dysregulation of the MET pathway [34, 35]. MET expression can be influenced by mutation, constitutive kinase activation, and genetic amplification [36]. Activation of the MET pathway can result in increased signaling via the hepatocyte growth factor receptor, which in turn can affect cell survival, cell adhesion, and invasion. MET mutations are found in most patients with hereditary pRCC type 1 and in 13% of sporadic cases [35]. Moreover, increased MET expression has been found in over 80% of sporadic pRCC type 1, with a trend toward worse prognosis in those tumors that do have increased MET expression [37]. pRCC type 2 has been shown to represent an entirely different molecular entity [38]. Whereas pRCC type 1 tumors are often low-grade and have a better prognosis, pRCC type 2 tumors are often high-grade and have a worse prognosis [39]. Furthermore, pRCC type 2 is a heterogeneous disease with multiple distinct subgroups, with the CpG island methylator phenotype (CIMP) being associated with the poorest prognosis [38]. pRCC type 2 has been associated with

fumarate hydratase (FH) tumor-suppressor gene loss [40, 41] and MYC pathway activation [42]. These pathways can upregulate HIF proteins, with a similar end-result as VHL mutations. These contrasts and commonalities between ccRCC and pRCC highlight the need for further study into the pathobiology of RCC subtypes.

Gene expression profiling may help further understand the different clinical behavior of pRCC subtypes. Patients with pRCC type 1, low-grade pRCC type 2, and mixed tumors were found to have a superior prognosis than those with high-grade pRCC type 2. This survival difference corresponded to G1-S and G2-M checkpoint gene dysfunction in good-risk and poor-risk tumors, respectively [43].

The optimal treatment strategy for metastatic pRCC is debatable. Although the pivotal phase III clinical trial of sorafenib included only ccRCC [44], an expanded access trial of sorafenib included non-clear cell histologies [45]. Previously treated patients, elderly patients, and patients with brain metastases were also included. Unfortunately, central pathology review and rigorous radiologic review were not conducted. The median progression-free survival was 8.5 months (95% CI, 8–11 months), and the median overall survival was 12.5 months (95% CI, 11.5–13) for the entire study population. In patients with pRCC, the clinical response rate, defined by patients with stable disease or partial response duration of a minimum of 8 weeks, was 84%. No complete responses to sorafenib were observed in pRCC patients. The side-effect profile of sorafenib was similar among patients with ccRCC and pRCC. Common side effects included fatigue, rash, hypertension, and hand-foot skin reactions.

Similarly, the pivotal trial of sunitinib excluded non-clear cell renal cancers [46, 47]. The subsequent expanded access trial was made up of 14% non-clear cell subtypes [48]. The overall response rate in the intention-to-treat population was 17% with a median progression-free survival of 10.9 months (95% CI, 10.3–11.2), and overall survival was 18.4 months (95% CI, 17.4–19.2). Sunitinib was less efficacious in non-clear cell RCC, with a response rate of 11%, but this may have resulted from the absence of a standardized procedure for measuring disease response, variable local practices, and lack of central pathology review. A phase II trial was conducted with sunitinib in 57 patients with advanced non-clear cell RCC (pRCC, 27; chRCC 5; uRCC, 8; sarcomatoid, 7; CDC/RMC, 6; others, 4) [49]. Median progression-free survival for 55 evaluable patients was 2.7 months (95% CI, 1.4–5.4). Median progression-free survival for patients with pRCC was 1.6 months (95% CI, 1.4–5.4). Median overall survival for all 57 patients was 16.8 months (95% CI, 10.7–26.3). Only three patients (two with chRCC and one with uRCC) had a confirmed partial response for an overall objective response rate of 5%. A Korean multicenter phase II study of sunitinib in 31 patients with non-clear cell RCC reported a response rate of 36% including eight partial responders among 22 patients with pRCC, a clinical benefit rate (combined response and stable disease) of 91%, and a median progression-free survival of 6.4 months [50]. In this study, estimated median survival was 25.6 months (95% CI, 8.4–42.9) for all patients, which included pRCC, chRCC, translocation RCC, and uRCC. Ethnic differences in the biology or response to sunitinib therapy in non-clear cell RCC may explain the conflicting results between the American study and the Korean study.

The Global Advanced Renal Cell Carcinoma phase III clinical trial of temsirolimus included non-clear cell renal histologies [31]. However, only ten patients with pRCC were accrued to each arm of the trial: interferon-alpha, temsirolimus, or the combination of both agents. Because of the small number of pRCC patients, the hazard ratio for death was not statistically significant, but favored the use of temsirolimus (HR 0.37; 95% CI, 0.13–1.06). When all non-clear cell histologies were analyzed, temsirolimus was clearly superior to interferon with median progression-free survival of 7.0 months versus 1.8 months, and median overall survival of 11.6 months versus 4.3 months, respectively [51]. Quality of life, as measured by the EuroQol-5Dimention index and EuroQol-Visual Analogue Scale, was also improved significantly in this patient population

(P = 0.0279 and P = 0.0095, respectively) [52]. No central pathology review was undertaken, limiting the available scientific information.

Erlotinib, an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, may have a role in the management of pRCC. EGFR activation has been shown to induce synthesis of HIF-1 in cell-lines [53]. EGFR inhibition in non-clear cell RCC lines with a monoclonal antibody results in significant decreases in growth rates, but only when the VHL tumor-suppressor gene remains functional [54]. The EGFR/HIF-1 pathway may still play an important role in VHL inactivated RCC tumors as short hairpin RNA-mediated inhibition of EGFR has been shown to down-regulate the HIF-dependent pathways and reduce tumor growth in these tumors [55]. One phase II single-arm clinical trial with erlotinib has been completed in patients with metastatic pRCC [56]. The overall response rate was 11% (95% CI, 3–24%), with a disease control rate, which includes patients with stable disease, of 64%. The median overall survival of this cohort was 27 months (95% CI, 13 to 36 months). There was no correlation between EGFR expression and response rate or survival. VHL mutation was present in only two patients and their best response was stable disease. Diarrhea, rash, and fatigue were common, but one patient died secondary to pneumonitis. The trial was not considered successful, because it did not reach its pre-specified end-point of a 20% response rate or greater. A related compound to erlotinib, gefitinib, has been studied in the metastatic and recurrent ccRCC without success in the phase 2 setting [57]. Further study of anti-EGFR therapy, either alone or in combination with other treatments, is being undertaken.

The ESPN trial was a randomized phase II trial of everolimus versus sunitinib in patients with metastatic non-clear cell RCC and no prior systemic therapy. Seventy-three patients were enrolled including 14 patients in the sunitinib arm and 13 patients in the everolimus arm with pRCC. At an interim analysis, both overall survival and progression-free survival favored sunitinib, and the trial was closed to new patient enrollment. However, the final analysis was not powered to detect differences in overall survival, progression-free survival, or the overall response rate. The median overall survival for patients with pRCC was 16.6 months in the sunitinib arm and 14.9 months in the everolimus arm. The ESPN trial was the first study to compare a VEGFR-TKI with an mTOR inhibitor but was limited by small sample size and heterogeneity of histologic subtypes [58].

The ASPEN trial also compared everolimus versus sunitinib in patients with metastatic non-clear cell RCC. There was a weak trend towards an increase in progression-free survival with sunitinib compared with everolimus (hazard ratio 1.41, 95% CI 0.87–2.28, P = 0.16), and the analysis of overall survival was inconclusive (hazard ratio 1.12, 95% CI 0.7–2.1, P = 0.6). Overall radiographic responses were noted in 9/51 evaluable patients (18%) treated with sunitinib and in 5/57 evaluable patients (9%) treated with everolimus. Thirty-three out of 51 patients (65%) in the sunitinib arm and 37 of 57 (65%) in the everolimus arm had pRCC. Of these patients, only four (sunitinib arm) and two (everolimus arm) had pRCC type 1. The overall response rate for patients with pRCC was 24% with sunitinib and 5% with everolimus. With regard to toxicity, 78% of patients in the sunitinib arm experienced serious adverse events (grade 3 or worse) compared to 60% of patients in the everolimus arm [59].

In 2018, Park et al published the results of a multicenter, single-arm phase II trial of axitinib in patients with recurrent or metastatic non-clear cell RCC who had been previously treated and progressed on the mTOR inhibitor temsirolimus. This study included 40 patients; 24 with pRCC type 2, 7 with translocation RCC, 4 with chRCC, 1 with pRCC type 1, and 3 others. The median progression-free survival was 7.4 months (95% CI, 5.2–9.5 months), and the median overall survival was 12.1 months (95% CI, 6.4–17.7 months). The trial design and sample size do not allow a formal statistical comparison of response between RCC subtypes, but 100% of patients with chRCC and 85.7% of patients with translocation RCC achieved disease control (partial response or stable disease) [60].

If MET mutations or activation plays a role in pRCC proliferation, inhibition of this pathway may prove a useful therapeutic target. MET inhibition has been extensively tested in phase II trials. Foretinib, an oral multi-kinase inhibitor targeting MET, VEGF, RON, AXL, and TIE-2 receptors, has recently been studied in one of the largest clinical trials devoted exclusively to pRCC, with 74 patients enrolled. Overall response rate was only 13.5%, less than the prespecified desired response rate of 25%, with a median duration of response of 18.5 months. The one-year survival rate was 70% and median overall survival has not yet been reached. Fatigue, hypertension, and diarrhea were the most frequently observed toxicities. Notably, non-fatal pulmonary embolism was observed in 11% of patients treated with foretinib [61]. Patients in this trial were stratified based on MET pathway activation status. The presence of germline MET mutations correlated with activity of foretinib and achievement of partial response. However, other measures of MET pathway activation were not predictive of response [62]. The highly selective MET tyrosine kinase inhibitor savolitinib was studied in a phase II trial of 109 patients with pRCC in which 40% of patients had MET-driven tumors and MET status was unknown in 17%. The MET status was determined using next-generation sequencing of tumor samples. Eight patients (18%) with MET-driven tumors responded to treatment, and 0 patients with MET-independent tumors responded. Stable disease was reported in 50% of patients with MET-driven tumors and in 11% of those that were MET-independent. The progression-free survival in patients with MET-driven tumors was 6.2 months. In all study patients, the overall response rate was 7%. Nine patients (6%) discontinued savolitinib due to adverse events, but the side-effect profile of this therapy was generally mild with few serious adverse events [63]. A phase II trial of savolitinib versus sunitinib in pRCC began accrual in 2017 with estimated enrollment of 180 patients in an open-label, parallel assignment. The PAPMET trial is a randomized, phase II assessment of four different MET tyrosine kinase inhibitors (cabozantinib, crizotinib, savolitinib, and sunitinib) in metastatic pRCC is currently in progress [64]. These clinical trials have the potential to define a new standard of care for the treatment of this disease.

Capecitabine, an oral fluoropyrimidine analog that is converted to 5-FU in tumor cells, may be considered in selected cases for the treatment of pRCC. In a single-arm phase II trial of single-agent capecitabine, the observed response rate was 26% and stable disease occurred in 47% of patients [65]. Over 75% of the included patients had pRCC histology. The median progression-free survival was 10.1 months (95% CI, 8.7–11.5), and median overall survival was 18.3 months (95% CI, 15.5–21.1). Hand-foot syndrome, nausea, diarrhea, and fatigue occurred in over 50% of the patients treated.

The combination of carboplatin and paclitaxel has also been studied in 17 patients treated as part of a phase II clinical trial, but no patients responded. This chemotherapy combination should not be used in the management of pRCC [66].

Chromophobe Renal Cell Carcinoma

Chromophobe renal cell carcinoma (chRCC) arises from the intercalated cells of the distal nephron and thus harbors a high density of mitochondria [67]. These tumors have a distinct morphologic appearance and unique molecular features with potential management implications. Unlike other RCC subtypes, chRCC stains readily for c-KIT due to c-KIT proto-oncogene amplification [68]. ChRCC can also be defined by its hypodiploidy of multiple chromosomes including 1, 2, 6, 10, 13, 17, or 21 [69, 70]. The two histologic chRCC subtypes are classic chRCC (characterized by pale cytoplasm) and eosinophilic chRCC (characterized by pink cytoplasm due to high mitochondrial density) [71]. Classic chRCC is more likely to demonstrate monosomy of chromosomes 1, 2, 6, 10, 13, 17, and 21, and to contain more somatic inactivating mutations in TP53 and PTEN [72]. Eosinophilic chRCC is more likely to harbor mutations in mitochondrial genes, particularly those involving complex 1 of

the electron transport chain [72]. Furthermore, whole genome sequencing has revealed that chRCC, unique among RCCs, harbors genomic rearrangements in the TERT promoter region [72]. ChRCC can also be found in patients exhibiting the Burt-Hogg-Dube (BHD) syndrome of follicle tumors, lung cysts, and renal tumors; the Burt-Hogg-Dube tumor-suppressor gene folliculin (FLCN) may play a role in chRCC development [73]. FLCN mutations can lead to deregulated cell proliferation via the interaction of FLCN with the mTOR pathway [74]. Most chRCC tumors associated with BHD will stain positive for CK7, Ksp-cadherin, and CD82, distinguishing them from other BHD-associated tumors [75]. However, patients can also develop ccRCC or pRCC in conjunction with FLCN mutations, so the role of this gene in the pathogenesis of chRCC specifically is unclear [76]. Of note, FLCN inactivation in sporadic renal cancers, including sporadic chRCC, is very infrequent [77].

Since most trials of non-clear cell RCC have not distinguished between the various subtypes, the clinical benefit of targeted therapy for chRCC is less clear, especially since its biologic characteristics are different. Sunitinib, sorafenib, and temsirolimus have all included chRCC in their clinical trials [31, 45, 48]. In the sorafenib expanded access trial, the observed response rate was only 5%, but 90% of patients had stable disease. In one study that included 12 patients with chRCC, three patients (25%) achieved a response with either sorafenib (two patients) or sunitinib (one patient) [78]. In the single-arm phase II trial with everolimus plus bevacizumab, five patients with chRCC were treated with the combination and three remained on treatment for more than 12 months. The results of this trial lend some support to the effectiveness of rapalog therapies in these patients [79]. In a single case report of chRCC, a patient previously treated with interferon and sorafenib achieved stable disease for over 2 years with temsirolimus [80]. In another case report of chRCC with sarcomatoid dedifferentiation, pazopanib also resulted in a partial response [81].

Cytotoxic chemotherapy may have a role in the management of chRCC. A single chRCC patient in a phase II study of capecitabine and weekly docetaxel experienced prolonged stable disease [82]. Single-agent capecitabine has also been studied in non-clear cell RCC in the phase II setting [65]. The response rate of capecitabine was 26% in the total treatment population, which included seven patients with chRCC. Of the two patients who achieved a complete response with capecitabine, one had chRCC histology.

Translocation Renal Cancer

Translocation carcinomas share histological characteristics with both ccRCC and pRCC and are often described as having features of both cell types. Consequently, the incidence of this tumor subtype is less clear and may have been previously misclassified. It now appears as though translocation renal cell carcinoma may represent 1–5% of all RCC cases when systematically examining pathology specimens for the presence of a defined translocation [83]. Translocation RCC was only recently recognized as a distinct clinical entitity, and more than one third of pediatric and adolescent RCC may, in fact, be translocation RCC [84]. Although this renal cancer subtype may demonstrate various chromosomal abnormalities, the vast majority involve a break at Xp11 resulting in altered TFE3 transcription-factor gene expression [85–87]. The Xp11 translocation can be uncovered by molecular genetic analysis, but translocation RCC may also be diagnosed with immunohistochemistry utilizing nuclear antibodies to TFE3 and TFEB proteins, or fluorescence in situ hybridization (FISH) assays for the corresponding gene aberrations [88–90]. Translocations involving t(6;11) have also been described, causing altered TFEB function: a related protein of TFE3, with similar function [91, 92]. There are several similarities between these two subtypes of translocation RCC, and therefore they were grouped together in the family of MiT translocation RCC in the 2013 Vancouver Classification of Renal Neoplasia [93]. Both subtypes are more common

in younger patients. The morphologies of these tumors may overlap with each other and with other RCC subtypes, but those with Xp11 translocations usually have clear cells and papillary architecture while those with t(6;11) translocations may have a biphasic appearance and nodules of basement membrane material. Both subtypes underexpress cytokeratin and epithelial membrane antigen (EMA) relative to other RCC subtypes [90, 94]. RCC with TFEB amplification was more recently identified and appears to be more common and to confer a worse prognosis compared with t(6;11) TFEB translocation RCCs [90]. These TFEB-amplified RCCs arise as high-grade adenocarcinomas of the distal nephron, usually in the mid-to-late seventh decade of life with a slight male predominance [90].

Based on data from tumor microarrays, the mTOR pathway seems upregulated in translocation RCC [85]. Little is known about the prognosis of translocation RCC, but with increasing age at diagnosis, translocation RCC may behave more aggressively, with affected males having a greater propensity for metastases at diagnosis than females [95]. All patients with distant metastatic disease have poor outcomes. One study showed that tumors with Xp11 translocations are associated with higher tumor grade, higher pathologic stage, and poorer prognosis than tumors with non-Xp11 translocations [96]. Only a small proportion of the published cases of tumors with t(6;11) translocations developed metastases, but all translocation RCCs have the capacity to recur after many years. Therefore, careful long-term follow-up for these patients is essential [94].

Experience in the treatment of translocation carcinoma is limited. Anti-VEGF therapy with sunitinib, sorafenib, or bevacizumab may result in partial responses or disease stabilization. Of 15 patients studied in one retrospective review, three patients achieved a partial response, seven patients had stable disease, and five patients progressed through therapy [97]. Median progression-free survival was 7.1 months while median overall survival was 14.3 months. In the first-line setting, targeted therapy appears to improve progression-free survival over cytokines [98]. The response rate with sunitinib may be as high as 27%, with the potential for complete responses. In the second-line setting, anti-VEGF tyrosine kinase inhibitors and mTOR inhibitors may produce progression-free survival in the range of 6–11 months, with sunitinib appearing to be the most efficacious agent. Translocation carcinoma may also respond to temsirolimus or everolimus even when resistant to anti-VEGF therapy [98]. Genomic sequencing may identify potential therapeutic targets for this malignancy which remains difficult to treat.

Renal Medullary Carcinoma/ Collecting Duct Renal Cell Carcinoma

Renal medullary carcinoma and collecting duct carcinoma are highly aggressive RCCs that arise from the distal nephron. In contrast to most RCCs, RMC has a clear clinical association: sickle cell trait and other sickle hemoglobinopathies [99–102]. The typical RMC patient is a male of African descent, young, has sickle cell trait, and presents with local and/or systemic symptoms. The median age at diagnosis is 28 years, although it can manifest in young adults and children as young as 9 years old [103]. RMC affects males over females in a 2:1 ratio and tends to be highly aggressive, with distant metastases often present at the time of diagnosis. The right kidney is involved in approximately 70% of cases, and this may be due to differences in the vascular anatomy between the right and left kidneys [102]. RMC is always characterized by loss of the tumor-suppressor gene SMARCB1, also known as INI1, hSNF5, or BAF47 [104, 105]. RMC is resistant to anti-VEGF targeted therapies and mTOR inhibitors, and these therapies should not be used in these patients [49, 103]. Renal cell carcinoma, unclassified with medullary phenotype (RCCU-MP), is a very rare SMARCB1-negative RMC subtype that is histopathologically and clinically similar to RMC but occurs in individuals without sickle hemoglobinopathies [106].

RMC and collecting duct carcinoma may be difficult to distinguish by light microscopy. However, RMC is more likely to contain reticular/yolk sac tumor-like patterns (85% of cases) compared with CDC (8% of cases) [107]. In addition, sickled erythrocytes will be found within the tumor specimens in RMC but not in CDC or RCCU-MP cases [107]. The most important distinguishing factor is the lack of expression of SMARCB1 in RMC and RCCU-MP cases, whereas CDC tumors will show positivity for SMARCB1 by immunohistochemistry.

Cytotoxic chemotherapy is the mainstay for the therapy of both RMC and CDC. For RMC, platinum-based cytotoxic regimens are recommended [108]. The three-drug combination of either cisplatin or carboplatin, combined with paclitaxel and gemcitabine, has been reported to produce responses [109] as has the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) [110, 111], among others. However, no platinum-based treatment regimen has shown superiority, and durable complete responses have been noted in 2 out of 22 (9%) patients with metastatic RMC treated with the relatively low-intensity regimen of carboplatin plus paclitaxel [103]. The vast majority (>90%) of patients with RMC will present with nodal and/or visceral metastases [103]. Even those few patients who present with localized disease on imaging will develop distant metastases, often within weeks. For this reason, upfront systemic therapy (platinum-based cytotoxic chemotherapy or clinical trial) should be used for most patients with newly diagnosed RMC [108].

To date, the best studied regimen for CDC consists of gemcitabine in combination with either cisplatin or carboplatin [112]. The response rate for this regimen is 26% (95%CI, 8–44), with a complete response rate of less than 5%. This translates to a median progression-free survival of 7.1 months (95% CI, 3–11.3) and overall survival of 10.5 months (95% CI, 3.8–17.1). Because topoisomerase II may be highly expressed in RMC, targeting topoisomerase II may prove beneficial. A case report of doxorubicin and gemcitabine therapy in a patient with wide-spread metastatic RMC post gemcitabine/paclitaxel chemotherapy produced a significant response and progression-free survival for 9 months. Gene expression analysis confirmed that this patient's tumor over-expressed topoisomerase II [113]. A report of three patients with CDC treated with cabozantinib noted partial response in one patient and stable disease in two patients [114].

Novel agents may also emerge as treatment options for patients with RMC. The proteasome inhibitor, bortezomib, may be one such agent. Bortezomib, a proteasome inhibitor, exerts its effect by inactivating proteins required for cell cycle progression, mitosis, increasing cell susceptibility to apoptosis [115]. A phase II trial of patients with metastatic RCC demonstrated partial responses in 11% of patients (95% CI, 3–25) and stable disease in 38% of patients (95% CI, 23–55) [116]. A patient with RMC enrolled in this trial achieved a complete response. Since then, this single patient continued to respond, achieving a complete response after 7 months of therapy and remained without demonstrable disease for at least 72 months [117]. Nevertheless, other patients with RMC did not respond to single-agent bortezomib [103, 111], whereas the combination of bortezomib with cytotoxic chemotherapy achieved durable responses in two pediatric patients with RMC [118]. Given the overall aggressive course of RMC, it may be prudent to further investigate proteasome inhibitors as part of combination regimens, similarly to their use in hematologic malignancies. Accordingly, an ongoing clinical trial [119] has been designed to determine the efficacy of the second-generation proteasome inhibitor ixazomib in combination with gemcitabine and doxorubicin in patients with RMC and RCCU-MP. There may be potential synergy when combining bortezomib with sorafenib through dual inhibition of AKT and stress-related c-Jun NH2-terminal kinase (JNK). Sorafenib alone has only been reported to benefit patients with CDC [120]. Sunitinib was also reported to have activity in one patient with CDC [121], although in a phase II trial with sunitinib in advanced non-clear cell RCC, which included six

patients with RMC or CDC, no responses were observed, and median progression-free survival was only 3.1 months [49].

Miscellaneous Renal Cancers

Other tumor subtypes of RCC are beginning to emerge from the previously unclassified category or from re-classification as new pathology techniques are developed. Mucinous tubular and spindle cell carcinoma (MTSCC) and tubulocystic renal cell carcinoma (tcRCC) are two examples of RCC that have only recently been described. MTSCC is an extremely rare malignancy that develops from either the collecting duct or loop of Henle and, as its name implies, is defined by the presence of tubules, spindle-cells, and a mucinous stroma and foam cells [122]. MTSCC shows a female predominance [123] and may be associated with nephrolithiasis [124]. Immunohistochemical analysis for MTSCC resembles the staining pattern of papillary RCC and may represent an unusual variant of pRCC [125, 126]. Cytogenetic examination may reveal a host of abnormalities including loss or gains of all or parts of chromosomes 1–20, 22, X and Y [124]. Trisomies of chromosomes 7 and 17 have also been reported [127]. Deregulation of the Hippo pathway, with a low overall mutational burden and recurrent chromosomal losses, appears to be the defining molecular characteristics of MTSCC [128]. In general, MTSCC is considered an indolent tumor type, but it has been reported to metastasize to lymph nodes and distant organs [129]. Fluorodeoxyglucose positron emission tomography (FDG PET)/CT may be of diagnostic and clinical benefit in MTSCC [130]. Sarcomatoid dedifferentiation may also occur in conjunction with MTSCC, leading to a worse prognosis [131, 132]. The prognosis for MTSCC is generally favorable with few reported cases of recurrence after surgical resection or metastases [130]. TcRCC) is a low-grade malignancy, with a male predominance and similar IHC and chromosomal abnormalities as pRCC and MTSCC [133]. It is identified by the presence of packed tubules and cysts [134]. tcRCC can rarely metastasize, and sunitinib has been shown to induce a partial response in some of these cases [135]. Sarcomatoid dedifferentiation is extremely rare but has been noted in one case report [136].

Follicular renal cell carcinoma has also been newly described as a type of RCC, which histologically resembles follicular carcinoma of the thyroid. Until recently, all reported cases were incidental findings, confined to the kidney, and cured with surgery alone [137–139]. Gene expression profiling has shown multiple abnormalities including under-expression and over-expression of chromosomes 1, 2, 3, 5, 6, 10, 11, 16, and 17. A single case of thyroid-like follicular renal cell carcinoma presenting with lung and retroperitoneal lymph node metastasis has been reported [140]. This patient was treated with sunitinib for 1 year followed by cytoreductive nephrectomy and retroperitoneal lymph node dissection. She had stable disease for at least 4 years after diagnosis.

The Role of Surgery in Metastatic Non-Clear Renal Cell Carcinoma

Limited data exist on the benefit of cytoreductive nephrectomy in patients with non-clear cell carcinoma. Kassouf et al compared 92 patients with non-clear cell metastatic RCC with 514 patients with clear cell metastatic RCC [141]. Patients with non-clear cell histology were noted to be younger (54 vs. 57 years), have more sarcomatoid features (23% vs. 14%), have higher pathologic stage, and have more nodal metastases (77% vs. 26%). By multivariable analysis, higher T stage (HR = 3.6, 95% CI 1.5–8.5), worse performance status (HR = 2.1, 95% CI 1.1–3.9), and sarcomatoid features (HR = 2.8, 95% CI 1.5–5.2) were independently associated with worse overall survival in patients with non-clear cell histology treated with cytoreductive nephrectomy. Patients with non-clear cell histology had worse disease-specific survival when compared with those with clear cell features (median DSS 9.7 vs. 20.3 months), which was confirmed even in the subgroups of patients with node-negative disease (median DSS 7.7 vs. 24.6 months) and in the

absence of sarcomatoid features (median DSS 14 vs. 23.1 months). As a result of the poor survival and lack of effective systemic therapies in this patient population, some investigators have questioned the role of cytoreductive nephrectomy in the presence of known non-clear cell histology [142]. In 2017 Marchioni et al reported retrospectively that 68% of 851 patients with metastatic non-clear cell RCC underwent cytoreductive nephrectomy. Cancer-specific mortality at 2 years was 53% in the group that underwent nephrectomy and 78% in the group that did not, a significant clinical benefit [143]. Careful consideration should be given when faced with a patient with non-clear cell histology, in order to decide if surgery should be done, and if so, how to time it with the administration of targeted therapy.

Immunotherapy

In the current era, cytokine therapy is rarely used in the treatment of metastatic RCC and has no known clinical benefit in non-clear cell RCC. In the Programme Etude Rein Cytokines (PERCY) Quattro trial that compared medroxyprogesterone, interferon alfa, interleukin 2 (IL-2), and the combination of the 2 cytokines, there were no responders in patients with non-clear cell RCC [144]. In one study that examined pathology from patients with ccRCC and non-clear cell RCC after treatment with IL-2, only 1 of 17 patients responded to therapy [145].

The development of immune checkpoint inhibitors (ICIs) has resulted in a paradigm shift in the treatment of many cancers. The approval of nivolumab, a humanized monoclonal antibody to PD-1, for metastatic RCC was based on the results of CheckMate 025 trial, in which nivolumab was compared to everolimus and demonstrated an improved overall survival [146]. This trial resulted in the approval of nivolumab for patients with metastatic RCC in the second-line setting. ICIs were more recently approved for the first-line treatment of metastatic RCC based on the results of Checkmate 214, and the standard of care for this setting is now combination immunotherapy with nivolumab and ipilimumab, an antibody to CTLA-4 [147]. Both trials included patients with ccRCC exclusively. The efficacy and safety of ICIs in non-clear cell RCC has not yet been determined in randomized clinical trials, but retrospective studies have demonstrated their potential effectiveness. In one study of 41 patients (16 pRCC, 14 unclassified subtype, 5 chRCC, 4 CDC, 1 Xp11 translocation, and 1 MTSCC), treatment with nivolumab produced objective responses and was well tolerated. Of 35 patients evaluated for response, 20% achieved a partial response and 29% achieved stable disease. Randomized phase II studies evaluating the use of ICIs alone or in combination with other therapies are currently in progress for non-clear cell RCC subtypes. If the results of these clinical trials are similar to those for patients with ccRCC, dramatic changes to the treatment of non-clear cell RCC are on the horizon, and some cures may be possible.

Conclusion

Non-clear cell renal cell carcinoma represents a heterogeneous group of tumors. Their varied pathobiology and rarity complicate the design and execution of randomized clinical trials, leading to a paucity of high-level evidence. However, significant advances have been made in the understanding of non-clear cell RCC subtypes. Novel therapeutics, including VEGF inhibitors, mTOR inhibitors, and immune checkpoint inhibitors, have been shown to have activity in many types of non-clear cell RCC, but definitive evidence for the optimal agents and sequencing are still lacking. More work is required to determine the optimal agent, or combination of treatments, for specific histologic subtypes. Participation in a clinical trial should still be considered a priority for the majority of patients with metastatic non-clear cell RCC. Further basic, translational, and clinical research is required to improve patient outcomes. (Table 18.1).

Table 18.1 Notable clinical trials in non-clear cell RCC

NCI Trial ID	Histology	Treatment	Comments
NCT02724878	Non-clear cell RCC	Atezolizumab + bevacizumab	*Ongoing*
NCT03075423	Non-clear cell RCC	Ipilimumab + nivolumab vs. sunitinib	*Ongoing*
NCT02915783	Non-clear cell RCC	Lenvatinib + everolimus	*Ongoing*
NCT02626130	Clear cell and non-clear cell RCC	Tremelimumab with/without cryoablation	*Ongoing*
NCT01130519	Papillary RCC	Bevacizumab + erlotinib	*Ongoing*
NCT02019693	Papillary RCC	Capmatinib	*Ongoing*
NCT02495103	Clear cell and non-clear cell RCC	Vandetanib + metformin	*Ongoing*
NCT02761057	Papillary RCC	Cabozantinib or crizotinib or volitinib vs. sunitinib	*Ongoing*
NCT02819596	Papillary RCC	Durvalumab + savolitinib	*Ongoing*
NCT03319628	Papillary RCC	XMT-1536	*Ongoing*
NCT02363751	Collecting duct RCC	Gemcitabine + platinum + bevacizumab	*Ongoing*
NCT03274258	RMC	Nivolumab + ipilimumab vs. nivolumab + NKTR214	*Ongoing*
NCT03055013	Non-metastatic clear cell or non-clear cell RCC	Nivolumab	*Ongoing*
NCT02619253	Clear cell and non-clear cell RCC	Pembrolizumab + vorinostat	*Ongoing*
NCT03117309	Clear cell and non-clear cell RCC	Nivolumab and nivolumab + ipilimumab	*Ongoing*
NCT03587662	RMC and other tumors with loss of SMARCB1	Ixazomib, gemcitabine, and doxorubicin	*Ongoing*
NCT03541902	Clear cell and non-clear cell RCC	Cabozantinib vs. sunitinib	*Ongoing*
NCT03091192	Papillary RCC	Savolitinib vs. sunitinib	*Ongoing*
NCT02915783	Non-clear cell RCC	Lenvatinib + everolimus	*Ongoing*
NCT02721732	Rare tumors	Pembrolizumab	*Ongoing*
NCT01108445 [59]	Non-clear cell RCC	Everolimus vs. sunitinib	Sunitinib improved PFS
NCT01185366 [58]	Non-clear cell RCC	Everolimus vs. sunitinib	Modest efficacy of both agents
NCT01798446 [60]	Non-clear cell RCC	Axitinib	Promising efficacy

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19 Surgical Management for Transitional Cell Carcinoma of the Upper Tract

Jason R. Gee

Epidemiology

According to the National Center for Health Statistics, upper tract malignancies are relatively uncommon, with an estimated annual incidence of 1–4 per 100,000 [1–3]. Renal pelvic tumors account for 15% of all renal tumors, whereas ureteral cancers comprise 1–2% of urologic cancers [4, 5]. An important exception is the incidence of upper urinary tract urothelial cancer (UTUC) in the Balkan endemic nephropathy region, in which UTUC has been reported to account for 65% of kidney cancers [6]. While the vast majority of these cancers are urothelial in origin, up to 10% may feature squamous histology [7]. Relatively rare histologic variants include adenocarcinoma, small cell carcinoma, and micropapillary urothelial carcinoma [8–10], and benign pathology such as fibroepithelial polyps and glomus tumors may also be encountered [11, 12]. Upper tract urothelial carcinoma is more prevalent in Caucasians and males [13, 14]. However, women who are diagnosed with upper tract urothelial cancers have a 25% higher risk of death from this disease which for unclear reasons is gender-specific [15]. This has been confirmed by a more recent multi-institutional study in which a statistically significant association was identified between female gender and both disease recurrence (hazard ratio [HR] 1.7, $p = 0.03$) and cancer-specific mortality (HR 2 = 0.009) [16].

Patients who are at highest risk of developing upper tract urothelial malignancy are those who have been diagnosed with bladder tumors. With 5-year follow-up, the estimated risk of developing upper tract disease following diagnosis of bladder cancer ranges from 2% to 4% [17]. More significantly, patients who are diagnosed with upper tract tumors are at high risk for developing bladder cancer. As justification for regular cystoscopic surveillance, an estimated incidence of 25–75% of these patients can develop bladder cancer [18–21].

More recent studies have focused on the stratification of patients with UTUC in predicting their risk of bladder cancer recurrence (BCR). For instance, in a multicenter study, Fradet et al. identified clinical parameters including age, tumor location within the renal pelvis versus ureter, extravesical ureterectomy, and treatment with adjuvant systemic chemotherapy as significant factors in predicting BCR following nephroureterectomy [22]. Pathologic parameters including lymphovascular invasion and papillary histology have also been reported as factors affecting BCR [23]. However, yet other investigators have identified parameters including tumor grade and stage, location, and gender as significant in determining the risk for BCR, suggesting that discrepancies among these studies exist. The

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presently accepted clinical factors for BCR risk stratification by the European Association of Urology include gender (male), history of bladder cancer, preoperative renal disease, and smoking status. Additionally, the presence of tumor invasion, necrosis, and multifocality, as well as ureteral tumor location and a positive urine cytology, have been determined to be significant tumor-related risk factors for BCR. And technical aspects of treatment, including positive surgical margins and an extravesical approach to bladder cuff removal via laparoscopy, have also been implicated as risk factors for BCR [24]. A trial currently underway will evaluate the role of preoperative intravesical mitomycin C in reducing the risk of BCR. This study, the REBACARE-trial, is significant given the concern that instillation of mitomycin C immediately following radical nephroureterectomy may result in toxicity due to extravesical extravasation of this medication [25].

Fortunately, synchronous and metachronous involvement of the upper tracts occurs uncommonly in only 5% of patients with this disease [26].

Biology

In general the prognosis associated with upper tract urothelial malignancies tends to be worse than that of bladder cancers, in that >60% of these patients present with invasive disease at the time of diagnosis. In contrast, 25–30% of patients with bladder cancer are initially diagnosed with muscle invasion [27, 28].

This may be due to differences in biology of these cancers. Since the first edition of this chapter, much work has been done in this area.

In 2016, a genomic comparison of germline and tumor DNA from UTUC (n = 83) and UCB (n = 102) was reported by Sfakianos and colleagues. In this significant and well-designed study, they actually identified a similar array of genetic alterations between UTUC and UCB. However, significant differences were seen in the prevalence of recurrent gene mutations for HRAS (p = 0.001), TP53 (p < 0.001), and RB-1 (p < 0.001). Furthermore, mutations in the FGFR3 gene, known to occur in association with low-grade UCB, were also identified in low-grade UTUC in 22 of 23 specimens. Surprisingly, no RB-1 mutations were identified in this UTUC cohort whereas they were identified with a frequency of 18.6% in UCB [29].

In contrast, Lee and colleagues reported their findings for UTUC and UCB by genomic profiling of commonly mutated genes for urothelial carcinoma. As has been established by The Cancer Genome Atlas (TCGA) [30] and others, the primary molecular alterations for both UTUC and UBC were identified for TP53, PIK3CA, and FGFR3 genes. However, the frequency of mutations between both UTUC (n = 31) and UBC (n = 61) was not statistically different (p = 0.13). One notable exception was that again no RB-1 mutations were identified in UTUC, as compared to 19.7% RB-1 mutations found in UCB (p = 0.02) [31].

Other research would imply that molecular urothelial expression profiles of upper tract urothelium differ from that of bladder urothelium. Microsatellite alterations have been identified in urothelium which are specific to the upper tract as compared to the bladder [32]. Furthermore, uroplakin is a urothelium-specific marker which has been identified in bladder and upper tract disease and has been utilized in transgenic mice capable of spontaneously generating urothelial tumors [33]. However, multiple subtypes of uroplakin exist, and recent studies have revealed that upper tract urothelium expresses a different uroplakin expression profile as that compared to bladder urothelium [34]. As such, differences in cellular and biologic properties do exist based on the location of native benign urothelium in the urinary tract which may explain differences in tumor biology which have been reported based on location [35–38].

Given the similar histopathology of UTUC and urothelial bladder cancer (UBC) and relative rarity of UTUC, treatment of UTUC is typically based on our available data and experience in treating patients with UBC [39, 40]. However, in more recent studies, identification of biomarkers elucidating the biology of UTUC has been

reported. These efforts will hopefully permit tailoring of treatment specific to UTUC, given its relative unfavorable biology. These biomarkers are particularly of interest as potential targets for molecular-based therapies.

These markers include HER2 and other mediators of PI3K/AKT pathway activation, p53, and Ki-67 among others. Human epidermal growth factor receptor 2 (HER2), a biomarker that has been found to be aberrantly overexpressed in UBC and is a known target for tyrosine kinase inhibitor therapy, has also been found to be overexpressed in high-grade UTUC, whereas the vast majority of low-grade tumors were negative (94% vs 6%). These findings would imply that UTUC overexpressing HER2 may be amenable to HER2-targeted (Herceptin) treatment [41]. Furthermore, activating mutations of PIK3CA and loss of PTEN expression have been identified in UTUC which in turn lead to activation of the PI3K/AKT pathway. This signaling cascade can in turn mediate cellular proliferation and resistance to apoptosis [42].

Aberrant expression of p53 has been well established for UBC, and likewise overexpression of this gene in UTUC has been associated with higher tumor stage and grade [43]. Significant differences in survival (overall and cancer specific) have been identified in association with overexpression of p53 in UTUC [43, 44]. Significant work on the role of p53 in tumorigenesis of UTUC has been accomplished in patients with Balkan endemic nephropathy, in that aristolochic acid (AA)-p53 DNA adducts have been implicated in cell cycle dysregulation. Specifically, point mutations in p53 have been confirmed in this group of UTUC patients as a molecular signature of AA exposure [45].

Ki-67 is a mediator of cell proliferation which has been found to be overexpressed in UTUC and associated with grade, stage, and lymphovascular invasion (LVI) [46]. Overexpression of this biomarker has also been found to correlate with bladder recurrence and adverse prognosis in multiple studies [47, 48]. And a recent large-scale meta-analysis by the International Upper Tract Urothelial Carcinoma Collaboration revealed that LVI, higher tumor stage and nodal metastasis, tumor necrosis and sessile tumor features, and the presence of carcinoma in situ were all significantly associated with the overexpression of Ki-67 [49]. Gene promoter hypermethylation has also been described for renal pelvic cancers. Hypermethylation in turn is a mechanism whereby oncogene and tumor suppressor gene expression may be regulated [50].

Additionally, tissue-based microRNA signatures have been found to hold prognostic significance in urothelial carcinoma. In a multi-institutional tissue-based analysis by *Summerhayes* and colleagues, miRNA-20 and miRNA-200 have been identified in association with invasive urothelial carcinoma of the bladder [51]. Similarly, Montalbo et al. have identified the significance of miRNA in upper tract urothelial carcinoma, in which miRNA-151b has been correlated with disease progression and cancer-specific survival [52].

Carcinogenesis

The development of urothelial carcinoma of the upper tract is attributed to carcinogen exposure in a manner similar to bladder cancer. Tobacco exposure remains a primary contributing factor, in which aromatic amines including benzopyrene, dimethylbenzanthracene, and arylamines have been implicated. These carcinogens are metabolized into less toxic derivatives by multiple enzymes including CYP1A1, glutathione S-transferase, and N-acetyl transferase. Genetic mutations of these genes have been attributed to differing susceptibility to these carcinogens [53]. Aromatic amines in industrial dyes have also been implicated [54]. Analgesic consumption has also been identified as a risk factor in the development of upper tract TCC. Phenacetin, for instance, was noted to induce mutations and to also cause papillary necrosis which can trigger the development of upper tract tumors [55]. And as discussed earlier in this chapter, region-specific susceptibility has also been identified with Balkan endemic nephropathy [56, 57]. Interestingly, in China, the regular consumption of Chinese herbs containing aristolochic acid (AA) has been associated with specific mutations

of upper tract cancer and may prove to be a common factor in the development of this disease in individuals who consume these herbs [58–60]. And as mentioned above, recent work in this area has revealed AA-DNA adducts resulting in A:T point mutations involving the p53 gene. The carcinogenic effects of AA have also been hypothesized to be based on metabolic susceptibility. Specifically, this could be due to pharmacogenomic differences and specific genetic polymorphisms affecting the expression/function of CYP1A1/2 and other enzymes which have been shown in laboratory studies to affect AA metabolism [45].

Diagnosis and Clinicopathologic Risk Factors

Patients with a history of bladder cancer are at the highest risk of developing upper tract tumors. Guidelines for surveillance of the upper tracts following diagnosis of bladder cancer vary but have been based primarily on risk stratification [61–63]. For instance, patients who have high-grade or invasive bladder tumors are at the highest risk of developing upper tract recurrence, in which upper tract surveillance is recommended every 1–2 years. Carcinoma in situ of the bladder in particular has been shown to be a significant risk factor for upper tract recurrence [64, 65]. Intermediate-risk patients with low-grade bladder tumors with either multiple recurrences or high-volume disease should undergo upper tract surveillance every 1–2 years. However, upper tract surveillance is typically not recommended for the lowest-risk patients with low-grade, small-volume tumors [63]. Following radical cystectomy, the majority of early recurrences can be detected through routine oncologic surveillance [66]. However, long-term recurrences may only be detected following the development of symptoms [67]. This is significant in that flank pain on presentation has been correlated with non-organ-confined disease [68].

Retrograde pyelography and excretory urography have traditionally been the standard radiologic imaging modalities in evaluating the upper urinary tracts for evidence of tumor. A ureteral tumor is typically visualized as a filling defect corresponding to the tumor within the ureter. This is classically referred to as a "goblet sign" as shown in Fig. 19.1. Infundibular tumors may yield the appearance of calyceal amputation. In either case, a stipple sign may be observed in which contrast is caught among papillary fronds of tumor [69]. An example of a stipple pattern by CT scan for a papillary calyceal tumor is shown in Fig. 19.2.

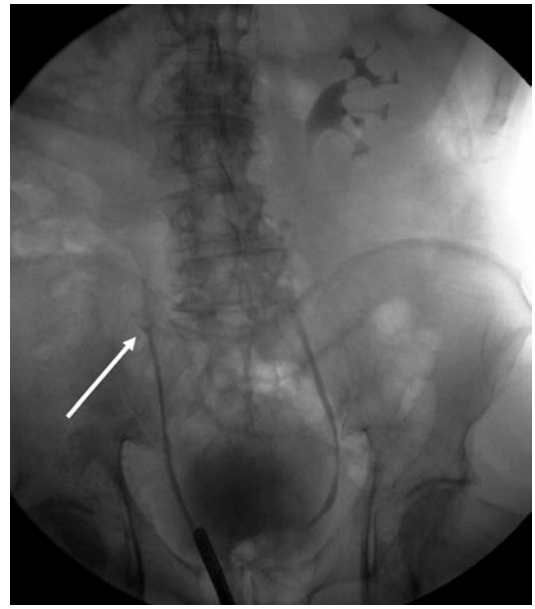

Fig. 19.1 Patient with a right mid-ureteral tumor exhibiting a "goblet sign" by retrograde pyelography

With the advent of CT urography, excretory urography is being utilized less frequently. Reasons for this change is that CT urography with enhanced sensitivity can provide much more detailed anatomic information in regard to the primary tumor and may reveal the presence of locoregional or distant metastasis as well. Whereby the sensitivity of CT scan imaging has previously been reported to be as low as 50% [70], with newer helical CT and multidetector computed tomography (MDCT) technology, a recent meta-analysis revealed a sensitivity and specificity of 96% and 99%, respectively [71]. This compares much more favorably to the reported sensitivity of excretory urography of 50% [72].

MRI may also be utilized for patients for whom the use of iodine-based intravenous contrast is contraindicated, although MR urography remains an evolving technique. The reason for this is that the resolution is inferior to that of CT urography and motion artifacts secondary to breathing and peristalsis can occur. Nevertheless, MRI can also provide detailed anatomic information and is considered to be comparable to CT urography [69].

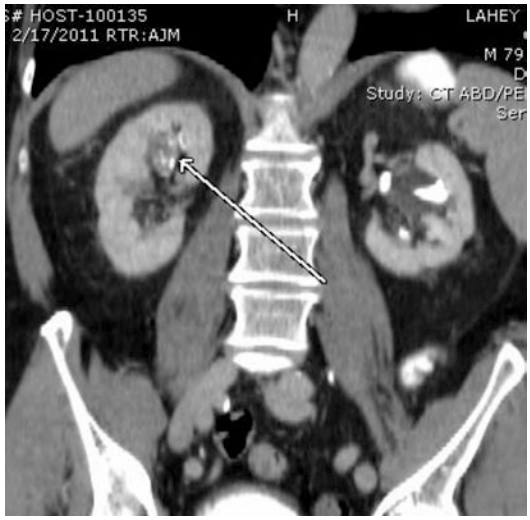

Fig. 19.2 Upper calyx papillary tumor with a stippled contrast pattern

Diagnostic Ureteroscopy: Biopsy When Feasible

Ureteroscopy is typically performed when evaluating an upper tract radiologic abnormality concerning for urothelial tumor. For instance, a filling defect identified by retrograde pyelography or a renal pelvic or centrally located lesion by CT scan would be indications for upper tract endoscopy, at which time a biopsy may be performed. It can be challenging to obtain sufficient biopsy tissue for histopathology. As such, in instances where an obvious upper tract tumor is seen and biopsies of upper tract lesions are either nondiagnostic or are not performed for other reasons, surgical removal may be performed on the basis of the visible tumor itself (Fig. 19.3).

Clinicopathologic Prognostic Factors

Ureteral tumor location has been correlated with a worse prognosis. One hypothesis associated with this finding is that the ureteral adventitia is relatively thin and has a more extensive network of blood vessels and lymphatic drainage which contribute to the potential for invasion and metastasis. Another hypothesis is that the renal parenchyma can act as a protective barrier to

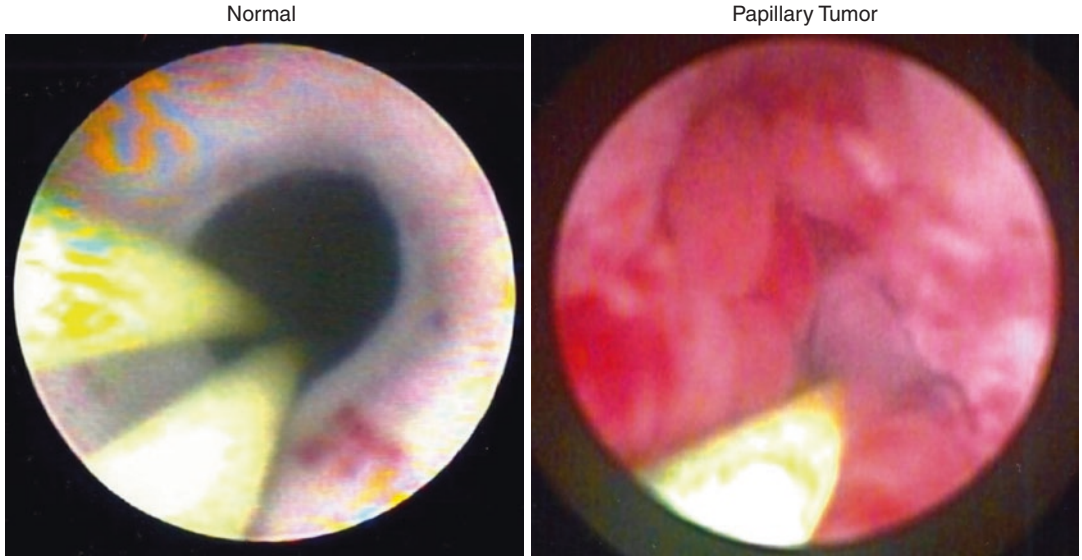

Fig. 19.3 Ureteroscopic evaluation of the upper tract with normal mucosa versus obvious papillary tumor

tumor spread in some instances [73]. However, this remains controversial as there are conflicting studies to suggest renal pelvic tumors portend a more severe prognosis than ureteral tumors [38]. And in yet other research, investigators have reported no difference in tumor aggressiveness between ureteral and renal pelvic tumors [74, 75]. Clearly biomarkers seem more promising than tumor location as a definitive prognostic tool.

More reliable predictors of cancer-specific survival for upper tract urothelial carcinoma have been established. Among these, pathologic stage is presently one of the most important [76]. The most recent TNM staging criteria for these tumors is shown in Table 19.1 [77]. Multiple series have validated pathologic stage as an indicator of metastatic potential and prognosis [78–80]. Accordingly, investigators have also identified tumor grade and architecture as prognostic factors [81]. Lymphovascular invasion, tumor necrosis, and the presence of hydronephrosis have also been identified as indicators of worse prognosis in patients with these tumors [80, 82–84]. Various predictive tools based on established prognostic markers have been described [85].

Table 19.1 TNM staging

TNM stage	Disease extent
Ta	Noninvasive papillary carcinoma that is confined to urothelium and projecting toward the lumen
Tis	Carcinoma in situ: flat tumor with high-grade histologic features that is confined to urothelium
T1	Tumor invades subepithelial connective tissue (lamina propria)
T2	Tumor invades muscularis
T3	Renal pelvis: tumor invades beyond the muscularis into the peripelvic fat or renal parenchyma
	Ureter: tumor invades beyond the muscularis into the periureteric fat
T4	Tumor invades adjacent organs or through the kidney into the perinephric fat
N0	No regional lymph node metastases
N1	Metastasis to a single lymph node that is <2 cm in greatest dimension
N2	Metastasis to a single lymph node that is 2–5 cm in greatest dimension or to multiple lymph nodes, none of which is >5 cm in greatest dimension
N3	Metastasis to a lymph node that is >5 cm in greatest dimension
M0	No distant metastasis
M1	Distant metastasis

TNM staging of upper urinary tract transitional cell carcinoma. (Adapted from [77]).

Endoscopic Approaches to Treatment

Upper tract TCC features, multifocality, and recurrence of these cancers tend to be ipsilateral, with only 1 to 5.8% developing tumors in the contralateral kidney [86]. Given this natural history, nephroureterectomy has been traditionally considered the gold standard in treating upper tract TCC for over 60 years [87]. However, in patients in whom nephroureterectomy will lead to dialysis, nephron-sparing treatment options may be preferred. Since the concept of nephron-sparing surgery for upper tract TCC was introduced by Vest in 1945, endoscopic resection was reported infrequently in the 1950s and 1960s but did not gain wider acceptance until the mid-1980s [88–90]. The development of better rigid and flexible scopes, with more maneuverability and better optics, has resulted in the emergence of endoscopic procedures in the diagnosis and treatment of upper tract TCC.

In terms of diagnosis, ureteroscopy permits direct visualization of upper tract tumors. Furthermore, washings for cytologic analysis and tumor tissue may also be obtained for pathologic evaluation. While staging of upper tract tumors by ureteroscopy has been reported to be inaccurate [91], tumor grading by cytology is accurate with 90% correlation with that of final pathology of the tumor specimen [92]. Furthermore, both CT and MRI imaging of these tumors have been shown to be accurate such that tumors which are noninvasive and low grade may be reliably selected for endoscopic management [92, 93].

Endoscopic management of upper tract TCC has traditionally been reserved for patients with a

Table 19.2 Currently accepted indications for endoscopic management of upper tract TCC

(a) Renal insufficiency
(b) Solitary kidney
(c) Bilateral disease
(d) Severe medical comorbidities
(e) Palliation
(f) Low-grade, papillary tumors

solitary kidney, bilateral involvement, or renal insufficiency. The currently accepted indications for endoscopic management of upper tract TCC include renal insufficiency, solitary kidney, bilateral disease, severe medical comorbidities, palliation, and low-grade, papillary tumors (Table 19.2) [94].

More recently, however, endoscopic treatment of upper tract TCC has been effectively utilized in patients with a normal contralateral kidney. In a series by Elliott et al. [95], patients with a normal contralateral kidney who had limited upper tract disease were managed endoscopically. Inclusion criteria for this study included tumors with a papillary/superficial appearance, tumor size <2 cm in diameter, complete tumor visualization and resection, lack of CT evidence of invasion, and close postoperative surveillance. A recent large-scale meta-analysis underscores this strategy, in which selected patients with low-grade disease appear to have favorable short-term (5-year) outcomes, although long-term (10-year) outcomes are still less certain, and therefore in many instances the advantages of renal preservation and endoscopic surgery need to be weighed against the increased risk of tumor recurrence and progression as compared to radical nephroureterectomy. And following their review of contemporary studies of endoscopic management of upper tract urothelial carcinoma, high-grade disease continues to be a relative contraindication [96].

With the development of smaller ureteroscopes with better optics, upper tract tumor ablation may be achieved safely and accurately. Rigid ureteroscopy may be ideal for distal and mid-ureteral tumors in which scope deflection is not necessarily required in accessing the tumor. The working channel of these scopes is somewhat larger as well, which can facilitate specimen acquisition. Tumor tissue may be excised with the Piranha (Boston Scientific) ureteroscopic biopsy forceps. However, more recently the BIGopsy forceps (Cook) has been designed for the purpose of obtaining larger tissue samples [97].

When more maneuverability is required in the proximal ureter and renal pelvis, flexible ureteroscopy may be employed. Electrocautery may be utilized for tumor ablation with a 2-French Bugbee electrode. However, laser energy is more frequently used in which a 200 uM fiber provides the least reduction in scope deflection. Both the holmium (Ho:YAG) and neodymium (Nd:YAG) lasers are effective in tumor ablation, although given deeper tissue penetration with Nd:YAG, there is a higher risk of ureteral stricture [98]. Nevertheless, Nd:YAG can be useful in treating bulky, vascular tumors. A ureteral stent can be left following this procedure to facilitate drainage or should a staged procedure be necessary in removing more extensive tumor [99].

Complications associated with ureteroscopic management of upper tract tumors tend to be less significant than that of percutaneous resection [100]. These include ureteral perforation (0–10%) and ureteral stricture (5–14%) [101]. Dissemination of tumor cells outside of the urinary tract or seeding of uninvolved urothelium is also a potential risk although this is considered by some to be theoretical [99].

Percutaneous resection has also been utilized for larger tumors of the renal pelvis. This procedure is generally reserved for patients who are unable to undergo nephroureterectomy for the reasons stated above and have tumors larger than 1.5–2 cm. This approach can also be utilized for upper tract recurrence following radical cystectomy in which a retrograde approach to the upper tract is not feasible. Another advantage of the percutaneous technique is that deeper and more extensive biopsies can be obtained [102]. Once access is obtained, the tumor can be completely ablated by any of a number of modalities which have been described including monopolar and bipolar cautery, laser ablation, and electrovaporization [103]. The entire tumor should be ablated

and flexible nephroscopy can be subsequently performed to inspect the tumor bed and remaining renal pelvis [104].

A major concern regarding percutaneous resection of upper tract tumors remains the risk of seeding of the nephrostomy tract and/or retroperitoneum. However, in a series of 36 percutaneous procedures, no tract seeding was observed [105]. Bleeding with transfusion requirement is a significant risk of percutaneous surgery. This can be attributed to the vascularity of the kidney, and renal vein injury during percutaneous resection has been reported as well [106].

Treatment with Topical Agents

Topical treatment of upper tract tumors can be utilized either as primary treatment or adjuvant therapy following tumor ablation. For this purpose, instillation of BCG or chemotherapeutics such as mitomycin C and thiotepa have been shown to be effective in which these agents can be administered via an indwelling nephrostomy tube. Following ureteroscopy, retrograde instillation of the upper tracts can be achieved by placing an indwelling ureteral stent into the affected ureter(s) prior to bladder instillations. Mitomycin C is most commonly utilized following ureteroscopy in which 40 mg of mitomycin C diluted in 100 ml saline can be delivered over 1 h via a retrograde catheter [107]. While the distal ureter may be treated effectively in this fashion, delivery of medication to the proximal upper tract may be less certain. A more direct approach would consist of retrograde catheterization via cystoscopy with each instillation. This has been described by O'Donnell and colleagues in which 1/3 to 1/10 strength BCG combined with 50–100 million units interferon-alpha2b can be instilled in the office setting following cystoscopic placement of a ureteral stent for upper tract instillation [108]. In their experience, a 70% response rate was achieved, with the greatest response occurring in patients with carcinoma in situ [109]. Also utilizing this approach, Katz et al. report 80% complete response to BCG-interferon retrograde instillation [110]. Another approach described by Patel and Fuchs avoids the need for repeated cystoscopy and stent placement, in which the distal end of a single-J stent is brought out through a percutaneous cystotomy and secured to the skin [111]. However, Studer et al. [112] prefer antegrade instillation of topical agents via a nephrostomy tract to achieve optimal delivery even when percutaneous access is not otherwise required. Given a paucity of randomized trials, the benefit of adjuvant BCG following resection remains unclear. One comparison study failed to demonstrate benefit with the exception of a lower recurrence rate in patients with low-grade tumors who received BCG versus those who did not [113].

Disease-related outcomes following ureteroscopic treatment of upper tract tumors are favorable. In a series of 23 patients with these tumors and a normal contralateral kidney, 100% disease-specific survival was reported with 83% organ sparing [114]. In another series of 21 patients without imperative indications for endoscopic management, a 38% recurrence rate was reported whereas there was an organ preservation rate of 81% and no death resulted from conservative treatment [95]. Survival rates ranging from 86% to 93% have been reported in studies with shorter follow-up, whereas recurrence rates range from 30 to 40% with ureteroscopic ablation [115–118]. Despite significant recurrence rates, survival does not appear to be adversely impacted by ureteroscopic management of upper tract tumors.

Cancer-related outcomes following percutaneous resection of upper tract tumors are typically a function of tumor grade and stage. For instance, recurrence rates ranging from 18% to 28% have been reported for low-grade disease, whereas approximately 50% of high-grade tumors can recur [119]. Jabbour et al. found in a series of 54 patients that stage Ta tumors were associated with a recurrence rate of 30% and disease-related survival of 93%. Conversely, 57% of patients with stage T1 disease recurred and a disease-specific survival of 64% was observed [113]. Percutaneous tract seeding remains a concern, although only two cases to date have been reported [120, 121]. Furthermore, many other clinical series have reported no tract seeding with this technique [113, 117, 122–125].

Nephroureterectomy

Radical nephroureterectomy has been the gold standard for treating upper tract urothelial cancer. This was first performed in 1898 by Le Dentu and Albarran [126]. This was based on the observation of frequent recurrence in the remnant distal ureter in patients who do not undergo removal of the entire ureter [127, 128]. In select patients with both upper tract tumor and locally advanced bladder cancer, a nephroureterectomy en bloc with radical cystectomy is sometimes necessary. This can be achieved best via an extended midline incision (Fig. 19.4). In most patients undergoing open nephroureterectomy however, a flank incision and ipsilateral Gibson incision for the bladder cuff resection are typically performed.

While the open nephroureterectomy with bladder cuff excision has been the standard approach upon which other procedures are compared, this procedure can involve considerable morbidity with two incisions. The advent of laparoscopic nephrectomy has been to reduce this morbidity with port incisions, and as a result patients have in general had faster recovery and less blood loss. Oncologic outcomes also appear to be similar to that of the open approach, although longer-term follow-up studies are

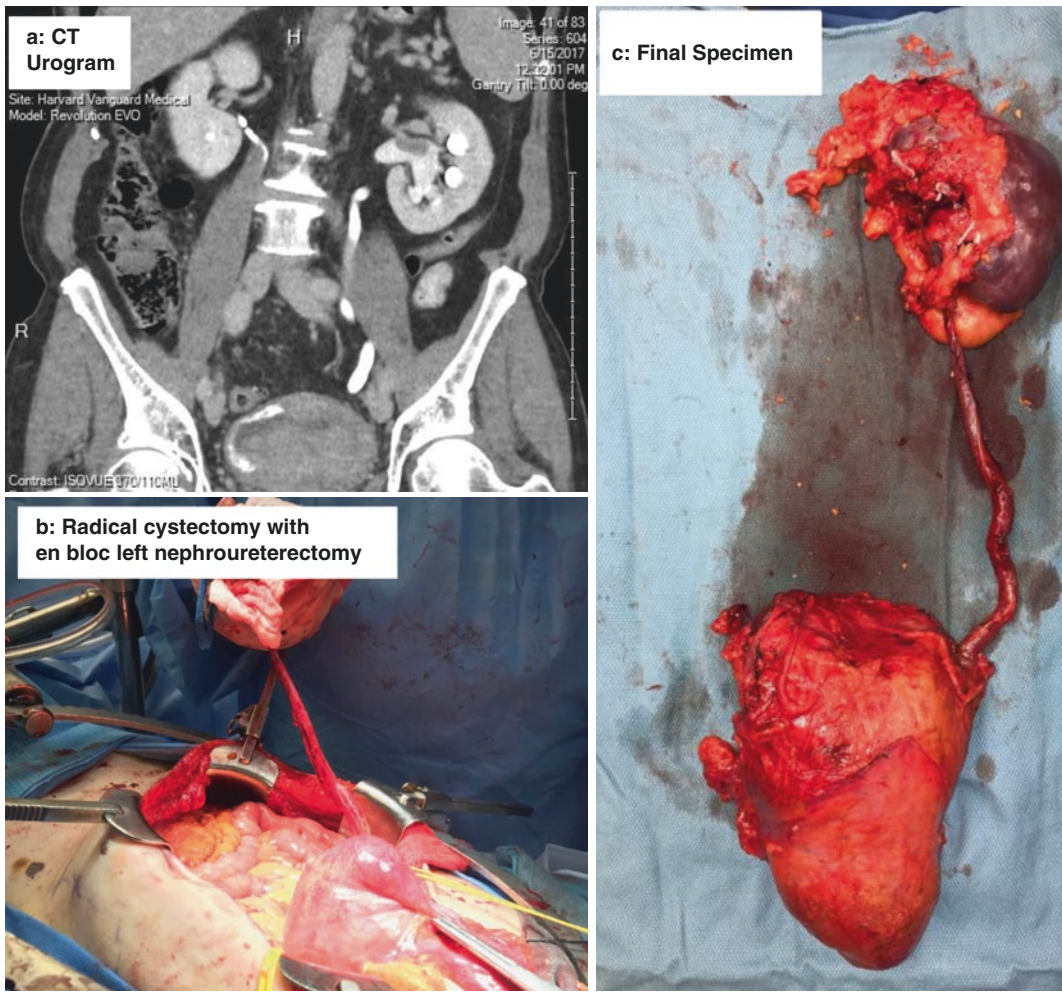

Fig. 19.4 A patient with locally advanced bladder cancer and left renal pelvic cancer managed by left nephroureterectomy with en bloc radical cystectomy via a midline approach

needed to further establish oncologic efficacy. Nevertheless, regardless of which approach is used, oncologic outcomes are based primarily on grade and stage of disease. This was demonstrated by Hall et al., in which 5-year cancer-specific survival rates were 100% for Ta/cis, 92% for T1, 73% for T2, and 41% for stage T3 cancers, and less than 5% for stage T4 cancer with a median survival of only 6 months [129]. Earlier studies have also revealed a direct correlation between prognosis and tumor stage [130, 131].

Now that laparoscopy is well established in renal surgery, major medical centers utilize this approach on a regular basis. This approach has been shown to be associated with less morbidity, less blood loss, and acceptable oncologic outcomes with limited follow-up. The debate has switched from whether or not to utilize laparoscopy to which approach should be utilized for the distal ureter.

Bladder Cuff Removal

Open Technique

Following the nephroureterectomy portion of the operation, the ureter is mobilized to the level of the pelvic brim. Dissection of the distal ureter and bladder cuff is then performed through a Gibson incision or lower abdominal incision. The intact specimen can then be retrieved through this incision. Hand-assisted laparoscopic nephrectomy was described by Nakada et al. [132], and more recently, adaptation of this technique for nephroureterectomy has been described in which the hand-port incision can also be utilized for bladder cuff dissection and specimen retrieval [133].

Intussusception

Intussusception was described by Clayman and colleagues in 1983 as an endoscopic method of managing the distal ureter, thereby avoiding the need for two incisions for open nephroureterectomy [134]. As recently reported in a large series of patients with renal pelvic cancer and proximal ureteral tumors, the ureter is divided following nephrectomy and a negative surgical margin is confirmed by frozen section. Subsequently, a 7-French ureteral catheter is advanced antegrade through the ureter, into the bladder, and directed distally out of the urethra. The ureteral catheter is secured to the proximal ureter with a suture. The distal ureter is then deeply cauterized circumferentially and the catheter is then advanced into the ureter proximally while the catheter is simultaneously pulled distally, thereby intussuscepting the ureter which is then detached from the bladder. The mucosal defect overlying the trigone is then cauterized [135].

Oncologic outcomes were similar in a comparison of patients undergoing bladder cuff removal versus intussusception in a retrospective study by Hara et al. [135]. When evaluating recurrence outside of the urinary tract, 5-year recurrence-free survival for patients undergoing bladder cuff removal was 71.4% versus 74.8% for patients undergoing intussusception (p = 0.766, log rank). Five-year urinary tract recurrence-free survival at 65.0% versus 76.6%, respectively, actually favored the intussusception group, although this was not statistically significant (p = 0.089, log rank) [135].

Pluck Technique

Another method which has been utilized to avoid a lower abdominal incision for removal of the distal ureter is commonly referred to as the "pluck" technique. Following nephrectomy, the ipsilateral ureteral orifice is resected deeply into perivesical fat, such that the ureter could then be avulsed with the removal of the entire specimen through the nephrectomy incision. More recently, ureteral catheterization has been utilized to facilitate the distal resection. However, this procedure has been criticized by some in terms of oncologic efficacy with reports of local seeding following this procedure [136–138].

Transvesical Approach

Gill and colleagues have also reported the transvesical approach, in which two 5 mm cystotomy trocars are placed to permit endoscopic bladder cuff dissection through the bladder. A resectoscope is also utilized for visualization, and with distal traction on the ureter, extravesical dissection of 3–4 cm of extravesical ureter is also performed through the bladder wall defect utilizing

the resectoscope. Early oncologic efficacy comparison between this approach and open bladder cuff excision revealed similar outcomes, although follow-up was limited [139].

Unroofing Technique

The unroofing technique refers to initial mobilization of the intramural ureter and bladder cuff via a cystoscopic approach. Following placement of a 7-French ureteral dilating balloon within the intramural ureter via fluoroscopy, the balloon is instilled with dilute contrast to less than 1 atmosphere of pressure. The ureter is then unroofed with an electrosurgical knife, thereby exposing the intramural tunnel. The balloon is then removed and the floor of the intramural ureter is cauterized with the rollerball electrode. A 7-French ureteral balloon catheter is then placed into the renal pelvis and placed to gravity drainage to prevent tumor seeding during dissection and mobilization of the kidney and proximal ureter. With extended follow-up, a comparison study of open nephroureterectomy versus laparoscopic nephroureterectomy utilizing the unroofing technique revealed similar tumor recurrence rates [140, 141].

Segmental ureteral Resection

While nephroureterectomy remains the standard of treatment of upper tract urothelial carcinoma, endoscopic ablation of ureteral tumors has also been effective in select patients and can be preferable in terms of nephron sparing for low-grade, low-volume disease. Accordingly, ureteral tumors which are too large to treat endoscopically may be removed by segmental ureteral resection when nephron sparing is critical. In properly selected patients, this procedure has been shown to be an effective surgical option for ureteral tumors [142, 143].

Autotransplantation

Patients with upper tract urothelial carcinoma involving a solitary kidney face nephroureterectomy with resulting hemodialysis and therefore pose a significant treatment challenge. While contraindicated in patients with a normal contralateral kidney, open excision/partial nephrectomy/open excision of ureteral and/or renal pelvic tumor with autotransplantation of the solitary kidney is feasible and has been described in select patients. Following removal of the kidney and infusion of University of Wisconsin solution, the kidney is placed on ice and bench surgery is performed to resect the tumor. Figure 19.5 illustrates bench surgery with resection of a renal pelvic tumor and surgical reconstruction of the renal pelvis. In these instances, pyelovesicostomy has been described [144], in which direct access to the renal pelvis via cystoscopy with fulguration of recurrent renal pelvic tumors is feasible. Another advantage is the proximity of renal pelvic mucosa for direct instillation of intravesical agents. However, reports of long-term freedom from recurrence with this procedure are sporadic, and eventual metastatic recurrence with transplantectomy and hemodialysis has been described for other patients. Nevertheless, two patients with high-grade noninvasive renal pelvic disease had long-term freedom from recurrence following this operation [145]. However, it is difficult to know whether these outcomes were due to biology of their disease as opposed to this technique based on more robust data, and there is consensus that this technique should be considered in the rarest of cases in which endoscopic management is not feasible [146].

Role of Lymphadenectomy

The role of lymphadenectomy in upper tract TCC remains controversial. Part of the reason for this is that there is a paucity of data and reports of lymphadenectomy for upper tract urothelial carcinoma are typically retrospective. However, one clear advantage of lymphadenectomy is that these patients may be more accurately staged. This is important given that patients with nodal involvement have significantly worse survival as compared to patients with pN0 status [79, 147]. Indeed the 5-year cancer-specific survival of these patients ranges from 0% to 39% and therefore these high-risk patients should be identified

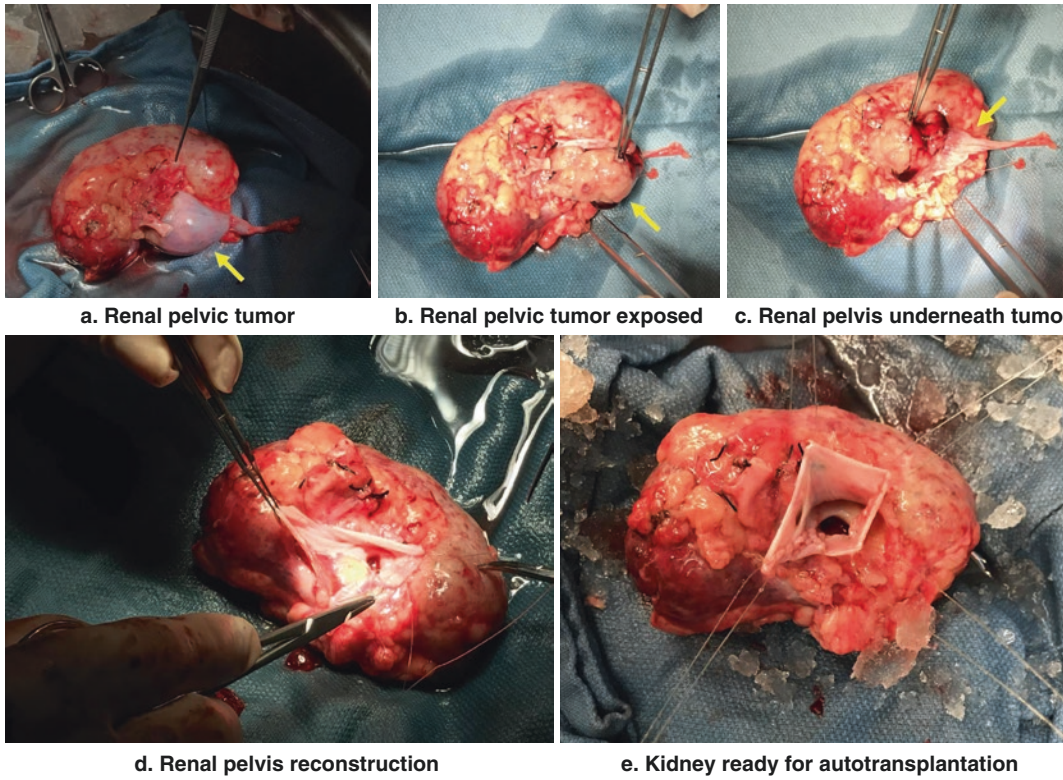

Fig. 19.5 Renal autotransplantation: ex vivo kidney bench surgery. (Courtesy J. Libertino, MD)

as they may benefit from adjuvant therapies [148]. Depending on the imaging modality utilized (PET, MRI, or CT), nodal metastases may be missed in 20–50% of cases, which further justifies the use of lymphadenectomy for staging [148–150].

While it is postulated that selected patients with limited nodal involvement (pN1/pN2) are potentially cured by lymphadenectomy [150, 151], a clear survival advantage for patients undergoing lymphadenectomy has not been demonstrated [152, 153]. Part of the criticism of these studies in addition to their retrospective nature is that a dissection template is not uniformly applied. While renal pelvic tumors drain preferentially to the hilar lymph nodes, the lymphatic drainage of ureteral tumors varies depending on location. For instance, right-sided, upper, and mid-ureteral tumors drain to the retrocaval and interaortocaval nodes, whereas left-sided ureteral tumors drain to the para-aortic nodes. Lower ureteral tumors drain to their respective common and internal iliac nodal beds in the pelvis [154, 155].

Another aspect of lymphadenectomy which has also been explored in bladder cancer is whether patients undergoing lymphadenectomy without nodal involvement (pN0) have a survival advantage as compared to those patients who do not undergo lymphadenectomy (pNx). The hypothesis is that micrometastatic disease to lymph nodes may be removed with lymphadenectomy and therefore a survival advantage is conferred. In a multi-institutional study, Roscingo and colleagues reported a survival advantage for patients undergoing lymphadenectomy (HR 0.7, $p = 0.007$) [156]. Furthermore, Abe et al. reported that locoregional recurrence as well as distant metastasis was higher in patients with pT2 or greater disease who did not undergo lymphadenectomy [157]. However, most other studies have not measured a survival advantage [158], including a large population-based study utilizing the SEER database in which multivariate analysis

revealed no significant survival difference between pN0 and pNx patients (HR = 0.99, $p = 0.9$) [159]. In summary, while the advantages of lymphadenectomy have been reported for other genitourinary cancers, the role of lymphadenectomy in upper tract urothelial cancer remains to be determined.

Role of Neoadjuvant Versus Adjuvant Chemotherapy

The role of perioperative chemotherapy for urothelial carcinoma has been described primarily for bladder cancer. In a large randomized trial of MVAC, neoadjuvant chemotherapy was found to confer a benefit in terms of disease-free survival [160]. Adjuvant chemotherapy has also been found to be effective in this disease [161]. In upper tract urothelial carcinoma, adjuvant chemotherapy has been used selectively in patients with high-risk disease, whereas minimal benefit has been reported, particularly for patients with unresectable or metastatic disease [162, 163]. Furthermore, a recent multi-institutional study revealed no significant survival benefit for adjuvant chemotherapy [164]. As such, limited efficacy, and concern for toxicity including nephrotoxicity, has prevented widespread use of this strategy. Nevertheless, less toxic regimens have been explored. For instance, Bamias et al. demonstrated that 4 cycles of paclitaxel and carboplatin were well tolerated in a study of 36 patients with high-risk UTUC (defined as >=T3 or with nodal involvement). The 5-year disease-free survival was 40.2% and the rate of distant metastasis was reduced in this study [165]. Another encouraging study of cisplatin-based neoadjuvant chemotherapy has revealed significant downstaging with an overall response rate of 53% and complete remission in 2 of 15 (13%) patients [166]. While perioperative chemotherapy is commonly offered to patients with advanced upper tract urothelial cancer, more effective therapies and better patient selection will hopefully lead to a defined survival benefit with this strategy.

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20 Outcomes: Prognostic Factors, Models, and Algorithms

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Introduction

Renal cell carcinoma remains one of the most common malignancies encountered in modern urologic practice, and the rising incidence and ever-expanding treatment armamentarium for kidney cancer – including medical, surgical, and surveillance strategies – have renewed interest among urologic oncologists in the development of treatment algorithms and outcome prediction in recent years [1, 2]. The American Cancer Society estimates that over 65,000 new cases of renal cancer are diagnosed yearly, and more than 15,000 deaths will be attributable to cancer of the kidney [3]. The spectrum of presentation, though, is wide, and while approximately ¾ of patients will present with disease confined to the kidney, 20–30% of these patients with clinically localized disease will go on to develop systemic recurrence [4]. Of the remaining patients who present with locally advanced or systemic disease, various clinicopathological and individual patient factors can influence overall prognosis and treatment outcomes. With advances in targeted therapies, including receptor tyrosine kinase inhibitors such as sunitinib and the results of recent trials such as CARMENA for cytoreductive nephrectomy [5], more and more patients with advanced disease will have therapeutic choices to make.

Taken together, the heterogeneity of disease presentation and the significant cost and toxicity of some of the novel targeted therapies have established the need for prediction models and algorithms that can help to identify which patients will experience the most amount of therapeutic benefit and incur the least amount of treatment-related harm. Of particular recent interest is the aid in selecting patients for various treatment strategies for patients in specific treatment dilemmas, such as cytoreductive nephrectomy in the era of targeted therapy. In this chapter, we will discuss the staging systems for renal cell carcinoma as well as other recognized prognostic factors. We will further delve into predictive nomograms that have been developed in both the preoperative and the postoperative settings for renal cancer. Finally, we will discuss criteria utilized in the setting of metastatic disease to determine both prognosis and therapeutic options in this high-risk patient population.

Staging Systems

Historically, the knowledge of the most up-to-date cancer staging system was essentially the only important factor in staging, as it would optimize predictions of outcomes. With the increasing availability of large clinical databases spanning multi-

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ple years, such as SEER and the National Cancer Database, a more precise knowledge of staging systems, including the version and years of application, is required for appropriate matching and stage-for-stage analysis in retrospective investigations. A patient with the same specific factors may have an apparently different stage if diagnosed in 2018 than in 2002, which may confound analyses which span these time periods. An understanding of the specific changes from year to year may allow investigators to account for these differences during retrospective analyses. At the same time, the availability of longer-term data that incorporate cases from multiple iterations of staging systems underscores the importance of incorporating direct data, such as tumor diameter, in place of a computed data point such as a T stage.

While one of the primary goals of modern staging systems is to best approximate outcomes on a stage-for-stage basis, the initial renal cancer staging system composed by Flocks and Kadesky in 1958 was based primarily on anatomical factors and observed patterns of tumor spread [6]. The subsequent Robson staging system – a modification of the earlier staging model – was employed primarily through the early 1990s but has since been supplanted by the more prognostically accurate TNM (tumor, nodes, metastasis) staging system [7]. The TNM system was first introduced in 1974 by the International Union Against Cancer but has subsequently undergone major revisions under the guidance of the American Joint Committee on Cancer in 1987, 1997, 2002, 2010, and, most recently, 2016 [8–10]. The most major recent update was in 2010, with more minor changes in 2016. The 2010 update reclassified ipsilateral adrenal gland involvement into the T4 category (previously T3a) to capture the overall poor prognosis associated with this pathologic feature, and the T2 tumor group was divided into T2a (7–10 cm) and T2b (>10 cm) to more accurately reflect the worse prognosis of this latter group of larger tumors (Table 20.1). Additionally, tumors that

Table 20.1 2016 American Joint Committee on Cancer TNM staging for renal cancer with expected 10-year cancer-specific survival rates (from similar 2010 staging system)

TMN stage		10-year cancer-specific survival rate[a]
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	Tumor ≤7 cm, confined to the kidney	
T1a	Tumor ≤4 cm, confined to the kidney	96%
T1b	Tumor >4 cm but ≤7 cm, confined to the kidney	80%
T2	Tumor >7 cm, confined to the kidney	
T2a	Tumor >7 cm but ≤10 cm, confined to the kidney	66%
T2b	Tumor >10 cm, confined to the kidney	55%
T3	Tumor extends into major veins or perinephric tissues but not beyond Gerota's fascia	
T3a	Tumor extends into renal vein or major branches or invades the pelvicalyceal system, or tumor invades into perirenal fat and/or renal sinus fat but not beyond Gerota's fascia	36%
T3b	Tumor extends into the inferior vena cava below the diaphragm	26%
T3c	Tumor extends into the inferior vena cava above the diaphragm or invades the wall of the vena cava	25%
T4	Tumor invades the ipsilateral adrenal gland or extends beyond Gerota's fascia	12%
NX	Regional lymph nodes not assessed	
N0	No regional lymph node metastasis	
N1	Metastasis into regional lymph node(s)	
M0	No distant metastasis	
M1	Distant metastasis	

[a]Data from Kim et al. [12]

involve the renal vein without direct extension into the inferior vena cava have been downgraded from stage T3b to T3a, which indicates an improved prognosis associated with this disease state, and the nodal staging has been simplified to include only N0 (no evidence of nodal metastasis) and N1 (positive nodal disease) states. The eighth edition of the AJCC staging system, applied to cancers diagnosed after January 1, 2017, further modified the T3a classification to include tumors invading the pelvicalyceal system. It is thought that the extension beyond the kidney is primarily via the renal sinuses, and thus involvement of the pelvicalyceal system may represent higher-risk tumors [11]. When comparing literature from different eras, it is imperative to keep in mind these regular modifications to the staging system in the interest of apple-to-apple comparisons. According to single-center validation of the 2010 AJCC TNM staging system performed by Kim et al. in a Mayo Clinic cohort, the estimated cancer-specific survival rates range from 96% in pT1a disease to 12% in pT4 disease, with an excellent overall concordance index equaling 0.85 (Table 20.1) [12]. A multi-institutional cohort of patients further evaluated the prognostic abilities of the updated staging system, highlighting the overlap in outcomes between the substages of pT3a and pT3b [13]. Given the relatively minor changes between the seventh and eighth editions of the AJCC staging system, updated validations of the staging system are sparse and add relatively little to the understanding of prognostic abilities of the system.

Grading System

In addition to tumor stage, tumor nuclear grade for renal cell carcinoma (RCC) has demonstrated significant correlation with both pathologic stage and survival outcomes. Historically, the Fuhrman classification system had been applied for aid in predicting synchronous metastases, lymph node involvement, renal vein involvement, perirenal fat involvement, tumor size, and survival outcomes [14]. The Fuhrman system is based on nuclear size, irregularity, and nucleolar prominence [15]. This system was not recommended for use in chromophobe-type renal cell carcinoma, however, and has also not been validated in many of the newer subtypes of renal carcinoma described in the 2016 WHO pathology update. In the updated AJCC consensus statements, the Fuhrman system has been replaced by the WHO/ISUP grading system. The WHO classification assigns increasing grades to increasingly prominent nucleoli for grades 1–3, with grade 4 comprising cells with multinucleate giant cells and rhabdoid and/or sarcomatoid differentiation [16]. This is a significant change from the Fuhrman system which incorporated both nucleolar and nuclear factors. Dagher et al. directly compared the Fuhrman and WHO/ISUP grading systems in a cohort of 681 patients. They found that the WHO/ISUP system stratified patients more clearly than the Fuhrman system, could be applied to a greater number of cases, and overall provided better prognostic information than the Fuhrman system [17]. This analysis, in concert with prior multivariate analyses, demonstrated nuclear grade with either WHO/ISUP or Fuhrman grade to be an independent predictive factor of staging and survival outcomes in RCC [18].

Notes on Staging Systems

Traditional staging systems have relied on stratifying patients into approximate risk groups based on various factors, as described above for TNM and cellular characteristic systems. While helpful for counseling and for the application of broad guidelines-based treatment recommendations, a major limitation of these systems is the loss of information when binning data from either a continuous or multileveled form into a factored variable. This is of particular interest when considering patients who are on the border of two classification levels, such as a patient with a roughly 7 cm kidney tumor. A hypothetical patient with a 6.99 cm tumor is classified as a T1, the same risk category as a 4.01 cm tumor, but a 7.01 cm tumor is a T2. It is likely that the behavior of both the 6.99 and 7.01 cm tumors is similar (all else equal) and that these both will be more

likely to recur or metastasize than the 4.01 cm tumor, and yet they are in different risk categories. It is difficult to draw delineations in staging, particularly when designing clinical trials to test treatments, which often creates the need for an easily applicable stratification method such as these size cutoffs. As more data become available for analysis, however, incorporating characteristics with as much raw data as possible will become both feasible and important to improving prognosis for patients. Treatment recommendations and prognostication can be more accurately tailored to each patient by applying tools to complete data as opposed to more restricted stage classifications.

Other Prognostic Factors

While stage and grade have proven to be significant predictors in RCC, many other variables have now been accepted as carrying prognostic value in the disease, and the addition of these factors into the prognostic algorithm has allowed for improved stratification of patients at the time of kidney cancer diagnosis (Table 20.2) [19]. Poor performance status and constitutional symptoms such as weight loss and cachexia have both been associated with worse outcomes. Basic laboratory values can also provide worthwhile information; anemia, thrombocytosis, hypercalcemia, and elevated C-reactive protein and erythrocyte sedimentation rate all confer a worse overall prognosis.

In 1997, Kovacs et al. produced the Heidelberg classification system for renal cell tumors, and it is well recognized that the natural history and subsequent patient outcomes differ considerably between histologic subtypes of this disease [20]. When localized, the papillary (10–15% of all RCC) and chromophobe (3–5% of all RCC) subtypes are thought to confer better overall prognoses when compared to the more common clear cell RCC (70–80% of all RCC) [21, 22]. On the other hand, rarer subtypes such as collecting duct and renal medullary carcinoma are very adverse prognostic features and are often associated with locally advanced or metastatic disease at the time of presentation [23, 24]. Sarcomatoid differentiation of the primary tumor is another extremely poor prognostic factor with median survival less than 1 year in most series [25].

While a full discussion of the molecular prognostic factors is beyond the scope of this chapter, there has been a rapid growth in the number of markers identified – including both positive and negative prognostic factors. However, some of the work that has been done demonstrates dis-

Table 20.2 Prognostic factors by category in renal cell carcinoma

Prognostic factors in renal cell carcinoma	
Anatomic factors	Clinical factors
Tumor size Extension into perinephric or renal sinus fat Venous involvement Extension into ipsilateral adrenal gland Lymph node metastasis Distant metastasis	Performance status Cachexia Platelet count Blood count Calcium Alkaline phosphatase C-reactive protein Erythrocyte sedimentation rate
Histologic factors	Molecular factors
Nuclear grade Histologic subtype Presence of sarcomatoid features Presence of necrosis Vascular invasion Invasion of collecting system	*Hypoxia-inducible factors*: CA-IX, CA-XII, CXCR3, CXCR4, HIF, IGF-1, VEGF, VEGFRs *Co-stimulatory molecules*: B7-H1, B7-H3, B7-H4, PD-1 *Cell cycle regulators*: p53, Bcl-2, PTEN, cyclin A, p27, Skp2 *Adhesion molecules*: EpCAM/KSA, EMA, E-Cad, alpha-catenin, Cad-6 *Other factors*: Ki-67, XIAP, Survivin, EphA2, vimentin, CA-125, annexin II

Data from Lane and Kattan [19]

crepancies between the survival effects of different factors. For example, hypoxia-inducible factor (HIF)-1-alpha – a downstream factor in the von Hippel-Lindau angiogenic pathway – has been associated with both improved survival and worsened overall survival among different cohorts of patients [26, 27]. Similarly, while one study of the transmembrane enzyme carbonic anhydrase IX (CA-IX) linked low CA-IX expression to worse survival in localized RCC with no effect in metastatic RCC, a more recent study reported findings exactly to the contrary [28, 29]. Yet another study demonstrated no significant prognostic effect for low levels of CA-IX [30]. These discrepancies notwithstanding, several markers have demonstrated significant promise in terms of prognostic capacity; a more comprehensive list of molecular factors can be found in Table 20.2. As a result, there has been a paradigm shift in more contemporary prediction modeling to include molecular markers as part of the multivariate analysis, and indeed, there is evidence that the addition of these markers significantly improves model predictive accuracy when compared to tools that are based on tumor stage, grade, and patient performance status alone [31]. One such recent study incorporated cell cycle progression scoring based on a multigene proliferation signature into the Karakiewicz nomogram on 565 patients and found that the use of the CCP score outperformed the Karakiewicz nomogram alone for prediction of disease-specific mortality (c-index 0.87 compared to 0.84) [32].

A Word About Prediction Tools

Contemporary cancer patients differ from their historical counterparts in not only their ever-expanding access to vast amounts of disease-specific information via the internet but also in their desire to further augment that data with facts, figures, and more concrete prognostic information during their clinic appointments. As savvy consumers of medical goods, services, and knowledge, many modern patients have the expectation of their initial visit that physicians will be able to provide them with synthesized clinical and pathologic data, individualized risk estimations, and in-depth disease consultation – a task that can prove challenging in the midst of a busy clinic schedule. The evidence points to the fact that, despite the amount of information available to patients, physicians are not adequately meeting their information needs [33] and patients in general would actually prefer to receive even more information than is presented to them [34]. Furthermore, it is clear that patients who are better informed experience improved psychosocial outcomes following therapy [35].

Fortunately, as patient demand for information and individual risk estimations has grown, the field of outcomes research has answered the bell with a surge in the number of prediction tools available to patients and physicians alike. The majority of these prediction models have developed into "bedside" tools that can be seamlessly incorporated into the patient visit and allow for the rapid calculation of prognostic information in an unbiased, reproducible, and evidence-based format. Moreover, some of the instruments – and, in particular, nomograms, which are graphical representations of a complex mathematical formula – have the capacity to serve as counseling tools themselves insofar as they contain a clear and easily digestible illustration of what factors bear the most weight in terms of outcome prediction. The adoption of electronic medical records has also fostered the expansion of computers into the clinic and exam rooms. Alongside the smartphone, this allows for more complex prediction tools to be used quickly and effectively at the bedside in the form of smartphone and web-based apps. Whereas previously clinicians would need to sacrifice precision by grouping patients into stages or convenience by using a graphical interface such as a nomogram, easy-to-use web-based applications such as the Memorial Sloan Kettering renal cancer risk of recurrence following surgery calculator (https://www.mskcc.org/nomograms/renal/post_op) and Cleveland Clinic risk calculators (rcalc.ccf.org) facilitate quick and efficient aids to patient counseling in real time. Further, these nomograms can be dynamic, meaning the predictions are updated and honed as more patient data are available. As a result,

prediction tools can replicate the synthesization of data regularly performed by physicians and provide a wealth of information in a short period of time, which should provide physicians with more time to adequately address the needs of the patient during disease-specific consultation.

In urologic oncology, clinical algorithms and nomograms have become increasingly popular in large part for prostate cancer but also for renal cancer. They have a broad range of applicability, as they may be used in the preoperative and postoperative settings as well as in the setting of metastatic disease. As such, we will describe some of the currently available models categorized by the settings in which they are meant to be applied.

Preoperative Models

While RCC is malignancy that is primarily managed surgically, the use of modern imaging techniques with the incidental discovery of small renal masses has triggered a stage migration of renal tumors, and as a result, surveillance of these renal "incidentalomas" has become a viable option in a subset of patients and is now a treatment alternative in the American Society of Clinical Oncology renal cancer guidelines [36]. Moreover, approximately 20% of clinical stage I renal masses will ultimately prove to be benign, and only around 1/4 of cases will exhibit potentially aggressive pathologic features [37–40]. The effectiveness of surveillance of small renal masses was studied in the prospective DISSRM trial, which compared 274 patients with small renal masses undergoing primary intervention to 223 patients who underwent active surveillance. At 5 years, the overall and cancer-specific survival was similar between the two groups [41]. Surveillance in larger tumors has not been extensively investigated but may be an option for patients with significant comorbidities making them poor surgical candidates. A small series of 100 patients at Memorial Sloan Kettering analyzed the history of patients with larger renal masses of at least 4 cm and estimated a 5-year probability of metastasis of 6%, compared to a 5-year probability of non-RCC-related death of 22% [42]. This study was too small to reliably identify factors associated with metastasis but does suggest that surveillance is a potential option even for patients with larger masses. There is a general focus within urologic oncology of minimizing the accompanying risks and harms of surgery by applying improved predictive tools and monitoring strategies. Consequently, many of the preoperative models have focused on differentiating benign from malignant renal tumors and, thus, ideally identifying which patients may be appropriate candidates for surveillance protocols. Ultimately, these models, if sufficiently operationalized, could serve as tools to improve patient counseling and possibly outcomes.

There have been a number of studies aimed at predicting which masses will be malignant prior to surgery. Pierorazio et al. performed a systematic review and meta-analysis that included 20 studies with a total of 12,149 patients [43]. While they found significant heterogeneity in the studies, owing to the difficulty in developing consistent criteria and in finding predictive criteria, they did find some consistent associations. Larger tumor size was associated malignancy, with a summary estimated increased risk of 1.33-fold [95% CI 1.22–1.43] for each centimeter of tumor size. Additionally, men were at an estimated 2.71-fold [95% CI 2.39–3.02] increased risk for malignancy compared to women. Other factors, including RENAL nephrometry score and BMI, were predictive of malignancy in individual studies but could not be meaningfully analyzed due to heterogeneity.

The discussion surrounding treatment decision-making for cancer in the current era of active surveillance debate generally revolves around predicting the biology of a tumor, with the analogy of identifying the "rabbit" tumor that develops quickly and should be treated compared to the "turtle" tumor that is slowly growing and will unlikely cause problems in any meaningful time frame. However, the timeline for treatment and anticipated effect on both quality and length of life must be considered as well. Even if a tumor has a fast-growing "rabbit" biology, an individual patient may have other conditions that are more pressing and/or life threatening, and

intervention for the tumor may be inappropriate and harmful. Preoperative, or pre-intervention, modeling can aid in patient selection incorporating these competing risks. Kutikov et al. created a "comprehensive" nomogram that incorporates clinical factors and competing risks for predicting the benefit of specific cancer treatments. In a separate but related study, his group analyzed competing risks based primarily on comorbidities as an adjunct to cancer biology–based predictions and as an aid to clinicians in predicting the likely benefit of actively intervening in localized renal cancer [44, 45] (Fig. 20.1).

When surgery is determined to be the best treatment option, minimizing the harms of surgery becomes the next important step. In renal surgery, offering nephron-sparing surgery in the form of a partial nephrectomy is preferred when this approach does not significantly affect oncologic outcomes. While for most small kidney tumors oncologic outcome is similar or slightly better for partial versus radical nephrectomy, some predictive models may aid in selecting patients who would likely benefit from a radical nephrectomy instead of a partial [46, 47]. Some studies have suggested that factors such as a higher RENAL nephrometry score are associated with higher risk of extrarenal extension resulting in poorer survival outcomes [48–50]. With a more aggressive push toward partial nephrectomy in patients previously ineligible for such nephron-sparing procedures, it will be increasingly important to evaluate outcomes and predictors of survival in these patients.

It is apparent from these models that the combination of several prognostic factors for RCC may be especially helpful to patients deciding between definitive therapy and active tumor surveillance. As data collection and validation continues, preoperative evaluation will add more precise and valuable information that can be effectively clinically applied. The recognition

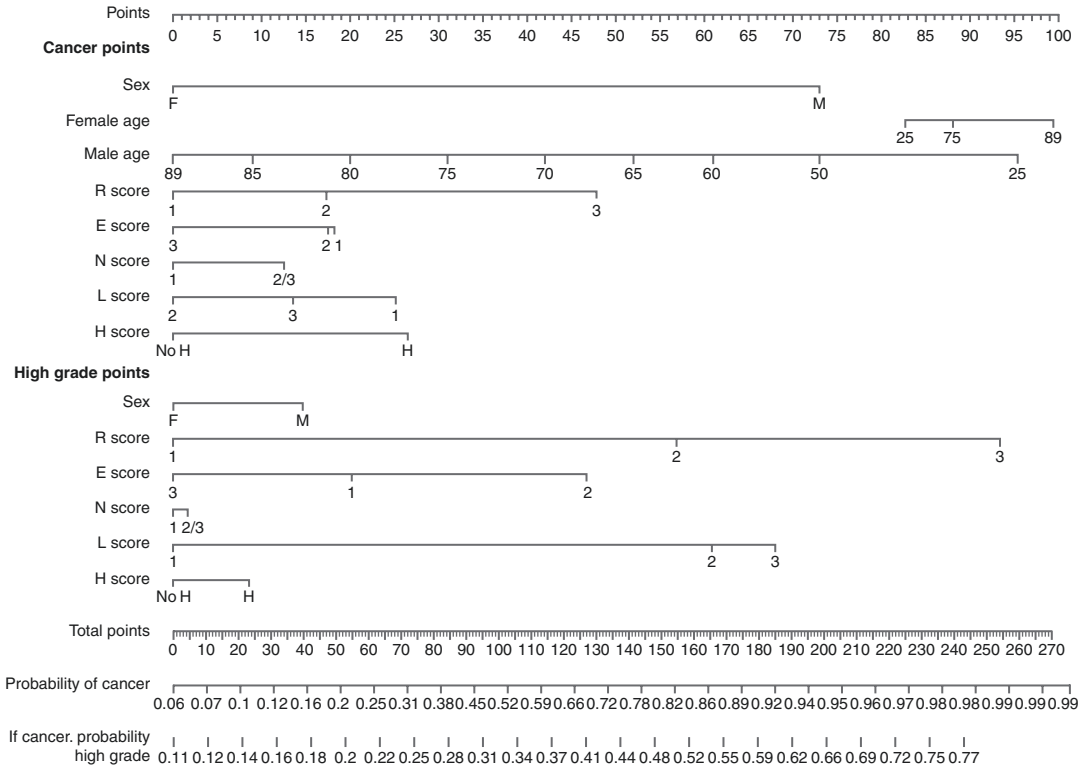

Fig. 20.1 Preoperative nomogram that incorporates RENAL nephrometry score to predict the risk of malignancy and high-grade pathology in renal tumors. (Modified from Kutikov et al. [75])

that treatment-related harm may exceed therapeutic benefit represents a shift toward a more sophisticated medical decision-making paradigm, and in the future, predictive models of this sort will continue to facilitate optimal patient stratification and treatment selection.

Postoperative Models

Given the prognostic significance of pathologic features of RCC, postoperative prediction tools that incorporate this data may be able to provide a better overall representation of prognosis, and indeed, several groups have developed models that have been shown to perform well in this setting. These models provide potentially helpful information both for patient counseling and for determination of postoperative surveillance schedules. Patients with a greater likelihood of early recurrence, for example, may warrant a shorter interval to follow-up and/or imaging postoperatively.

There are a number of factors that predict recurrence-free survival in RCC patients postoperatively. Speed et al. summarize individual factors from retrospective studies that are associated with recurrence-free survival [51]. Increasing tumor size, symptoms at presentation, microvascular invasion, sarcomatoid features, collecting system invasion, tumor necrosis, thrombocytosis, and elevated CRP have all been associated with shorter time to recurrence.

While many studies have found individual associations for postoperative outcomes, there have been few published models which operationalize these findings into a usable predictive tool for recurrence risk. A postoperative model developed by a group from Memorial Sloan Kettering Cancer Center (MSKCC) predicted the probability of postoperative recurrence for patients with conventional clear cell RCC [52]. The predictive factors included tumor size, pathologic T stage, Fuhrman nuclear grade, presence of necrosis, presence of vascular invasion, and clinical presentation (Figs. 20.2 and 20.3). The model was developed using data from 701 patients from MSKCC and validated externally with data from 200 patients from Columbia University in the original report, and the concordance index from external validation was excellent at 0.82. Note that by examining the nomogram visually, one can easily distinguish the factors that are most influential – in this case, tumor size, pathologic T stage, and Fuhrman nuclear grade – which illustrates the manner in which nomograms can serve not only as prediction tools but also as counseling tools. This model

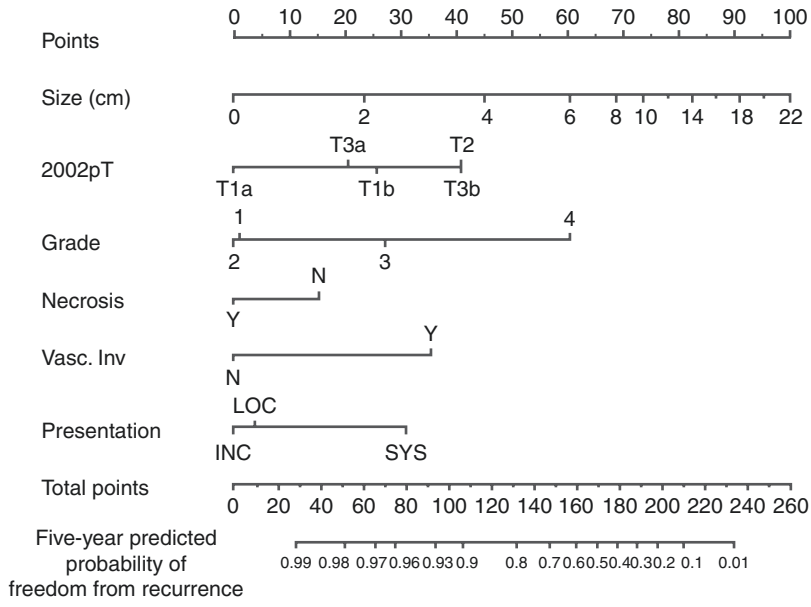

Fig. 20.2 Postoperative nomogram predicting the probability of freedom from recurrence following nephrectomy for conventional renal cell carcinoma. (Modified from Lee et al. [53])

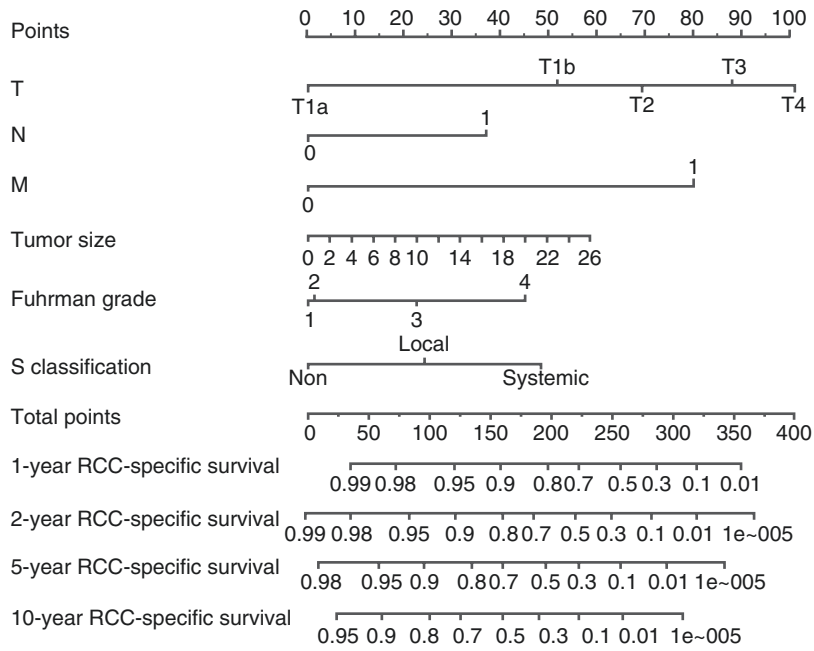

Fig. 20.3 Postoperative nomogram for cancer-specific survival in renal cell carcinoma. (Modified from Karakiewicz et al. [63])

was later updated with contemporary patient data to comprise 1642 patients, with an updated median follow-up time of 39 months [53]. The updated data reflected an excellent concordance index of 0.81 and suggested the original nomogram slightly underestimated the recurrence-free probability. The nomogram was updated to increase calibration utilizing the updated cohort which maintained similar performance to the prior nomogram.

Researchers from the University of California, Los Angeles (UCLA), have developed a prediction table known as the UCLA Integrated Staging System (UISS) that stratifies patients into low-, intermediate-, and high-risk categories in the metastatic and nonmetastatic settings (Table 20.3) [54]. The outcomes are based on three prognostic factors – TNM stage, Fuhrman nuclear grade, and patient performance status – and by stratifying patients into risk categories, one would ideally be able to identify those patients who are at high risk of disease recurrence and/or progression and may be optimal candidates for adjuvant therapy. While the UISS is beneficial in terms of patient counseling and has been externally validated with reasonable performance, models that utilize risk groupings for prognosis are inherently less informative than those prediction tools that can provide individualized risk estimations in terms of percentage risk [55]. Indeed, in a multicenter European study, the UISS fared worse in terms of discriminating accuracy when compared to other models including a postoperative nomogram [56].

Subsequent to the UISS, a group from the Mayo Clinic produced the stage, size, grade, and necrosis score (SSIGN) which assigns numerical values to the assorted prognostic parameters and ultimately produces an overall score for the individual patient; this score can then be cross-referenced with a table of outcome predictions that include 1-year, 5-year, and 10-year cancer-specific survival rates (Tables 20.4 and 20.5) [57]. The model was based on more than 1800 patients who underwent nephrectomy between 1970 and 1998, and all of the variables included in the model demonstrated a significant relationship to cancer-specific survival in the multivariate analysis. It should be noted that this model applies only to patients who exhibit clear cell RCC on final pathology. The SSIGN score has been validated in multiple patient cohorts, with concordance indices ranging between 0.81 and 0.88, and when compared directly to UISS in a

Table 20.3 University of California, Los Angeles Integrated Staging System (UISS) for patients with renal cell carcinoma

Nonmetastatic disease										
Stage	T1				T2	T3				T4
Fuhrman grade	1–2		3–4		Any	1		2–4		Any
ECOG performance status	0	≥1	0	≥1	Any	0	≥1	0	≥1	Any
Risk	Low	Intermediate							High	
Metastatic disease										
Stage	N1M0	N2M0 or M1								
Fuhrman grade	Any	1		2		3		4		
ECOG performance status	Any	0	≥1	0	≥1	0	≥1	0	≥1	
Risk	Low		Intermediate	Low	Intermediate				High	

Data from Zisman et al. [54]

Table 20.4 Tumor stage, size, grade, and necrosis (SSIGN) score for prognosis in patients undergoing radical nephrectomy for clear cell renal cell carcinoma

	Score
T stage	
pT1	0
pT2	1
pT3 or T4	2
N stage	
pNx or pN0	0
pN1 or N2	2
M stage	
pM0	0
pM1	4
Tumor size	
<5 cm	0
≥5 cm	2
Fuhrman nuclear grade	
1 or 2	0
3	1
4	3
Necrosis	
Absent	0
Present	2

Data from Frank et al. [57]

Table 20.5 Prognostic outcome predictions for 1-year, 5-year, and 10-year cancer-specific survival rates based on the SSIGN score

SSIGN score	1-year CSS (%)	5-year CSS (%)	10-year CSS (%)
0–1	100	99.4	97.1
2	99.1	94.8	85.3
3	97.4	87.8	77.9
4	95.4	79.1	66.2
5	91.1	65.4	50.0
6	87.0	54.0	38.8
7	80.3	41.0	28.1
8	65.1	23.6	12.7
9	60.5	19.6	14.8
≥10	36.2	7.4	4.6

Data from Frank et al. [57]

European cohort, SSIGN demonstrated a superior AUC, particularly in the nonmetastatic setting [58–61]. The SSIGN system was reexamined by Parker et al. more recently in a contemporary cohort, as the initial included cohort comprised patients diagnosed from 1970 to 1998 and may not necessarily reflect modern disease patterns [62]. Parker et al. applied the SSIGN to 1038 radical nephrectomy patients and 767 partial nephrectomy patients who presented to the Mayo Clinic between 1999 and 2010 and compared these to the original SSIGN cohort. A reevaluation of SSIGN in the initial cohort confirmed an excellent bootstrap-corrected c-index of 0.82 for cancer-specific mortality in the initial cohort with an increased 20.1-year follow-up period. In the contemporary cohort, SSIGN was similarly excellent with a c-index of 0.84 for cancer-specific mortality over a median 9.2-year follow-up. This analysis also found a c-index of 0.82 for cancer-specific mortality in the partial nephrectomy group over median of 7.6 years of follow-up.

A multi-institutional group developed a separate nomogram based on tumor characteristics for predicting 1-, 2-, 5-, and 10-year RCC-specific survival [63]. The accuracy at these time points for the nomogram was 87.8%, 89.2%,

86.7%, and 88.8%, which represented an improvement of 2–3% over the UISS model. This model was externally validated in a cohort of 1480 patients, demonstrating a c-index of 0.91 and 0.90 at 2 and 5 years, respectively [64]. This study also performed a decision curve analysis which demonstrated a net benefit to application of the nomogram for most ranges of cancer-specific survival prior probability. Further, the Karakiewicz model was compared directly to the Sorbellini and Kattan nomograms in a cohort of 423 patients undergoing nephrectomy in Singapore. The Karakiewicz nomogram outperformed both the Kattan and Sorbellini nomograms in this set in predicting overall, cancer-specific, and recurrence-free survival [65].

Metastatic RCC Models

The most widely applied prognostic algorithm employed in the setting of metastatic RCC is the criteria defined by Motzer from MSKCC first developed in 1999 and subsequently updated in for differing populations in 2002, 2004, and 2011 [66–69]. In its initial iteration, the prognostic criteria included Karnofsky performance status, elevated serum lactate dehydrogenase, anemia, elevated serum calcium, and absence of prior nephrectomy, and patients were stratified into favorable-, intermediate-, and poor-risk categories with estimated median survival times of 20 months, 10 months, and 4 months, respectively. The 2002 update included data from patients treated with interferon-alpha as initial systemic therapy, and the 2004 update examined patients who had previously failed cytokine therapy. Utilizing data from a randomized trial of sunitinib vs. interferon-alpha as first-line therapy for metastatic RCC, the group has since confirmed that the MSKCC model is applicable to patients who have been treated in the era of targeted therapy. The Motzer criteria have been validated in an external cohort of 353 patients in a Cleveland Clinic study, from which other independent prognostic factors were identified, including prior radiotherapy and sites of metastasis [70]. The utility of these criteria lies primarily in their ability to stratify patients for the purposes of clinical trials, including the recently published CARMENA trial, but from a patient counseling standpoint – as with UISS – risk stratification into three broad categories can obscure the heterogeneity that exists within groups and may not be able to provide patients with the most accurate representation of prognosis [5].

Motzer and colleagues did embrace the movement toward nomograms by producing one of their own. This model predicted 12-month progression-free survival for patients receiving sunitinib therapy; the predictive variables included serum calcium, number of metastatic sites, hemoglobin level, nephrectomy status, presence of lung or liver metastases, thrombocytosis, ECOG performance status, time from diagnosis to treatment, and serum alkaline phosphatase and lactate dehydrogenase [71]. The model was internally validated, and the calculated concordance index was 0.63.

Subsequently, Karakiewicz et al. utilized data from a randomized phase III study of bevacizumab plus interferon-alpha vs. interferon-alpha alone to construct a nomogram that predicts progression-free survival [72]. The model allows calculation of survival at 4 time points – 6, 12, 18, and 24 months – and the variables that were significantly predictive of these outcomes were age, Karnofsky performance status, time from diagnosis to therapy, serum albumin, and serum alkaline phosphatase. The predictive accuracy was assessed and compared to that of the Motzer criteria, and the group found that the nomogram provided superior risk estimations for each time point outcome.

Prior to the publication of the CARMENA trial, cytoreductive nephrectomy was the accepted standard of care for metastatic RCC in combination with systemic therapy. A group at MD Anderson utilized a cohort of 601 patients who underwent a cytoreductive nephrectomy from 1991 to 2008 to construct a nomogram predicting cancer-specific survival after cytoreductive nephrectomy [73]. Their pre- and postoperative models showed good discrimination (0.76 and 0.74, respectively) and performed

well in a decision curve analysis for net benefit in decision-making. However, patients selected in this study were largely from the pre-targeted therapy era, so this model may be of limited benefit in contemporary cohorts. A validation study from Memorial Sloan Kettering applied this model to a cohort of 298 patients spanning 1989–2015 and found poorer discrimination than the MD Anderson data (AUC 0.65 compared to 0.76) [74]. This may be secondary to a greater number of patients being treated with targeted therapies and is likely to change further with the results of new randomized controlled trials emerging and being further analyzed.

As more models are constructed and appropriately validated, the therapeutic choice among the burgeoning selection of targeted therapies should continue to improve – hopefully in concert with patient outcomes. While current models for metastatic RCC clearly lag behind the preoperative and postoperative models in terms of both quantity and quality, it is evident that the analysis of recent randomized trials of targeted therapies will continue to provide extremely valuable data upon which more models can be based. Furthermore, as the prognostic role of molecular markers becomes more clearly defined in the metastatic setting, their incorporation into nomograms will only further our ability to identify the therapies to which patients will best respond.

Conclusion

Renal cell carcinoma has a wide and varied clinical presentation and natural history, and this heterogeneity can be problematic when it comes to providing the individualized outcome predictions that contemporary patients crave. Tumor stage and nuclear grade, among other clinicopathological factors, were once considered the primary determinants of overall prognosis but have now become components of more refined clinical algorithms and nomograms. These prediction tools have the capability to provide individualized risk estimations in an unbiased, reproducible, and evidence-based format, and currently, models have been constructed and validated in the preoperative, postoperative, and metastatic settings for RCC. As our understanding of the implications of molecular markers continues to develop, the incorporation of these variables into existing models should improve not only our selection of systemic therapies and clinical trials but also patient satisfaction and outcomes.

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Postoperative Surveillance Protocols for Renal Cell Carcinoma

21

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Introduction

Cancers of the kidney and renal pelvis accounted for approximately 3–5% of all malignancies diagnosed in the United States in 2017, with 63,990 new cases and 14,400 deaths. [1] The majority of these cancers are renal cell carcinomas (RCC). The incidence of RCC continues to rise, increasing by 2% per year, in part secondary to the increasing use of abdominal imaging resulting in the incidental finding of renal masses. Despite the potential advantage of identifying and treating asymptomatic patients at earlier disease stages, one-third of patients will eventually develop local or distant recurrence following surgical extirpation [2–4].

Prognosis of patients with untreated recurrent disease is poor, with 5-year survival rates of 3–9% [5, 6]. If identified early, however, metastasectomy with or without systemic therapy has been shown to improve overall survival [7–10]. Therefore, the use of surveillance to effectively identify those at risk for recurrence is of paramount importance.

This chapter reviews the recurrence patterns of RCC and the prognostic factors associated with risk of recurrence as a rationale for the establishment of surveillance protocols. Although there is no single consensus on the optimal guidelines for follow-up, there are several evidence-based recommendations and reviews that are currently being used in the postoperative setting, following radical and partial nephrectomy, as well as ablative therapies for RCC.

Natural History of RCC and Recurrence Patterns

Renal cell carcinoma originates from the proximal tubular epithelium and typically grows slowly, forming discrete focal lesions. Local disease progression occurs by invasion through the renal capsule into Gerota's fascia and further local extension to surrounding structures. In addition, renal cell carcinoma spreads to distant sites through both hematogenous and lymphatic routes. The lung, bone, and liver are the most commonly affected, although RCC can also metastasize to the brain, contralateral kidney, adrenal gland, and soft tissues [11]. Involvement of lymph nodes without distant metastases is uncommon, although disease progression can be unpredictable secondary to the variable lymphatic drainage of the kidneys [12].

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Distant Recurrence

Lung

The most common site of metastasis from RCC is the lung, with a reported incidence of 3–16% [13–17]. Median time to development of pulmonary recurrence is correlated with tumor stage, with an earlier time to recurrence for higher-stage disease. One series reports the median time to metastasis to be 53 months for pT1 disease, 31 months for pT2 disease, and 14 months for pT3 disease. In this same observational study, none of the patients with pT1 disease were symptomatic at diagnosis of recurrence, 11% with pT2 disease were symptomatic, and only 9% with pT3 disease presented with symptoms [14].

Symptoms associated with pulmonary metastasis include pleuritic chest pain, hemoptysis, cough, dyspnea, and weight loss. Multiple other studies have confirmed the low rates of symptomatic lung recurrences, with pulmonary lesions being found in over 90% of asymptomatic patients with metastases undergoing routine surveillance imaging [16, 18, 19].

A meta-analysis reviewing post-nephrectomy pulmonary metastasis reports the latest pulmonary lesion discovered at 67 months for pT1 tumors, 97 months for pT2 tumors, and 138 months for pT3 tumors, emphasizing the importance of surveillance up to at least 5 years postoperatively and ideally longer [14–16, 20].

The high percentage of asymptomatic recurrences for all stages of disease has led to recommendations for routine chest imaging in the form of CXR or chest CT for all stages of disease with emphasis on the first 3–5 years postoperatively.

Bone

Bone metastasis occurs in approximately 2–8% of all patients after nephrectomy for RCC and comprises 16–27% of patients with recurrent disease [14–16, 19]. Although reported to be less common for patients with pT1 disease (0–25%), bone metastasis for patients with pT2 and pT3 disease occurs in 17.6–45% and 16–26.5%, respectively. Recurrence is at a median time of 39 months for pT1 disease, 24–40 months for pT2 disease, and 7–20 months for pT3 disease [14–16, 20].

As with pulmonary metastasis, tumor stage is correlated with median time to recurrence. In contrast to pulmonary recurrence, however, most patients with bone metastasis present with symptoms. Bone pain is reported in 67–90% of patients and alkaline phosphatase levels are elevated in 33–55% [14, 19, 20]. In a study by Shvarts et al., 68% of patients with bone metastasis were also found to have extraosseous metastasis and 95.5% had an ECOG performance status of 1 or more [21]. Given these data, routine surveillance with nuclear scintigraphy is not warranted in the absence of symptoms or an elevated alkaline phosphatase level.

Liver

The reported incidence of liver metastasis is between 1% and 7%. It is rarely reported for patients with pT1 disease, with an incidence of 0 in several studies [14–16, 20]. In one series, an incidence of 12% is reported for patients with pT2 disease and 9% for pT3 disease, with a median time to recurrence of 53–83 months and 5–67 months, respectively [14, 20]. Most patients (pT2, 60–100%; pT3, 73–100%) were diagnosed after presenting with abdominal pain and/or elevated liver function tests (LFTs).

Brain

Brain metastasis occurs in 2–4% of all patients after nephrectomy [19]. Data derived from a meta-analysis by Skolarikos et al. report the incidence of brain metastasis for pT1 tumors to be from 0% to 12%. However, the 12% was derived from a single study in which one patient with pT1 disease in a cohort of 8 developed brain metastasis [14]. For pT2 and pT3 disease, the reported incidence ranges from 0% to 15% and 4% to 11%, respectively. All patients who developed

brain metastasis presented with symptoms such as headache, mental status change, or other neurologic deficits [14–16, 20]. For this reason, routine imaging has not been recommended in the absence of focal or new-onset neurological symptoms.

Lymph Nodes

Development of new lymph node metastasis was identified in up to 25% of patients with pT2 and pT3 disease. In all cases, patients were asymptomatic, diagnosed by routine CT scans, and found to have concomitant sites of recurrent disease [14, 16].

Local Recurrence After Radical Nephrectomy

Local recurrence involving the renal fossa, ipsilateral adrenal gland, or axial musculoskeletal anatomy is rare and incidence varies between 3% and 27% depending on the literature reviewed [14, 22, 23]. A retrospective study from the Mayo Clinic published in 2000 followed 1737 node-negative patients who underwent nephrectomy for RCC. Authors reported a 1.8% incidence of isolated renal fossa recurrence at 5 years, with 60% of patients being symptomatic upon diagnosis [24].

An updated cohort from the Mayo Clinic that included 2502 patients with localized RCC reported the overall incidence of isolated renal fossa recurrence to be 1.3%, with a median time to recurrence of 1.5 years [25]. In this study published in 2017, the authors found advanced pathologic stage and coagulative necrosis in the primary tumor to be independently associated with increased risk of developing an isolated renal fossa recurrence. They also reported significantly better oncologic outcomes for patients treated with local definitive therapy including metastasectomy, ablation or radiation, versus systemic therapy, or observation (3-year cancer-specific survival 64% vs. 50% vs. 28%, respectively).

Margulis et al. reviewed 2945 patients who had a radical nephrectomy with curative intent and reported an isolated local recurrence in 54 (1.8%) of those patients [26]. Local recurrence was defined as any RCC, proven by pathologic evaluation, and localized in the renal fossa, ipsilateral adrenal gland, or ipsilateral retroperitoneal lymph nodes. Consistent with the Mayo Clinic series, 61.2% of patients were symptomatic (28 patients with local symptoms and 5 with systemic symptoms) at presentation. In this population, the authors identified five risk factors that portend poor prognosis: size >5 cm, positive surgical margins, presence of sarcomatoid elements, abnormal LDH, and abnormal alkaline phosphatase. Patients with none of these risk factors ($N = 34$) had a median survival of 111 months. Patients with only 1 risk factor ($N = 9$) had a median survival of 40 months, while patients with more than 1 risk factor ($N = 11$) had a median survival of only 8 months after resection. Tumor size was a poor prognostic indicator, suggesting that earlier detection of such recurrence could lead to improved resectability and achieving of negative surgical margins, decreased surgical morbidity, and ultimately improved survival.

Recurrence After Partial Nephrectomy

Historically, there was a concern of increased risk of local recurrence in the ipsilateral kidney following partial nephrectomy. However, multiple studies over the past decade have found recurrence rates to be similar to radical nephrectomy despite utilization of a nephron-sparing approach. A study from the Cleveland Clinic reviewed 327 patients who underwent partial nephrectomy and demonstrated a local recurrence rate of 4% and a metastatic recurrence rate of 7.6% over 55.6 months [13]. A follow-up study from the same group observed 107 patients over 10 years and found no local recurrence for patients with localized pT1 and pT2 disease. For patients with pT3a and pT3b disease, local recurrence rates were 10% and 12%, respectively. Distant metastatic disease occurred in 2%, 29%, 0%, 33%,

and 53% of patients with pT1a, pT1b, pT2, pT3a, and pT3b, respectively [27].

In more recent years, the size threshold for renal masses amenable to partial nephrectomy has been expanded to include masses up to 7 cm and in some cases >7 cm, when technically feasible and clinically indicated. The feasibility of partial nephrectomy in larger renal masses has come with concern regarding long-term oncological outcomes [28]. The group from the Mayo Clinic studied 5-year survival rates for patients with renal masses 4–7 cm who underwent either partial or radical nephrectomy. They concluded that after controlling for stage, grade, tumor necrosis, and histological subtype, there was no statistical difference in cancer-specific survival or distant metastatic-free survival for those undergoing partial or radical nephrectomy [29].

Aside from the influence of size on recurrence patterns after partial nephrectomy, the effect of positive surgical margins (PSMs) has also been investigated. A study conducted by Memorial Sloan Kettering Cancer Center and the Mayo Clinic reviewed 1344 patients who underwent partial nephrectomy at one of these institutions between 1972 and 2005 [30]. A total of 77 patients (5.5%) were noted to have PSMs. Of the entire cohort, 39 patients had local recurrence and 57 had progression to metastatic disease. For patients with PSMs, the 5-year freedom from local recurrence was 98% and from metastatic progression 95%. There was no significant difference in freedom from local recurrence or metastatic progression between patients with positive surgical margins and patients with negative surgical margins [30].

A retrospective multi-institutional review collected data from 26 centers throughout Europe and North America and reported similar results [31]. They identified 119 positive surgical margins following partial nephrectomy. A negative surgical margin cohort was obtained from a multi-institutional database and was matched for surgical indication, tumor size, and Fuhrman grade. There was no difference in recurrence-free survival between patients with negative surgical margins and those with positive surgical margins. Rates of cancer-specific survival and overall survival were comparable for both groups [31].

Contrary to previous literature, a recently published paper from MD Anderson Cancer Center reported a significantly higher rate of local tumor bed recurrence following partial nephrectomy for patients who had positive surgical margins (15.9% vs. 3% in a matched control group). Consistent with other publications, they reported a 1.9% incidence of local tumor bed recurrence following partial nephrectomy in a contemporary cohort of 2256 patients undergoing surgery between 2000 and 2014 [32]. On multivariate analysis, male gender, a solitary kidney, positive surgical margins, more than two tumors excised, pT3 tumors, and RENAL nephrometry score of 10 or greater were variables that predicted a shorter time to local tumor bed recurrence. The authors suggest that the higher rate of local tumor bed recurrence for patients with positive surgical margins in this series could be influenced by the inclusion of higher-stage tumors (23% pT3) and potentially more challenging partial nephrectomies with higher nephrometry scores (53% score 7–9).

Collectively, these data indicate that recurrence and survival rates are similar following partial and radical nephrectomy regardless of tumor size and positive surgical margins. As such, contemporary surveillance strategies for the two groups have not markedly differed.

Surveillance Following Radical or Partial Nephrectomy

Rationale for Surveillance

According to observational data from the National Cancer Data Base for patients diagnosed with RCC between 2001 and 2002, the 5-year overall survival rates are 81% for stage T1, 74% for T2, 53% for T3, and 8% for T4 [33]. Given that adjuvant therapy has not been proven to be beneficial to date, early detection of metastatic disease is imperative to improving clinical outcomes. In early stages, chest and abdominal metastases are usually asymptomatic, with

symptoms only appearing in advanced stages [14]. In patients with surgically resectable metastases, early intervention in the absence of symptoms when complete resection is still possible could result in higher survival rates [34]. The Mayo Clinic recently reported that complete metastasectomy confers a cancer-specific survival (CSS) advantage in patients who present with multiple synchronous and asynchronous metastatic lesions. Alt et al. reviewed 887 patients who underwent nephrectomy for renal cell carcinoma and were diagnosed with metastatic disease [35]. One hundred twenty-five patients underwent complete surgical metastasectomy and were found to have an improved median CSS compared to patients who did not undergo metastasectomy (4.8 vs. 1.3 years). Patients with pulmonary metastasis who underwent complete surgical resection had a 5-year CSS of 73% vs. 19% for those who did not have complete resection. Patients with multiple, nonpulmonary lesions also benefited from complete resection compared to those who did not undergo complete resection (5-year CSS 32.5% vs. 12.4%). A survival advantage was seen following metastasectomy for both patients with localized disease who developed synchronous or asynchronous metastasis and patients who initially presented with metastatic disease and then developed asynchronous metastasis [35].

Components of Surveillance

There is currently no consensus on the optimal surveillance protocol following surgical resection or ablative therapy for the treatment of RCC. Historically, surveillance has included history, physical examination, laboratory work, and periodic chest and abdominal imaging studies at intervals based on established recurrence patterns.

A thorough history and physical examination is important for promptly identifying signs and symptoms that suggest disease recurrence and warrant further investigation. Constitutional symptoms such as fever, weight loss, and fatigue are concerning for metastatic disease. A complete review of systems should be performed to identify the presence of pleuritic chest pain, dyspnea, hemoptysis, epistaxis, abdominal pain, flank pain, bone pain, change in mental status, or focal neurologic deficits. Physical exam findings such as a palpable abdominal mass and groin and supraclavicular or axillary lymphadenopathy, lower extremity swelling are also concerning for metastatic disease and should elicit further workup.

Current National Comprehensive Cancer Network (NCCN) guidelines recommend lab work to include a comprehensive metabolic panel (CMP), which consists of liver function, LDH, calcium, electrolytes, BUN, and creatinine studies.

Routine blood work plays a prognostic role in surveillance of oncological as well as non-oncological parameters. Motzer et al. identified that a lactate dehydrogenase level > 1.5 times the upper limit of normal, a hemoglobin level < lower limit of normal, a corrected serum calcium level > 10 mg/dl, a Karnofsky performance score ≤ 70, and an interval of less than 1 year from the original diagnosis to start of systemic therapy predicted short survival in patients with advanced renal cell carcinoma. In this study, patients with three or more of these factors had a poor prognosis, with a median survival of 5 months and a 1-, 2-, and 3-year survival rate of 20%, 6%, and 2% [36]. Patients with elevated liver function studies should be evaluated with abdominal imaging and those with elevated alkaline phosphatase should receive a nuclear bone scan to evaluate for metastatic disease.

Aside from monitoring lab work that relates to oncological outcomes, it is also important to follow kidney function parameters including creatinine, estimated glomerular filtration rate (eGFR), and urinalysis. Chronic kidney disease (CKD) is defined as eGFR < 60 ml/min or the presence of factors that suggest kidney damage, such as albuminuria or abnormal renal imaging, occurring for 3 months or greater [37]. CKD has been shown to be associated with a higher risk of morbidity and mortality [38]. Early identification of worsening serum creatinine, eGFR, and development of proteinuria identifies patients who are developing

chronic kidney disease following surgery and allows for early referral to a nephrologist, who will work with the patient to control medical comorbidities and optimize renal function.

Prognostic Factors Influencing Recurrence

Early recommendations for surveillance have been guided mostly by the correlation of tumor stage with time to recurrence and site of recurrence [14–16, 20]. The likelihood of developing metastatic disease has been shown to be greatest in the first 3 years after nephrectomy and directly correlates with tumor stage. In one series, the risk of metastatic disease was 7.1% for those with T1 disease, 26.5% for T2 disease, and 39.4% for T3 disease [14]. Chae et al. reviewed patterns of tumor recurrence in 194 patients and found that 21% of patients recurred in a mean time of 17 months. Eighty-three percent of those who recurred were diagnosed within the first 2 years after surgery, and the rate of recurrence was higher for patients with tumor size of >5 cm [39].

More recent literature published in 2013 demonstrated the impact of length of survival on future survival probability, otherwise known as conditional survival [40]. In this series, 42,090 patients from the Surveillance, Epidemiology, and End Results (SEER) database who underwent nephrectomy from 1988 to 2008 were reviewed, and the 5-year cancer-specific survival rate immediately following surgery was reported to be 83.5%. For those patients surviving ≥1, ≥2, ≥3, ≥4, and ≥5 years after nephrectomy, the probability of surviving an additional 5 years were 87.0%, 89.6%, 90.9%, 92.0%, and 92.3%. Even patients with advanced disease had a more favorable prognosis if they had already survived 1–2 years.

Over the last decade, data has emerged that supports the addition of other important prognostic factors to models that predict postoperative recurrence of RCC. In 2001, Kattan and colleagues at Memorial Sloan Kettering Cancer Center (MSKCC) constructed a nomogram to predict 5-year disease-free survival rates following radical or partial nephrectomy. In addition to tumor stage, tumor size, histology, and symptomatic presentation were analyzed for 601 patients and determined to be important prognostic factors influencing disease recurrence [41].

Tumor size has been demonstrated to be an independent predictor of disease-free survival [42–44]. Five-year survival rates in one publication were reported to be 84% for tumors less than 5 cm, 50% for tumors 5–10 cm, and 0% in tumors greater than 10 cm [45]. In a follow-up study, the MSKCC group also confirmed the importance of tumor size in predicting disease recurrence independent of pathologic stage [46].

Histology by itself has also been shown to predict disease-specific survival and effect recurrence patterns. Of the four subtypes of RCC, chromophobe RCC confers a better prognosis than conventional (clear cell) RCC or papillary RCC [47]. Papillary type II, however, has been shown to independently predict poor survival [48, 49]. The presence of sarcomatoid dedifferentiation on final pathology indicates poor prognosis and has been utilized in risk stratification algorithms to predict disease recurrence [50, 51]. A subgroup analysis of the phase 3 ECOG-ACRIN E2805 trial evaluated patterns of recurrence for patients with high-risk non-clear cell renal cell carcinoma. Patients enrolled in this trial had complete resection of their localized disease and received adjuvant therapy with sunitinib, sorafenib, or placebo. Although 5-year recurrence rates were similar between patients with ccRCC and non-clear cell RCC, patients with non-clear cell RCC had higher rates of abdominal recurrences and were less likely to recur in the chest [52].

The MSKCC group published an externally validated postoperative nomogram in 2004 that analyzed a cohort of 701 patients diagnosed specifically with clear cell RCC. The prognostic factors in this nomogram included tumor size, symptomatic presentation, pathologic stage, Fuhrman grade, presence of necrosis, and presence of microvascular invasion [46]. Both Fuhrman grade and microvascular invasion were predictive of disease-free survival on multivariate analysis.

Other literature has also confirmed the importance of Fuhrman grade, microvascular invasion, and necrosis in predicting disease recurrence [42, 53, 54]. The group from Mayo Clinic constructed a scoring system, SSIGN, based on tumor stage, tumor size, Fuhrman grade, and presence of tumor necrosis. All four factors were predictive of cancer-specific survival on multivariate analysis and used in an algorithm to predict clinical outcomes [53].

Authors from University of California Los Angeles (UCLA) demonstrated the importance of the Eastern Cooperative Oncology Group (ECOG) performance status score in predicting overall survival. Based on stage, grade, and ECOG performance status, they established a risk classification system predicting 2- and 5-year survival rates [55]. This model was later used to create a surveillance strategy that has been recommended by the NCCN and is widely used today [22].

A preoperative nomogram from MSKCC and Mayo clinic was published in 2008 that was developed after reviewing clinicopathologic factors and outcomes of 2517 patients. Gender, symptomatic presentation, lymphadenopathy by imaging, tumor necrosis, and tumor size were used to create a preoperative nomogram predicting disease-free recurrence at 12 years [54].

Other nomograms and predictive tools have been previously reported and will be the subject of a separate chapter in this book.

Surveillance Following Radical or Partial Nephrectomy in Patients with Sporadic RCC

Since the early 1990s, multiple investigators have used their institutional databases to put forth recommendations for postoperative surveillance for patients with RCC. These will be described in detail in this section and summarized in Table 21.1.

In 1994, Montie et al. proposed a 5-year surveillance protocol that included physical exam, laboratory studies, and CXR every 6 months as well as an abdominal CT at 12, 24, and 48 months, independent of pathologic stage after nephrectomy [60]. While more metastases are potentially detected using this unselected schedule, one has to keep in mind the cost-effectiveness of such an approach, as well as potential radiation risk.

In 1995, in order to sub-select surveillance tools based on stage, Sandock and colleagues [16] from Case Western Reserve University retrospectively reviewed 137 patients without nodal or metastatic disease at presentation who underwent radical nephrectomy between 1979 and 1993. Nineteen patients were pT1 and had no recurrence at a mean follow-up of 44.4 months. Eighty-two patients were pT2 and 15.9% recurred at mean of 29.5 months. Thirty-six patients were pT3 and 52.8% recurred at mean of 22 months. Of those patients who experienced recurrence, chest metastases occurred in 53.8% (7 of 13) of patients with pT2 and 63.2% (12 of 19) with pT3. For patients with pT2 and pT3 disease, 71% (5 of 7) and 75% (9 of 12), respectively, were specifically symptomatic with dyspnea, cough, hemoptysis, and/or pleuritic chest pain. Abdominal metastases occurred in 38.5% (5 of 13) of patients with pT2 and 42.1% (8 of 19) of patients with pT3. 12 of these 13 patients with abdominal metastases (liver 8, local 3, both 2) had signs or symptoms of metastatic disease. Bone metastases developed in 38.5% (5 of 13) patients with pT2 and 26.4% (5 of 19) patients with pT3, and all 10 patients with bone metastases presented with bone pain that prompted further workup. Brain metastases developed in two patients with pT2 and four patients with pT3. In all six patients, brain metastases were symptomatic with headaches or mental status changes. Lymphadenopathy occurred in 25% (3 of 13) patients with pT2 and 25% (5 of 19) patients with pT3, and all 8 recurrences were not isolated but were associated with other findings. Most recurrences (85%) occurred in the first 3 years after radical nephrectomy. From the authors' dataset, only 1 of the 137 patients they studied benefited from routine CT scan. The authors concluded that bone scans and CT scans should not be routinely performed and that follow-up should include only a history and physical examination in patients with pT1 disease. For patients with pT2 and pT3 disease, they

Table 21.1 Surveillance guidelines after nephrectomy and partial nephrectomy

	Clinical assessment (history, physical exam, laboratory studies)	Chest X-ray	Abdominal CT
pT1			
Sandock (1995) [16]	Not specified	Not recommended	Not recommended
Hafez (1997) [13]	Yearly	Not recommended	Not recommended
Levy (1998) [14]	Yearly	Yearly	Not recommended
Ljunberg (1999)[a] [15]	Not recommended	Not recommended	Not recommended
Mickisch (2001) [56]	Every 6 months for 3 years, then yearly from years 3 to 5	Every 6 months for 3 years, then yearly from years 3 to 5	Not recommended
Stephenson (2004) [57]	Yearly	Yearly	Not recommended
Novick (2005) [58]	Yearly	Not recommended	Not recommended
Kassouf (2009) [59]	Yearly	Yearly	At years 2, 5 (optional at 3 months)
pT2			
Sandock (1995) [16]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years and then yearly	Not recommended
Hafez (1997) [13]	Yearly	Yearly	Every 2 years
Levy (1998) [14]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years and then yearly	At years 2, 5
Ljunberg (1999)[b] [15]	At 3 and 6 months and then every 6 months until 3 years and then yearly	At 3 and 6 months, then every 6 months until 3 years, and then yearly	Not recommended
Mickisch (2001) [56]	Every 6 months for 3 years and then yearly from years 3 to 5	Every 6 months for 3 years and then yearly from years 3 to 5	Not recommended
Stephenson (2004) [57]	Yearly	Yearly	Not recommended
Novick (2005) [58]	Yearly	Yearly	Every 2 years
Kassouf (2009) [59]	Every 6 months for 3 years and then yearly	Every 6 months for 3 years and then yearly	12, 36, 60, 80, and 108 months
pT3			
Sandock (1995) [16]	Every 6 months for 3 years and then yearly	Every 6 months for 3 years and then yearly	Not recommended
Hafez (1997) [13]	Yearly	Yearly	Every 6 months until 2 years and then every 2 years
Levy (1998) [14]	At 3 and 6 months, then every 6 months until 3 years, and then yearly	At 3 and 6 months, then every 6 months until 3 years, and then yearly	At years 2, 5
Ljunberg (1999) [15]	At 3 and 6 months, then every 6 months until 3 years, and then yearly	At 3 and 6 months, then every 6 months until 3 years, and then yearly	At 6 and 12 months (optional)

Table 21.1 (continued)

	Clinical assessment (history, physical exam, laboratory studies)	Chest X-ray	Abdominal CT
Mickisch (2001) [56]	Every 6 months for 3 years and then yearly from years 3 to 10	Every 6 months for 3 years and then yearly from years 3 to 10	Every 6 months for 3 years and then yearly from years 3 to 10
Stephenson (2004) [57]	Every 6 months for 3 years and then yearly	Every 6 months for 3 years and then yearly	At 6, 12, 24, and 36 months and then every 2 years
Novick (2005) [58]	Yearly	Yearly	Every 6 months for 2 years and then every 2 years
Kassouf (2009) [59]	Every 6 months for 3 years and then yearly	Every 6 months for 3 years and then yearly	At 6, 12, 18, 24, 36, and 60 months and then every 2 years
UCLA risk groups [22]			
Low risk	Yearly	Yearly for 5 years	At years 2, 4
Intermediate risk	Every 6 months for 3 years and then yearly until 10 years	Every 6 months for 3 years and then yearly until 10 years	At years 1 and 2 and then every 2 years for 10 years
High risk	Every 6 months for 3 years and then yearly until 10 years	Every 6 months for 3 years and then yearly until 10 years	Every 6 months for 2 years, then yearly until 5 years, and then every 2 years until 10 years
Nodal disease	At 3, 6, 12, 18, and 24 months and then yearly	At 3, 6, 12, 18, and 24 months and then yearly	At 3, 6, 12, 18, and 24 months and then yearly

[a]Includes pT1 tumors <5 cm, pT1 diploid, and pT2 diploid
[b]Includes pT1 >5 cm aneuploid/ploidy not assessed or pT2 aneuploid/ploidy not assessed

recommended a history, physical examination, liver function tests, and chest X-rays every 6 months for the first 3 years and then yearly thereafter.

In 1997, Hafez et al. from Cleveland Clinic reported oncological outcomes for 327 patients who underwent partial nephrectomy prior to December 1994. Mean follow-up was 54 months and recurrence developed in a total of 38 patients (11.6%). Thirteen patients (4%) had local recurrence, of which seven also had distant metastatic disease. Twenty-five patients (7.6%) presented with metastatic disease in the absence of local recurrence. Incidences for local recurrence and metastatic disease by stage were 0 and 4.4% for T1, 2.0 and 5.3% for T2, 8.2 and 11.5% for T3a, and 10.6 and 14.9% for T3b. Local recurrence was most often diagnosed from 6 to 24 months and after 48 months. Based on these data, the authors recommended that all patients should undergo a yearly history, physical exam, and lab work. No imaging was recommended for patients with T1 disease since the risk of recurrence was found to be low; however, a yearly chest X-ray was recommended for patients with T2 and T3 disease as metastasis to the lung was more common in these groups. Occasional follow-up every 2 years with CT abdomen was suggested for patients with T2 disease, and since local recurrence is highest in T3 disease, the authors recommend CT abdomen every 6 months for the first 2 years and then every 2 years thereafter [13].

In 1998, Saidi and colleagues [61] from Columbia University reported on 45 patients that were enrolled in an adjuvant autolymphocyte therapy trial for N+M0 high-risk patients. 12 patients were T2, 30 were T3, and 3 were T4. Sixty-four percent recurred after radical nephrectomy (29 of 45) at a mean of 14.9 months. Fourteen recurred in the retroperitoneal nodes at 13.9 months, eleven in the lung at 14.4 months, five in the liver at 14.9 months, five in the bone at 11.9 months, four in the mediastinal nodes at 11.8 months, three in the renal fossa at 6.9 months, and two in the brain at 20.7 months. Of those who had disease progression, 31% did so by 6 months, 59% by 12 months, 83% by 24 months, and 93% by 36 months. As such, the authors recommended routine chest X-ray and CT abdomen at least every 6 months for the first 3 years and then

yearly. Given that this study involved very high-risk patients (node-positive), the follow-up recommended cannot be necessarily applied to the general population of patients with renal cell carcinoma treated with surgery.

In 1998, Levy and colleagues [14] from MD Anderson Cancer Center proposed postoperative surveillance guidelines stratified by stage,and based on 286 patients that were surgically treated for renal cell carcinoma without nodal or distant metastases between 1985 and 1994. At a median follow-up of 23 months, 68 patients developed metastatic disease in a total of 92 sites. Eight of 113 patients with pT1, 17 of 64 patients with pT2, and 43 of 109 patients with pT3 developed metastases at a median of 38 months, 32 months, and 17 months, respectively. Sixty-four percent (59 of 92) of the metastases were asymptomatic (32 detected on chest X-ray and 12 on routine laboratory studies). Only six patients (9%) had an isolated intraabdominal metastasis without associated symptoms. All brain metastases presented with neurological symptoms that prompted further evaluation. In the eight pT1 patients with recurrent disease, four were in the chest (lung), two in the bone, and one each in the brain and uvula. In the 17 pT2 patients with recurrence, 9 were in the chest (lung), 5 in the abdomen (liver 2, lymph node 1, adrenal 1, pancreas 1), 3 in the bone, and 1 in the brain. In the 43 pT3 patients, 18 were in the chest (lung, 18% diagnosed <6 months after surgery), 10 in the abdomen (local 4, liver 4, adrenal 2), 7 in the bone, 5 in the lymph nodes (detected on physical examination), and 3 in the brain. Eleven of the pT3 patients were diagnosed with metastases <6 months after surgery. The authors suggested starting with abdominal CTs no earlier than 24 months after surgery, as in their experience, all 344 CT scans done in the first 24 months of surveillance did not yield any useful information. For patients with pT2 disease the authors recommended history, physical exam, laboratory studies, and chest X-ray at 12, 24, 36, 48, and 60 months after surgery for pT1 and history, physical exam, laboratory studies, and chest X-ray at 6, 12, 18, 24, 30, 36, 48, and 60 months and CT abdomen at 24 and 60 months for pT2. Recommended follow-up for pT3 was similar to pT2, with the addition of history, physical exam, laboratory studies, and chest X-ray at 3 months after surgery.

In 1999, Ljundberg and colleagues [15] from Umeå University in Sweden developed a surveillance protocol based on stage, tumor size, and DNA ploidy. They retrospectively reviewed 187 patients with no clinical nodal or distant metastases treated with radical nephrectomy between 1982 and 1997. Fifty-six patients developed a total of 98 metastases at a median of 14.5 months after radical nephrectomy. Thirty-seven were in the chest (lung), 24 were in the bone, 21 were intraabdominal (11 liver, 7 local or retroperitoneal, 3 abdominal), 4 were in the brain, 3 were in the skin, and 9 in other sites. In 43% of the 56 patients, the metastases were discovered in the first year, in 70% in the first 2 years, in 80% in the first 3 years, and in 93% in the first 5 years after surgery. Seven percent (5 of 70) of patients with T1 experienced a recurrence at a median of 40 months; however, all these patients had tumors larger than 5 cm in size. 14% (6 of 43) of patients with pT2 recurred at median of 8 months, 55% (26 of 48) of patients recurred at median of 12 months, and 73% (19 of 26) recurred at a median of 15 months. Of the 11 recurrences in patients with pT1 and pT2, 6 were in the lung (only 1 symptomatic) and 5 were in the bone (all symptomatic). In patients with pT3, only 1 of 24 lung recurrences was symptomatic, while all 10 bones, all 5 livers, and both liver recurrences were symptomatic. Patients with pT1–T2 homogenously diploid tumors did not experience a recurrence, while ploidy did not affect patient outcomes in patients with stage pT3. Based on these findings, the authors recommend no follow-up for patients with pT1 tumors <5 cm, pT1 diploid, and pT2 diploid. Physical examination, laboratory studies, and chest X-ray at 3, 6, 12, 18, 24, 30, 36, 48, and 60 months were recommended for patients with pT1 > 5 cm aneuploid/ploidy not assessed or pT2 aneuploid/ploidy not assessed and a similar follow-up as the latter category with the addition of optional CT abdomen and bone scan at 6 and 12 months for patients with pT3 or N1 disease.

In 2001, Mickisch and colleagues [56] from Erasmus University Rotterdam reviewed multiple publications [13, 14, 16] and established a follow-up protocol. For patients with pT1 and pT2 disease, the authors recommended history, physical exam, laboratory studies, and a chest X-ray every 6 months for the first 3 years and then yearly until 5 years. Abdominal CT was not recommended for this group. More intense follow-up for a longer period of time was recommended for patients with pT3 disease. A clinical assessment, chest X-ray, and abdominal CT were recommended every 6 months for the first 3 years then yearly up to 10 years [56].

In 2003, Frank and colleagues [62] from Mayo clinic retrospectively reviewed 1864 patients treated with partial or radical nephrectomy in the absence of distant metastases and defined recurrence locations into four major categories: chest, abdomen, bone, and brain. 16% (300 patients) recurred in the chest at a median of 1.6 years, 10% (185 patients) recurred in the abdomen at a median of 1.7 years, 7% (134 patients) recurred in bone at a median of 1.5 years, and 4% (81 patients) recurred in the brain at a median of 2.5 years. The authors then used analyses that included different combinations of risk factors (positive surgical margins, tumor stage, nodal status, size >10 cm, nuclear grade, tumor necrosis, sarcomatoid features, cystic architecture, and multifocality) to devise scoring systems that predicted the risk of metastases into each of these four locations. One important finding, in line with other studies, is that 98.2% of brain metastases and 90.5% of bone metastases were symptomatic at presentation, obviating the need for routine surveillance for these sites in the absence of specific symptoms. The authors, however, did not recommend a particular surveillance schedule based on these findings and recommended that the clinician should decide on the appropriate follow-up scheme on an individual basis that considers the scoring system as well as individual patient characteristics such as age and comorbidities among others.

In 2004, Stephenson and colleagues [57] retrospectively reviewed 495 patients who underwent partial or radical nephrectomy in five Canadian centers. Sixty-seven patients had a recurrence after surgery (63 distant, and 12 local) and only 4 patients had an isolated local recurrence. 16 of 303 patients with pT1 relapsed at a median of 35 months, with 15 of these relapses being solitary. Thirteen patients had symptoms with or without a chest recurrence that would have been found on physical examination or chest X-ray. There were three asymptomatic (two after partial nephrectomy and one after radical nephrectomy) and one symptomatic abdominal recurrences. 14 of 84 patients with pT2 recurred at a median of 25 months. All these 14 patients had symptoms with or without a chest recurrence, and only 10 of 14 recurrences were solitary. 23 of 74 patients with pT3a recurred at 14 months (only 16 recurrences were solitary), and 14 of 34 patients with pT3b recurred at 8 months (only 8 recurrences were solitary). Based on their findings, the authors recommended annual history, physical examination, and chest X-ray in patients with pT1 or pT2 disease. They recommended that patients with pT3a or pT3b should be followed up every 6 months for the first 3 years with history, physical examination, and chest X-ray and then annual follow-up while obtaining CT abdomen at 6, 12, 24, and 36 months after surgery and then every 2 years afterward.

In 2005, Lam and colleagues from University of California Los Angeles [22] developed a postoperative surveillance protocol based on the UISS – an integrated risk stratification model that incorporates the 1997 TNM staging, Fuhrman grade, and ECOG status into five categories – and have been shown to predict outcomes in patients post-nephrectomy for RCC [55] (Fig. 21.1). This UISS model has been validated in subsequent studies [63, 64]. In this retrospective study [22], 559 patients with nonmetastatic RCC treated between 1988 and 2003 were reviewed and risk stratified according to the established UISS model (low risk, intermediate risk, high risk, and node positive). Recurrence patterns were then analyzed, and a surveillance protocol was constructed based on their findings. 92.8% of patients had localized disease and 70% underwent radical nephrectomy. Median follow-up was 26 months

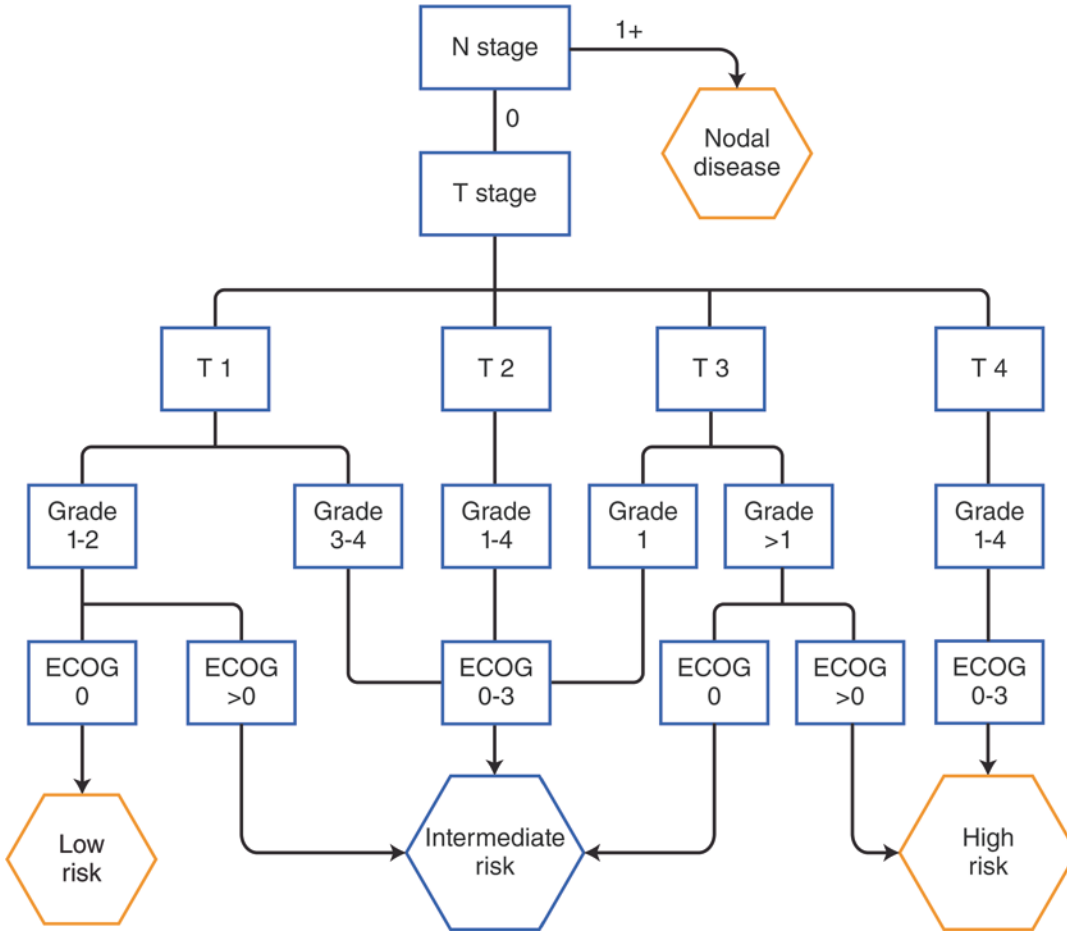

Fig. 21.1 Flowchart for UISS risk group assignment of patients with localized and locally advanced RCC. Progress from top to bottom using 1997 UICC N stage and T stage, Fuhrman grade, and ECOG-PS. (Reprinted from Lam et al. [22], with permission from Elsevier)

(Fig. 21.2). Patients identified as low risk ($N = 196$) had an overall 5-year recurrence rate of 9.6%, with a median time to recurrence of 28.9 months. 87.5% (7 of 8) had a solitary recurrence. The chest was the most common site of recurrence in the low-risk group accounting for 75% of the overall recurrences in this cohort. Recurrence was most common in the first 3 years following nephrectomy with a median time to recurrence of 23.6 months. No pulmonary recurrences were diagnosed after 5 years. Abdominal recurrences comprised 37.5% of the recurrences with a median time to recurrence of 32 months. None of the abdominal recurrences in the low-risk group occurred before 20 months or after 5 years. For the intermediate risk group (N, 251), the 5-year recurrence rate was 38.2% at median time of 17.8 months. 40.5% (25 of 62) had solitary recurrence, 77.4% of the recurrences were discovered in the chest, and 58.1% in the abdomen. 41.7% of patients with chest metastasis were diagnosed in the first year, and of those, 70% were diagnosed between 6 months and 1-year post-nephrectomy and 58% of the abdominal recurrences were diagnosed within the first year, of which 66.6% were discovered between 6 months and 1 year after nephrectomy. 44% of the bone recurrences occurred within the first year, while 33% occurred after 5 years. Brain recurrences in this group were rare. Patients

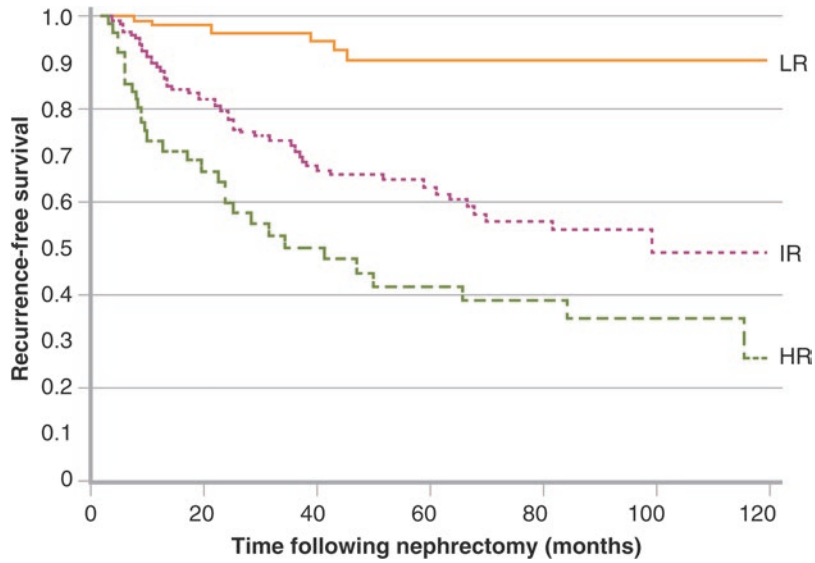

Fig. 21.2 Kaplan-Meier estimate of recurrence-free survival following nephrectomy among UISS risk groups. (Reprinted from Lam et al. [22], with permission from Elsevier)

classified as high risk ($N = 72$) had a 5-year recurrence rate of 58.1% at a median time of 9.5 months. 74.2% (23 of 31) of the recurrences were solitary. The chest was the most frequent site of recurrence accounting for 45.5% of the recurrences. 50% of chest recurrences were diagnosed in the first year and 42.8% of those within the first 6 months after surgery. Seven percent of the chest recurrences were found on routine imaging after 5 years of follow-up. Abdominal recurrences including the renal fossa, liver, and other abdominal organs together comprised 68.2% of recurrences. Of these, 62% occurred within the first year and 61.5% of those within the first 6 months. Only 5% of abdominal recurrences were diagnosed after 5 years. Patients with lymph node-only metastasis experienced a 64% 5-year recurrence after surgery. Of those who recurred, 58.8% had a chest recurrence and 76.5% had an abdominal recurrence. In patients who recurred in the chest, recurrence occurred in 25%, 12.5%, 25%, and 37.5% at months 0–3, 3–6, 6–12, and 12–24 after surgery, respectively. In patients who recurred in the abdomen, recurrence occurred in 28.6%, 21.4%, and 28% at months 0–3, 3–6, and 12–24 after surgery, respectively. Based on these data, a surveillance protocol was constructed [19], outlining the optimal follow-up for patients post-nephrectomy as risk stratified according to the UISS model (Fig. 21.3).

A more recent publication assessed the accuracy of the UISS model in predicting postoperative recurrences by comparing it to a similar model that also incorporated patient age and tumor histology [65]. While patient age had no association with recurrence patterns, the average risk of recurrence within the first year of surgery significantly decreased across all UISS risk groups for patients with low-risk tumor types (papillary type 1 and chromophobe). Their data suggest that low-risk histology is a more important predictor of recurrence than overall risk group and that these patients do not require the same degree of surveillance as patients with conventional clear cell renal cell carcinoma [65].

In 2005, Chae and colleagues from Asan Medical Center in Korea retrospectively reviewed 194 patients treated with surgery [39]. Twenty-one percent of patients experience disease recurrence at a mean of 17 months. Tumor recurred within 2 years after surgery in 34 (83%) patients. Disease recurrence occurred in the lung in 29, bone in 13, nephrectomy bed in 7, brain in 6, mediastinal lymph nodes in 5, liver in 5, contralateral kidney in 4, and the neck in 2. Patient with tumors >5 cm, stage III, or Fuhrman grade 3–4 had a higher risk of recurrence. With the lung being the most common site of metastasis in their series, the authors recommended that chest CT should be done every 6 months

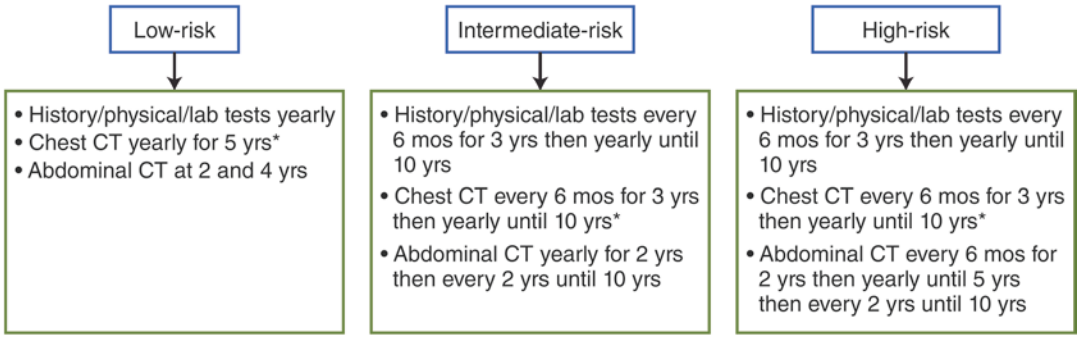

Fig. 21.3 Surveillance protocol following nephrectomy for localized renal cell carcinoma using the University of California Los Angeles Integrated Staging System. (Copyright © MedReviews®, LLC. Reprinted with permission of MedReviews®, LLC. Chin et al. [19]. *Reviews in Urology* is a copyrighted publication of MedReviews®, LLC. All rights reserved)

during the first 2 years after surgery and then annually for 2 years in patients with a high risk for tumor recurrence [39].

In 2009, Kassouf and colleagues from McGill University reviewed multiple series [2, 13–16, 20] before establishing the Canadian Urological Association guidelines for postoperative surveillance after nephrectomy [59]. The authors decided on a stage-based protocol to include a yearly history, physical exam, laboratory studies, and a chest X-ray for patients with pT1 disease. They recommend abdominal CT in this group at years 2 and 5, with an optional abdominal CT at 3 months and/or optional abdominal ultrasound yearly for patients who underwent partial nephrectomy. For patients with pT2 disease, history, physical exam, laboratory studies, and a chest X-ray were recommended every 6 months for 3 years and then yearly. Abdominal CT was recommended in this group at 12, 36, 60, 84, and 108 months postoperatively. Guidelines recommend the same follow-up in regard to clinical assessment and chest X-ray in patients with pT3 disease; however, abdominal CT should be done at 6, 12, 18, 24, 36, and 60 months and then continues every 2 years. For patients with node-positive disease, the authors recommended clinical assessment, chest X-ray, and abdominal CT at 3 and 6 months, every 6 months for 3 years, and then yearly [59].

In 2009, Siddiqui and colleagues from the Mayo Clinic [66] updated their prior surveillance protocol and included histological subtype as one of the additional risk factors for recurrence (in addition to the previously reported 1864 patients, the authors added 357 patients with papillary and 118 patients with chromophobe RCC). As such, tumor stage, grade, nodal status, margin status, and tumor necrosis were accounted for when recommending specific follow-up protocols. In addition, the authors recommended particular imaging at specific time intervals (Table 21.2), which was not provided in the prior manuscript in 2003 [62].

Stewart-Merrill et al. from the Mayo Clinic evaluated the performance of the 2014 NCCN and AUA guidelines at capturing recurrences after partial or radical nephrectomy. Despite guidelines being updated from previous versions to reflect a more risk-adapted approach, approximately one-third of recurrences were still missed [67]. The authors reviewed 1088 recurrences in patients who underwent partial or radial nephrectomy for RCC between 1970 and 2008 and determined that the 2014 NCCN guidelines would have detected 68.2% of recurrences, while the AUA guidelines would have detected only 66.9% of recurrences. They also estimated the cost of surveillance using both sets of guidelines and found that the older 2013 NCCN guidelines yielded a lower cost of

Table 21.2 Postoperative surveillance guidelines based on histological subtype – Siddiqui 2009

	Clinical assessment (history, physical exam, laboratory studies)	Chest X-ray or CT	Abdominal CT or US
Clear cell RCC			
Low risk	Yearly	Every 6 months until year 2 and then yearly	CT at 18, 24, and 30 months and then year 5, 7, 10 US at year 3, 4, 6, 8, 9
Intermediate risk	Yearly	Every 3 months	CT at 6, 9, 12, 15, 24, 27, and 30 months and then yearly from years 4 to 10; US year 3
High risk	Yearly	Every 3 months for 1 year and then at years 2, 5	CT every 3 months until year 2, then every 6 months for 1 year, and then yearly from years 3 to 10
Papillary RCC			
Low risk	Yearly	Not recommended	CT at years 1, 2; US at 6, 9 months
Intermediate risk	Yearly	At 12, 18,30, and 36 months and then yearly	CT year 3; US 6, 24 months and then every 2 years
High risk	Yearly	At 6, 9, 12, 18, and 24 months	CT at 6, 9, 12, 18, and 24 months and then every 2 years
Chromophobe RCC			
Low risk	Yearly	Not recommended	Not recommended
Intermediate risk	Yearly	Not recommended	CT year 3, 7; US year 5, 10
High risk	Yearly	At 6, 9, and 15 months	CT 3, 6 months and at year 7; US at year 3, 5, 10

$1228.79 (vs. $3700.87 for the higher-risk patients using the 2014 NCCN guidelines) however captured only 35.9% of recurrences if strictly followed [67].

After exploring the performance of existing guidelines, the same group from the Mayo Clinic in 2015 proposed a risk-adapted individualized surveillance strategy. Using a median follow-up of 9 years, the authors identified 676 patients of 2511 who underwent surgery from 1990 to 2008 and had developed recurrence. By utilizing a competing-risk model, they found significant differences between patients depending on age, disease stage, comorbidities, and location of recurrence [68]. For example, patients age 80 or older with pT1Nx-0 disease and minimal comorbidities were at higher risk of an abdominal recurrence as compared with non-RCC death for 6 months after surgery but not after that time period, suggesting that follow-up beyond 6 months may not be warranted for this cohort. Conversely, for younger patients with the same stage disease and the same number of comorbidities, the risk of abdominal recurrence remained as high as the risk of non-RCC death, suggesting this patient population requires prolonged follow-up.

More recently in 2018, a multicenter study used the European Association of Urology RECUR database to evaluate long-term outcomes in patients with localized RCC (Debastani et al., long term). They also concluded that a better risk-adapted approach should be incorporated into contemporary surveillance protocols. The authors identified 131 potentially curable recurrences and 155 probably incurable recurrences in 1265 patients. The 5-year cumulative risk of recurrence for low-, intermediate-, and high-risk disease was 7.2%, 23.2%, and 61.6%, respectively. Of the high-risk patients that recurred, only 30.5% were potentially curable. Competing risk analysis revealed the highest risk of death in young and high-risk patients; however, comorbidities were not available for analysis. These findings highlight the need for more sophisticated surveillance modeling to capture potentially curable recurrences expeditiously while limiting over-imaging in patients with low risk of recurrence (Debastani et al. long-term outcomes).

Current NCCN and AUA Guidelines

The recently updated 2018 National Comprehensive Cancer Network (NCCN) guidelines do not differ greatly from the 2014 version and reflect a modified surveillance approach based on panel consensus while also emphasizing in a footnote that no single follow-up is appropriate for every patient [69]. The panel recommends that for patients with pT1a and pT1b after partial or radical nephrectomy, a history and physical exam (H&P) as well as laboratory studies to include a comprehensive metabolic panel (CMP) should be performed every 6 months for 2 years and then annually for up to 5 years. Baseline abdominal imaging (CT, MRI, or US) should be performed within 3–12 months of surgery. If imaging is negative for those undergoing a radical nephrectomy, further imaging may be performed at the discretion of the physician. For patients who underwent partial nephrectomy, annual abdominal imaging can be performed for up to 3 years based on individual risk factors including tumor size. Chest imaging should be performed annually for 3 years and then as clinically indicated.

For patients who underwent ablative therapies, the recommended follow-up is the same in regard to H&P and lab work; however, the panel recommends abdominal CT or MRI within 3–6 months after the ablation. CT, MRI, or US may then be performed annually for up to 5 years. Chest CT or CXR is recommended annually for up to 5 years for patients who had biopsy-proven low-risk RCC, nondiagnostic biopsy or no biopsy [69].

For patients with stage II or stage III renal cell carcinoma, the NCCN guidelines recommend an H&P every 3–6 months for 3 years, annually up to 5 years following radical nephrectomy, and then as clinically indicated. Laboratory work to include a CMP should be performed every 6 months for 2 years and then annually up to 5 years. Baseline abdominal imaging in the form of CT or MRI is recommended within 3–6 months of surgery, then CT, MRI, or US should be performed every 3–6 months for at least 3 years, annually up to 5 years, and then as clinically indicated. A baseline chest CT is recommended within 3–6 months following surgery and then CT or CXR should be performed every 3–6 months for at least 3 years, annually up to 5 years, and then as clinically indicated. The panel also suggests that contemporary surveillance protocols such as the UCLA-Integrated Scoring System (UISS) can allow for a more selective use of imaging modalities at appropriate intervals based on individual risk stratification [69].

The most recent version of the AUA guidelines on postoperative surveillance published in 2013 is similar to the 2018 NCCN guidelines. They recommend a routine history and physical exam at an unspecified time, as well as lab work to include BUN, creatinine, and urinalysis. The panel states that additional lab tests such as CBC, calcium, and liver function tests are at the discretion of the physician. In regard to imaging, the panel recommends a baseline abdominal CT or MRI within 3–12 months of surgery for patients with low-risk disease (pT1, N0, Nx) who underwent partial nephrectomy and US, CT, or MRI of the abdomen within 3–12 months of surgery for those who underwent radical nephrectomy [70]. Guidelines further state that additionally imaging may be performed for patients with low-risk disease who underwent radical nephrectomy if the initial baseline study is negative. Recommendations are for US, CT, or MRI of the abdomen to be performed yearly for 3 years in low-risk patients who underwent partial nephrectomy based on their individual risk factors. Additionally, these patients should undergo yearly CXR for a total of 3 years and only as clinically indicated thereafter.

For patients with moderate-/high-risk disease (pT2-4N0 Nx or any stage N+), the panel recommends a baseline abdominal and chest CT/MRI within 3–6 months following surgery and then continued surveillance with US, CXR, CT, or MRI of the abdomen and chest q 6 months for 3 years and then annually until 5 years. Imaging beyond 5 years is at the discretion of the physician [70].

Surveillance for Hereditary RCC

Patients with familial forms of renal cell carcinoma have a high risk of recurrence and often require multiple nephron-sparing surgeries to treat their disease process. Steinbach et al. [71] conducted a multi-institutional study that reviewed 65 patients with von Hippel-Lindau (VHL) disease. Sixteen patients underwent radical nephrectomy and 49 underwent partial nephrectomy with a mean follow-up of 68 months. Fifty-one percent of patients who underwent partial nephrectomy had local recurrence in the ipsilateral kidney at a mean follow-up of 99 months and required further surgical intervention. Given the high risk of recurrence in patients with hereditary forms of RCC and the potential for multiple further surgeries, the relationship between tumor size and risk of developing metastatic disease was evaluated. Duffey et al. [72] reported metastatic disease occurring in 27% of patients who had renal masses >3 cm, whereas no patients with tumors <3 cm were found to have evidence of metastasis. Therefore, active surveillance in this patient population has been recommended without surgical intervention until the largest tumor size approaches 3 cm. In patients who are diagnosed specifically with VHL, screening for other manifestations of their disease process is also warranted. The NIH recommends checking urinary catecholamines every 1–2 years from age 2, yearly ophthalmoscopy starting from birth, contrast-enhanced MR imaging of the brain and spine every 2 years starting at age 11 and then every 3–5 years from age 60, abdominal ultrasound yearly from age 11, and then CT abdomen every 1–2 years after age 20 [73].

Surveillance Following Ablative Therapies for RCC

As an increasing number of elderly patients with multiple medical comorbidities are diagnosed with renal masses, minimally invasive nephron-sparing ablative therapies have become more popular as an alternative to partial nephrectomy. Ablative technologies include radiofrequency ablation (RFA), cryoablation, microwave, high-intensity focused ultrasound, laser interstitial thermotherapy, and radiotherapy [74–77].

The two most established ablative modalities being utilized for the definitive treatment of small renal masses are RFA and cryoablation. Data exist to support good short-term cancer control following ablative therapy, and literature reports promising intermediate-term outcomes [33, 78–82]. Oncological success following ablative therapy is defined as a lack of contrast enhancement and absence of tumor growth on follow-up CT or MRI imaging. Currently, a universal protocol for post-ablation imaging is undefined. Surveillance strategies following ablative therapies for RCC are therefore at the discretion of the individual physician and vary based on the institution or according to individual patient characteristics.

Radiofrequency Ablation

Contrast imaging with CT or MRI is used post-ablation to monitor oncological success of treatment. Initially following therapy, the lesion visualized on CT is slightly larger. Over time, the lesions decrease in size at a rate slower than seen in lesions treated with cryoablation [83]. Unenhanced areas seen on CT correlate with tissue necrosis and often a hyperattenuating halo around the defect can also be seen [84]. On MRI the lesion is also initially larger with some minimal decrease in size over time, when compared to the original tumor size. T2-weighted images reveal the ablation defect to be hypointense, and on T1 it appears hyperintense relative to the renal cortex. There can also be a slight rim of enhancement seen initially on contrast-enhanced T1-weighted imaging; however, this becomes barely present after 3 months. Any persistent enhancement on gadolinium-enhanced MRI after 3 months or increase in tumor size is consistent with residual disease until proven otherwise [84, 85].

Despite promising data reporting favorable oncological outcomes, some studies have questioned the effectiveness of radiofrequency ablation.

Rendon et al. compared pathological outcomes after RFA in 10 patients with a mean tumor size of 2.4 cm. Partial or radical nephrectomy was performed in four patients with five renal masses immediately following intraoperative RFA of the renal mass. Six patients underwent percutaneous RFA and then delayed nephrectomy 7 days later. Pathologic evaluation of the nephrectomy specimens revealed residual viable tumor in four of five specimens in the acute group and three of six specimens in the delayed group [86]. The group from Cleveland Clinic also investigated the presence of residual viable tumor following RFA. They discovered that 46% of patients in their cohort had a positive biopsy 6 months following RFA despite the lack of enhancement demonstrated on CT or MRI [87]. The discrepancy between radiographic imaging and pathologic findings following RFA has made it difficult to determine the success of therapy based on imaging alone. However, accurate interpretation of the pathologic specimen has also been questioned and surmised to be time-dependent (i.e., not all positive pathology following RFA indicates true presence of disease). RFA causes heat fixation of tumor cells – a process that preserves atypical cellular architecture and delays degeneration and can make it difficult to distinguish treatment effect from viable tumor [88]. The time period in which cellular degeneration is complete is debated in the literature and further study is needed to reconcile these inconsistencies. Most investigators agree that biopsies should be done at least 6 months after RFA, when clinically indicated, to minimize false-positive results and avoid misinterpretation. However, there are currently no guidelines to support routine biopsy following RFA when recurrence or residual disease is not suspected radiographically [87].

Cryoablation

Since cryoablation does not uniformly freeze the lesion, most clinicians use a 1 cm margin beyond the tumor edge to ensure the entire tumor reaches the critical temperature for successful treatment [89]. Unlike RFA, histologic evaluation post-cryoablation reveals a fibrotic scar with inflammatory changes, and there is no preservation of tumor or normal renal parenchymal cellular architecture [33].

On CT imaging immediately following cryoablation, the lesion appears as a larger hypoattenuating defect. Over time, lesions decrease in size at a rate faster than that of RFA-treated lesions. Cryoablated tumors appear isointense to hyperintense on T1-weighted MR images and hypointense on T2 images [84]. It is not uncommon to see complete resolution of the ablation defect on follow-up imaging. Rukstalis et al. described 20 of 23 patients as having complete resolution of the treated mass or small residual scar on MRI at 3 months [90]. Gill et al. reported a 75% reduction in defect size over 3 years, with no evidence of scar detected in 38% of patients [91].

As many institutions began to incorporate minimally invasive ablative therapies into their treatment modalities for small renal masses, the accuracy of follow-up imaging to detect disease recurrence and the optimal timing of surveillance came into question. As with radiofrequency ablation, several groups set out to validate the definition of radiographic success following cryoablation. Weight et al. [87] investigated the correlation of radiographic imaging and histopathology following ablative therapy for renal masses. One hundred percent of the cryoablation cohort who had no evidence of enhancement on post-ablation imaging also had negative biopsies. A total of six positive biopsies were obtained from the cryoablation cohort, and all of these came from tumors that demonstrated some degree of enhancement. Peripheral enhancement was observed in 26 lesions at 6-month follow-up and of those only 2 yielded positive biopsies. There were 11 centrally enhancing lesions identified on imaging at 6 months and positive biopsies were found in 4 of those patients. The sensitivity of central enhancement on 6-month follow-up to predict a positive biopsy following cryoablation was 77.8%, with 95% specificity, 63.4% PPV, and 97.7% NPV [87].

A series by Beemster et al. concluded that at 6 months following cryoablation, persistent rim enhancement occurred in 20% of cryolesions

with a size reduction of 38% despite negative histopathological diagnosis. The rim enhancement disappeared on further follow-up imaging, and the authors concluded that persistent rim enhancement is common in the first few months following cryoablation and routine biopsies are not justified [92].

Recommendations for Surveillance Following Radiofrequency Ablation or Cryoablation

Given the variation in follow-up protocols after ablative therapy and the lack of a universal surveillance strategy, Matin et al. conducted a multi-institutional study with the objective of providing evidence-based recommendations [93]. In this retrospective review of data from seven institutions (Table 21.3), recurrence patterns were reviewed for 616 patients who underwent RFA or cryoablation. Residual disease was defined as enhancement seen on the first CT or MRI following ablative therapy. Recurrent disease was any enhancement demonstrated after an initial negative imaging study. Residual or recurrent disease occurred in a total of 63 patients, 55 of 410 (13.4%) undergoing RFA and 8 of 206 (3.9%) undergoing cryoablation. Approximately 70% of residual or recurrent disease was detected within the first 3 months of surveillance imaging, and 92% was detected within the first year of surveillance following ablative therapy. Of the 63 patients who had residual or recurrent disease, 46 underwent salvage ablative therapy and 37 patients had no further evidence of disease on follow-up imaging. Metastasis-free survival for the patients who had recurrent or residual disease following ablative therapy was 97.4% at 2 years. Survival did not differ based on type of approach (laparoscopic vs. percutaneous) or ablative modality utilized (RFA vs. cryoablation) [93].

Based on these findings, a minimum schedule of three–four imaging studies was recommended in the first year following ablative therapy for renal masses. A CT scan or MRI without and with intravenous contrast is recommended in months 1, 3, 6 (optional), and 12.

Table 21.3 Examples of surveillance protocols following ablative therapy of renal masses

	Preferred imaging modality and schedule	Technology used and year started	Access route	Routine biopsy on follow-up
Case Western Reserve University	MRI Week 2, month 3, 6, 9, 12, and then biannually	RFA, 1999	Percutaneous	No
Cleveland Clinic	MRI Day 1, month 1, 3, 6, 12, and then yearly	Cryoablation, 1999; RFA, 2002;	Percutaneous; laparoscopic	Yes; at 6 months
Fox Chase Cancer Center	CT Month 1, 3, 6, 12 and then every 6 months	RFA and cryoablation, 2002	Percutaneous and laparoscopic	No
Massachusetts General Hospital	CT Month 1, 3, 6 and 12 and then every 6–12 months	RFA, 1998	Percutaneous	No
M. D. Anderson Cancer Center	CT Month 1, 3, 6, 12 and then every 6–12 months	RFA, 2001; cryoablation, 2002	Percutaneous and laparoscopic	No
Southwestern Medical Center	CT Week 6, month 6, 12, and then yearly	RFA, 2001	Percutaneous and laparoscopic	No
Wake Forest University	CT Month 2, 8 and then every 6 months	RFA, 2000	Percutaneous	No

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The Future of Surveillance

The Incorporation of Molecular Markers into Surveillance Strategies

In the current era of targeted therapy, research efforts have focused on the molecular biology of renal cell carcinoma and the impact of individual molecular markers on diagnosis, prognostication, and surveillance. Several prognostic algorithms exist based on clinicopathologic factors that predict disease progression and survival with acceptable accuracy [94]. The addition of molecular markers to clinicopathologic factors has been shown, in limited studies, to improve accuracy of these prognostic models.

Many molecular biomarkers have been identified and demonstrated to predict cancer-specific survival as well as disease progression in patients with renal cell carcinoma. To name a few, Nogueria and Kim provide a thorough review of all prognostic molecular markers [95], and Crispen et al. evaluated the markers IMP-3, CXCR3, p53, Survivin, cIAP1, B7-H1, and B7-H4 that specifically predict disease progression following nephrectomy [94]. However, these are not in routine clinical use and are mainly limited to research studies. On the other hand, clinically available markers, such as C-reactive protein, have been shown to have potential in identifying patients at risk of recurrence after definitive surgery [96] and should be further validated in external cohorts. Recently, in 2014, Abel et al. evaluated immunohistochemical staining of a tissue microarray for 216 patients with renal cell carcinoma who underwent partial or radical nephrectomy. The authors reported Ki-67 to be an independent predictor of metastatic disease recurrence [97]. Other studies that have evaluated biomarkers as prognostic factors will be covered in a separate chapter.

Despite the valuable prognostic information that molecular markers confer, they also have several limitations in clinical practice. The majority of biomarkers that have been identified require histopathologic examination of the tumor specimen. In addition, the cost, reproducibility, need for special expertise, commercial availability of the antibodies, and lack of large-scale external validation limit the use of these biomarkers in clinical practice at present. Future research efforts should focus on identifying important molecular markers in the serum or urine that could potentially play a valuable role in identifying early diagnosis of disease recurrence as well as measure response of individuals to systemic therapy [94].

Use of F-18 Fluorodeoxyglucose Positron Emission Tomography in Surveillance and Reducing the Risk of Radiation Exposure

Computed tomography (CT) without and with intravenous contrast is the most common imaging modality being utilized in the postoperative setting for surveillance of disease progression in patients with renal cell carcinoma. With the number of diagnostic CT scans dramatically increasing in the United States over the past several decades, there has been a growing concern over radiation exposure and risk of developing a secondary malignancy [98, 99]. The National Council on Radiation Protection and Measurements (NCRP) reported that radiation exposure associated with medical technology has risen sixfold since the 1980s from 0.5 to 3.0 mSv [100]. In 2007, Brenner et al. estimated that as many as 1.5–2% of cancers could be a result of radiation from CT scans [98]. In response to these worrisome trends, the Food and Drug Administration (FDA) launched an initiative in 2010 to reduce radiation exposure from medical imaging and increase patient awareness about the risks of frequent exposure [100].

As the effort to minimize radiation exposure has been emphasized, and in search of more sensitive imaging modalities, several studies have investigated the use of alternative imaging modalities for surveillance. The use of F-18 fluorodeoxyglucose positron emission tomography (F-18 FDG PET/CT scan) has been investigated in preoperative setting with various results. While some groups have found it to be equally sensitive as CT imaging in detecting malignancy in the pri-

mary tumor, other groups have demonstrated the sensitivity of PET scans to be inferior [101, 102]. Use of PET scan to detect lymph node-positive disease has been shown to be superior to CT imaging, and these results suggest the use of PET scan may be more valuable as an adjunctive role in surveillance [102, 103]. A study by Nakatani et al. recently evaluated the potential clinical value of FDG-PET in the postoperative period to detect disease recurrence. They reviewed 28 scans in 23 patients who underwent a PET scan in addition to CT following nephrectomy for renal cell carcinoma. PET scan identified 17 true positive cases and 2 false positives. Metastatic lesions were correctly identified in all but four cases. Overall sensitivity, specificity, accuracy, PPV, and NPV were 81%, 71%, 79%, 90%, and 56%. This group also demonstrated 5-year survival rates of 46% for patients with positive PET scans vs. 83% for those with negative PET scans [104]. When compared to CT scan alone, the authors concluded that PET scan had little impact on therapeutic decisions.

Consistent with the findings above, Elahmadawy et al. also reported higher specificity for patients undergoing F-18 FDG PET/CT in the surveillance setting after surgery for renal cell carcinoma. They retrospectively reviewed 96 patients who underwent both F-18 FDG PET/CT and traditional contrast CT scan. Both imaging modalities had similar accuracy in diagnosing local recurrence; however higher sensitivity was demonstrated with contrast CT scan than for FDG/PET (100% vs. 96%), and higher specificity was reported with FDG-PET/CT than CT scan (100% vs. 98.6%) [105]. When stratified by location of recurrence, FDG-PET/CT was found to have a 100% sensitivity for nodal metastasis versus contrast CT, which missed three cases. Although the results are promising, further studies are needed to validate these findings and determine the value of this modality in surveillance.

In addition to limiting radiation exposure with PET/CT scan, MRI scans can be alternatively used. However, the utility of MRI for postoperative surveillance has not been well studied or established and is not currently routinely used.

Cost of Surveillance

In the current economic climate, increasing healthcare utilization and cost has been extensively scrutinized. The goal of an ideal surveillance protocol is to accurately detect the presence of disease progression in a timely fashion while minimizing the cost and radiation risk associated with unnecessary over-imaging. Levy et al. reviewed the number and cost of CT scans performed 24 months following nephrectomy in 286 patients. A total of 344 CT scans were completed in the first 2 years following nephrectomy, 95 CT scans for patients with pT1 disease, 102 for patients with pT2 disease, and 147 for those with pT3 disease. Each CT was estimated to cost $1200 for a total cost of $412,800 [14].

Dion et al. performed a cost analysis comparison of two surveillance strategies in a Canadian cohort [106]. The authors compared the follow-up practices performed at their own institution with a projected cost of surveillance had they followed the 2009 Canadian Urological Association (CUA) guidelines. Mean follow-up was 31 months for 75 patients who had undergone nephrectomy for localized renal cell carcinoma. They concluded that total medical costs, in Canadian dollars, were higher for their institutional strategy than the CUA guidelines ($181,861 vs. $135,054). Interestingly, when analyzing cost by tumor stage, the cost to survey patients with pT1 tumors at the authors' institution was more expensive than the calculated cost based on the CUA guidelines, whereas the cost to survey patients with pT3 tumors was more expensive as estimated by the CUA guidelines. This was likely secondary to over-imaging patients with pT1 tumors who may have had little indication for CT scan with low risk of abdominal recurrence [106].

Siddiqui et al. [66] performed cost analysis comparing the Mayo surveillance protocol to a traditional scheme, as well as other published work [14–16, 22] using Medicare part B reimbursement estimates. They reported that the Mayo algorithm was more expensive than stage-based algorithms for patients with clear cell RCC, while it resulted in more savings compared

to traditional protocols and the UCLA protocol in patients with papillary and chromophobe RCC.

In 2016, Lobo et al. compared the cost differences, radiation exposure, and cancer outcomes in the following CUA, AUA, EAU, and NCCN guidelines for patients who underwent partial nephrectomy by using a Monte Carlo simulation model. The results of their model estimated the 5-year cost of surveillance for low-risk patients to be $587(CUA), $1076(AUA), $1705(EAU), and $1768(NCCN), while for high-risk patients, the cost was $903(CUA), $2525(EAU), and $3904(AUA and NCCN) [107]. The EAU and CUA guidelines detected the highest numbers of recurrences in low-risk patients while all guidelines captured more than 92% of recurrences in the high-risk population.

A more recent publication in 2018 further supports a risk-adapted approach to surveillance that adheres to established national guidelines. Dabestani et al. evaluated outcomes of 1889 patients in the multicenter European database RECUR who underwent nephrectomy for localized RCC. Authors reported that patients who underwent more intensive follow-up, defined as greater than twice the recommended imaging by EAU guidelines, did not have an improved overall survival after a recurrence was detected [108, 109].

Conclusion

Patients with renal cell carcinoma are at risk of recurrence, even after definitive surgical therapy, and should be carefully monitored to detect recurrences early enough to allow for meaningful intervention that could lead to prolonged survival. While current guidelines use loose recommendations for follow-up with much discretion left for individual urologists, it is clear that a risk-based approach is needed to provide the optimal postoperative surveillance designed to capture the most recurrences while considering cost. Hopefully, advances in genomic sciences and molecular markers will lead to the development of more robust and individualized follow-up schema for patients in the future.

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Role of Radiation Therapy in Renal Cancer

22

Andrea McKee, Arul Mahadevan, and Timothy Walsh

Introduction

Discussions of the role of radiation therapy (RT) in the treatment of renal cell carcinoma (RCC) frequently begin by paying homage to the dogma that RCC is a radioresistant neoplasm. Indeed, Deschavanne [10] found RCC to be the least radiosensitive cell type of 76 different cell types in a review of studies of human cell radiosensitivity in vitro. However, as time has passed, authors have less vigorously stressed these observations, and words like "relatively" and "variably" have begun to find themselves preceding "radioresistant" in more recent reviews [34, 71]. Over this same period, technological advances have provided the ability to deliver larger doses of radiation with far greater precision. These ablative therapies are referred to as stereotactic radiosurgery (SRS) when delivered in a single fraction and stereotactic ablative radiation (SABR) or stereotactic body radiation therapy (SBRT) when administered over 3–5 fractions. Nonetheless, surgical resection justifiably remains the gold standard in the treatment of primary RCC [2, 29, 37] and the overall role of radiation therapy in the definitive treatment of RCC remains minimal (with several important exceptions) [21]. In this chapter, we will review the literature for radiation in the upfront management of primary RCC and in the treatment of adjuvant, oligometastatic, and palliative settings.

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Preoperative Neoadjuvant Radiation

Irradiation of human RCC before its transplantation into NMRI nu/nu mice yielded significantly lower acceptance rates than those for nonirradiated tumors (1/7 as compared to 13/13) [39]. These findings suggested a potential role for preoperative adjuvant radiation as it conceivably stands to lower the risk of intraoperative seeding of tumor cells [36]. A number of anecdotal accounts also suggested easier resectability as a result of tumor shrinkage and vessel sclerosis following radiation [47, 48]. Correspondingly, several retrospective series conducted prior to modern staging, surgery, and radiation therapy techniques reported positive outcomes following preoperative external beam radiation [13, 46].

Disappointingly, the two prospective randomized trials undertaken as a result of this prior research found little benefit. The Rotterdam Trial [69] examined 141 patients with carcinoma of the kidney randomized either to preoperative radiation (30 Gy in 15 fractions) and nephrectomy or to nephrectomy alone. There was no significant

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difference in 5-year survival between either group regardless of P-category, an older staging system. Nonetheless, interesting differences were observed between P-categories. Those with P-3 disease (tumor infiltrating intrarenal or extrarenal veins or lymph vessels) who were not randomized to preoperative radiation suffered incomplete tumor removal more frequently than other patients in the study. The study's authors reported that survival of patients with residual disease was poor as compared to those who enjoyed complete removal. After initial analysis, the trial was continued at a higher dose of 40 Gy but continued to fail to show survival benefit at the primary endpoint [70]. Increased resectability was not a prespecified endpoint in the trial's design and represents an area potentially deserving future research. Due to the lack of data at present, it has been suggested that patients with unresectable tumors should be considered for preoperative radiation therapy of 45 Gy in an effort to increase tumor resectability [34].

The Swedish Trial [24] examined 88 patients with renal carcinoma who were randomized to either radiation (33 Gy in 15 fractions) followed by nephrectomy or nephrectomy alone. Patients were analyzed according to histological subtype in addition to P-category. No significant difference was found between study arms even upon subgroup analysis, although tumor cells from these patients showed a marked loss of proliferative capacity on tissue culture after preoperative irradiation. The 5-year survival for the preoperative radiation and nephrectomy group as compared to that of nephrectomy alone was 47% and 63%, respectively. Even less encouraging was the discrepancy between study arms among patients with high-grade malignancy, 13% and 36%, respectively.

Currently under investigation is the value of SBRT, discussed elsewhere in the chapter, as neoadjuvant treatment in locally advanced RCC [64]. Figure 22.1 is an example of a patient with a right upper pole renal mass treated with preoperative stereotactic body radiation therapy (on protocol) with pathology showing complete necrosis with surrounding normal renal parenchyma.

Postoperative Adjuvant Radiation

Early retrospective data from the 1950s and 1960s reported improved survival at both 5 and 10 years following postoperative external beam radiation (EBRT) [5, 13, 46]. In a larger retrospective cohort, Rafla et al. found significantly improved survival and local control among those receiving postoperative radiation [44]. However, no information regarding dose or patient selection was offered by the investigators. Several years later, a prospective series failed to demonstrate survival benefit or improved secondary endpoints such as greater local control following postoperative adjuvant radiation [12]. Most discouraging was the Copenhagen Renal Cancer Study [27], a prospective trial where patients with stage II or III renal cell carcinoma were randomized to nephrectomy alone or nephrectomy followed by postoperative radiation (50 Gy in 20 fractions to the kidney bed, regional ipsi- and contralateral lymph nodes). The 5-year survival for those who received postoperative radiation was 38% as compared to the control group whose 5-year survival was 63%. The decision was made to close the study to further patient accrual in light of the number of complications associated with radiation therapy. Forty-four percent of patients experienced significant complications involving radiation-related toxicity affecting the stomach, duodenum, or liver. Most disturbingly, toxicity from radiation was deemed responsible for 19% of the deaths in the study.

A number of questions regarding both the safety and efficacy of postoperative radiation for renal cell carcinoma remained unanswered by these trials. In the Copenhagen trial, for instance, both the control and postoperative radiation groups exhibited very low local recurrence (0% and 1%, respectively). However, in a Memorial Sloan-Kettering series of 172 surgically treated patients, the actuarial local failure was 5% [43]. This fact suggests that the selection of Copenhagen Study participants (ideally those who would stand to benefit from radiation therapy) was far less than ideal. Additionally, 2.5 Gy per fraction represents an aggressive dose for a nonconformal radiation plan and the resulting toxicity superimposed upon

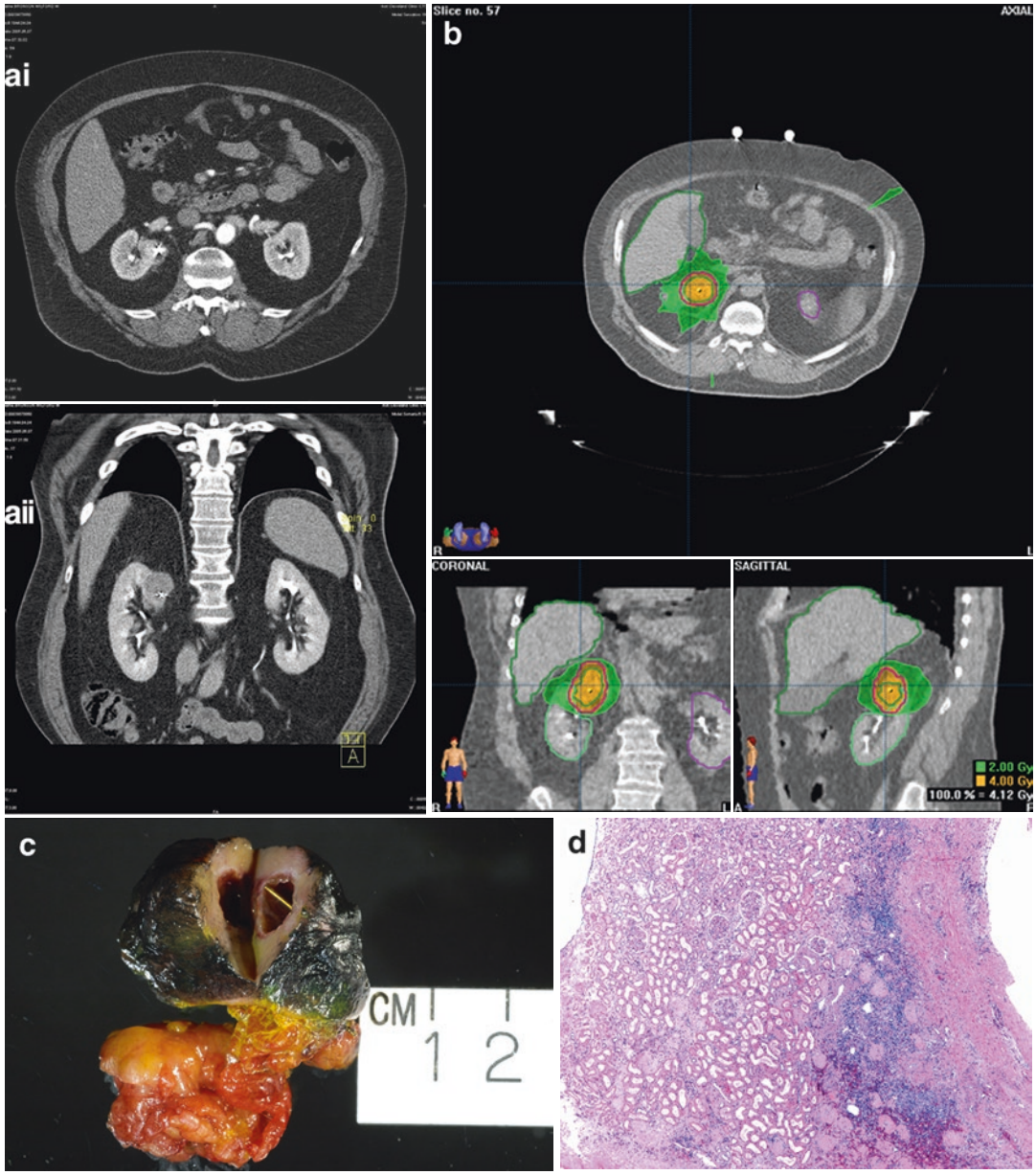

Fig. 22.1 (**ai**) A kidney lesion (clear cell type) with fiducial for SBRT – axial and (**aii**) coronal. (**b**) SBRT isodose plan (600 cGy×4 fractions in 2 days – twice daily), (**c**) Laparoscopic partial nephrectomy specimen with fiducial. (**d**) Pathology showing complete necrosis at the site of tumor (*right*) with normal surrounding renal parenchyma (*left*)

a study in which participants from the outset had an extremely low risk of local recurrence left very little room to find benefit. In response to these concerns, there have been a number of more recent retrospective trials reexamining the administration of postoperative radiation in patients at greater risk for local recurrence [18, 25, 31, 58]. These studies all demonstrated improved local control with adjuvant radiation but failed to produce any evidence of benefit to overall survival. A 2010 meta-analysis from Tunio [60] agrees that postoperative radiation significantly reduces

locoregional failure but has no effect on overall survival or disease-free survival and concludes that due to the frequent poor patient selection and heterogeneous and outdated radiation therapy techniques, there is a need for new trials to evaluate postoperative adjuvant therapy using current conformal and intensity-modulated radiation techniques.

Intraoperative Radiation

Clinicians from the Mayo Clinic, University Clinic of Navarra at Pamplona, the University of Heidelberg, and University of California, San Francisco have investigated aggressive approaches utilizing adjuvant intraoperative electron irradiation (IOERT).

At the Mayo Clinic, 49 patients between 1983 and 1994 received IOERT as a component of therapy for locally advanced unresectable genitourinary (GU) malignancies [15, 28]. The site of primary origin was the kidney in the majority [31] of these cases. Maximum resection and IOERT was either preceded or followed by EBRT (median dose 49.9 Gy; range 5–56 Gy) in 42 of the 49 patients. Electrons with energy ranging from 6 to 18 MeV were used to deliver a median dose of 15 Gy (range 7.5–30 Gy) intraoperatively. Ten patients received chemotherapy either concurrently with EBRT or following all other treatment. The 15 surviving patients were followed for a median of 3 years, while all other participants were followed until death. Survival among RCC patients was significantly better than that of the patients diagnosed with malignancies of other GU sites (5-year survival – 37% vs. 16%). Two patients (4%) suffered grade 3 toxicity associated with IOERT.

In Pamplona, at the University Clinic of Navarra, 11 patients with stage III (5 patients), IV (3 patients), or lumbar fossa recurrence (3 patients) of renal cancer were treated with IOERT and surgical resection [28]. Histological confirmation of clear cell adenocarcinoma was available in 10 of the 11 cases. Electrons with energy ranging from 9 to 20 MeV were used to deliver a dose ranging from 15 to 20 Gy. Seven patients received additional EBRT ranging from 30 to 45 Gy. With a median follow-up period of 8 months, upon the case series' initial publication, 3 patients were reported with a distant relapse. One of the 3 also suffered local recurrence at 7 months (no EBRT had been administered in this case). Further follow-up analysis revealed long-term survivors without evidence of recurrent disease (three patients with greater than 3 years follow-up). The investigators detected no early or late radiation-associated toxicity.

A multicenter study conducted by Paly and colleagues from 1985 to 2010 reported results with use of IOERT in patients with locally advanced RCC (28% of cohort) or local recurrence in the renal fossa (72% of cohort) [40]. Negative margins, small tumor size, and absence of sarcomatous features were found to be favorable prognostic variables in this high-risk group of patients who experienced a median survival time of 3.5 years.

At the University of Heidelberg, another series of 11 patients with RCC (locally advanced primary – 3, locally recurrent – 8) received treatment consisting of surgical resection, IOERT (15–20 Gy with 6–10 MeV), and postoperative EBRT (40 Gy in 20 fractions). After a mean follow-up of 24 months, distant metastases occurred in five patients. Local control for the entire group was 100%. Overall and disease-free survival at 4 years was 47% and 34%, respectively. No late adverse effects associated with IOERT were detected [28].

At the University of California, San Francisco, 14 patients with local recurrence of RCC underwent subsequent surgical resection with 10 of the 14 also receiving IOERT [28, 32]. Survival was 40% at 2 years and 30% at 5 years from surgery. Investigators found no difference in survival due to IOERT.

In a 2011 joint statement, the studies' authors concluded, "The addition of IOERT to surgery and EBRT is associated with a high rate of local control and acceptable toxicity. The best candidates are untreated patients with large tumor volume with risk of positive margins after radical nephrectomy and patients with local recurrences. Distant relapse is common, especially in

patients with recurrent disease. Accordingly, future treatment strategies should evaluate a systemic component of treatment (new targeted therapies)" [28].

Stereotactic Body Radiotherapy (SBRT) as Definitive Treatment

Renal cancer cells have been historically classified as radioresistant to fractionated conventional radiation therapy, and molecular mechanisms to explain this were recently published [22]. However, several recent clinical reports have observed excellent tumor control rates with high-dose stereotactic body radiation therapy (SBRT – five or fewer fractions) or radiosurgery (SRS – single fraction) [54]. Molecular and biological mechanisms to explain these excellent results have recently been proposed. Studies by Fuks [16] have indicated that single high-dose radiation exposure (greater than 8 Gy) engages a microvascular apoptotic component in tumor response by inducing a vascular collapse within the endothelium. This pathway does not appear to be engaged in fractionated regimens because the individual doses are too low to invoke this apoptotic stimulus on endothelial cells.

Investigators at Brown University agreed with Deschavanne [10] that of the various classes of tumor cells exposed to conventional EBRT doses, RCC could be categorized to fall in the more radioresistant group along with primary brain tumors, breast, prostate, ovarian, and head and neck cancers [30]. However, they also noted that there existed no correlation between this original taxonomy and the degree of radiosensitivity among different histological classes of neoplasms at single high doses (SRS). Adding some encouragement for stereotactic treatment, Walsh [72] reported quite recently that nude mice transfected with A498 human renal cell carcinoma cells exhibited a sustained decrease in tumor volume following high-dose-per-fraction radiation (3 fractions for total dose of 48 Gy).

In the clinic, the ability to deliver high-dose radiation therapy in a single (SRS) or multifraction (SBRT) regimen relies on robust tumor and normal tissue localization, patient immobilization, multibeam intensity-modulated treatment planning, and image guidance. These modifications result in highly conformal, steep gradient dose delivery to the target with maximal sparing of nearby normal tissue organs at risk (OARs).

The radiation techniques employed in the delivery of SRS and SBRT have revolutionized the field of radiation oncology. Not surprisingly, the use of these modalities in the management of RCC has risen dramatically over the past decade. Hague et al. queried the National Cancer Database for cT1a/bN0Mo RCC patients receiving definitive treatment in the years 2004–2013 [21]. Of all patients in the database 57,924 (41.8%) underwent partial necphrectomy and 67,168 (48.5%) radical nephrectomy, while only 308 (.2%) received EBRT including SBRT. The proportion of RT-treated patients receiving SBRT increased from 2.5% in 2004 to 95.4% in 2013. Similarly, the use of ablative radiation therapy in the management of metastasis-directed treatment for RCC has steadily increased over that time frame [42].

In an attempt to examine the efficacy of definitive radiation treatment, Beitler [4] reported a series of nine patients with nonmetastatic renal cell carcinoma who refused definitive surgery. Patients received 40 Gy in 5 fractions using conformal EBRT. With a median follow-up of 27 months, four of the nine patients were alive. The survivors' minimum follow-up was 48 months. In 2005, Wersall [74] reported on 58 patients with renal cell carcinoma who received stereotactic radiotherapy. Fifty of the patients received treatment for metastatic disease. However, eight received treatment for inoperable primary lesions or inoperable recurrent local disease following nephrectomy. High-dose-per-fraction SBRT (40 Gy in 5 fractions) was delivered with patients placed in a stereotactic body frame. Seven of the eight patients achieved local control. Six of eight were alive at publication. Median survival time was 58+ months. Local control rate was greater than 90% for the entire cohort of 58 patients.

Since then, there have been numerous retrospective and a few prospective trials evaluating

the efficacy of ablative radiotherapy in primary RCC, most with small numbers of patients, utilizing a variety of different fractionation and dosing schedules. A systematic review of ten studies (seven retrospective and three prospective) compiled 126 patients with inoperable RCC treated with SBRT was shed in 2012 [50]. This review demonstrated excellent local control of 92.9% at a median follow-up of 2–3 years. Toxicity was acceptable at 3.8% grade 3 or greater.

Additional prospective series including a prospective trial of 37 inoperable patients published in 2017 by Siva et al. continue to demonstrate greater than 90% local control with limited grade 3 or greater toxicity of 3% [52, 55]. This group also noted a dose response to GFR decline. For every 10 Gy of physical dose delivered, an exponential decline in affected kidney GFR was observed at 1-year follow-up. A 39% decrease in GFR when treatment was delivered in one fraction (SRS) of 26 Gy was observed and 25% GFR loss for those receiving 42 Gy over three fractions. No patient required dialysis at 1-year follow-up [52].

In the absence of randomized controlled clinical trials or extensive clinical evidence, a consensus statement from eight international centers with expertise in SBRT for RCC has summarized current treatment recommendations [51]. Before SBRT for primary RCC can be considered a standard of care multicenter prospective clinical trials are necessary and currently underway in several countries [61, 62].

Palliative Radiotherapy

Brain metastases are diagnosed in approximately 10% of patients with metastatic renal cell carcinoma [76, 77]. In a survey of patients treated at Massachusetts General Hospital for CNS metastases from renal cell carcinoma, Halperin [20] reported a disappointing response to conventionally fractionated radiation (30% response). At M.D. Anderson Cancer Center, the median survival time for 119 patients receiving whole brain radiation therapy for renal carcinoma metastases was 4.4 months following diagnosis [77]. Similarly, poor results over approximately the same time period (1976–1986) were reported at Memorial Sloan-Kettering [3]. More encouraging results have been reported following the advent of stereotactic techniques. Median survival with stereotactic treatment in a series of 29 patients from 1991 to 1998 at the Cleveland Clinic was 10 months [19]. Only 9% suffered CNS recurrence. The addition of whole brain radiotherapy yielded no improvement in local control. However, patients presenting with multiple CNS lesions are twice as likely to develop distant brain failure and merit consideration for whole brain and stereotactic radiotherapy combined. In a similar series reported by Amendola [1], local control following radiosurgical treatments was 98.5% with 18 of 21 patients dying of nonneurologic causes. A number of similar studies confirming efficacy and providing reassurance in regard to side effects emerged shortly thereafter [23, 41]. In 2003, Sheehan [49] reported an even more impressive median survival length of 15 months in a retrospective review of 69 patients following stereotactic radiosurgery. Local control was observed in 96% of patients. Recent studies suggest that radiosurgery has significantly reshaped the course of the illness. Early significant tumor response from high-dose stereotactic radiosurgery predicted improved survival for patients [26]. The patients were classified into the good response group when the sum of the volume of the brain metastases decreased to less than 75% of the original volume at the 1-month follow-up MRI. The good response group survived significantly longer than the poor response group (median survival times of 18 months and 9 months, respectively; $p = 0.025$). Staehler [57] recently reported that in a series of 51 patients, a treatment combination consisting of sunitinib and hypofractionated high-dose radiotherapy resulted in not a single death attributable to cerebral metastasis.

Osseous metastases are not an uncommon occurrence in patients with renal cancer. The most common site of these metastases is the spine. In fact, 30% of patients with renal cell carcinoma will ultimately develop spinal metastases [17]. In 1983, Halperin [20] reported that

radiation produced good pain control (77% response) for patients with metastatic bone pain. Time-dose-fractionation (TDF) equivalent ranged from 45 to 85. No correlation between response and TDF was observed. A larger series following 86 patients with painful osseous metastases found a 65% response rate for TDF ≥ 70 in comparison to 25% for TDF < 70, leading the authors to recommend that the lesions be treated to higher doses to obtain maximum response rates [38]. As we have mentioned before, stereotactic radiation offers the capability of delivering higher doses with a great amount of precision, the utility of which is particularly relevant in the context of treating bony lesions adjacent to the spinal cord. Gerszten [17] found spinal radiosurgery to relieve pain in 89% of patients treated for RCC spinal metastases. Similarly, favorable results confirming the safety and efficacy of stereotactic treatment of spinal metastases have been reported by a number of other authors [7, 78]. A reasonably large retrospective review of 105 extracranial metastatic lesions from renal cell carcinoma treated with either a single-dose, image-guided, intensity-modulated radiosurgery of 18–24 Gy or SBRT (less than 5 fractions) dose of 20–30 Gy reported local progression-free survival of 80% for high single dose (24 Gy) versus 21% and 17% for the low single dose (<24 Gy) or hypofractionated regimens [79]. Multivariate analysis revealed that 24 Gy vs. a lower dose (p = 0.009) and a single dose vs. hypofractionation (p = 0.008) were significant predictors of improved local progression-free survival.

A 2017 systematic review of the radiosurgery literature for spine disease from metastatic RCC compiled the results of nine published series [56]. The studies analyzed revealed improvement in pain for 41–95% of patients with excellent local control of 71–85.7% at 1 year. Vertebral body compression fractures (VCF) were seen in 16–27.5% with single fraction therapy increasing the VCF risk [56].

There are few reports in the literature on the use of SBRT as an alternative to cytoreductive nephrectomy. A prospective phase 1 dose-escalation trial of SABR as an alternative to cytoreductive nephrectomy for inoperable patients reported acceptable toxicity, renal function preservation, and stable quality of life in 12 patients with metastatic RCC [9]. Three successive dose cohorts were assessed: 25 Gy/3 fractions, 30 Gy/3 fractions, and 35 Gy/3 fractions. No dose-limiting toxicities were found at the 35 Gy dose level. Median primary tumor size reduction was 17.3% at a median follow-up of 5.3 months. All patients progressed systemically and median overall survival was 6.7 months. The authors concluded 35 Gy in 5 fractions yielded acceptable results in nonoperable metastatic RCC with further prospective investigation warranted [9].

It seems reasonable to believe that the palliative role of radiation therapy, especially stereotactic and hypofractionated RT, will continue to develop in the coming years. Figures 22.2 and 22.3 are representative examples of current radiation therapy techniques including stereotactic body radiation therapy for recurrent renal fossa mass (Fig. 22.2) and spinal radiosurgery for a spinal metastasis (Fig. 22.3).

Stereotactic Radiosurgery and Stereotactic Body Radiotherapy for Oligometastatic Disease

Oligometastatic disease is variably defined in the literature as having up to three or five metastases. In patients with RCC, metastases-directed therapy including surgical metastectomy, thermal ablation, and ablative radiation represent potentially curative options for individuals with oligometastatic RCC [42]. In patients receiving systemic therapy, the emergence of resistant clones, noted as a few areas of progressive metastatic deposits, is termed oligoprogression. Based on good initial reported outcomes, SBRT has been delivered to patients with oligometastatic and oligoprogressive disease with curative intent [45, 53].

The University of Texas Southwestern reported excellent local control with limited toxicity in its extracranial series utilizing SABR

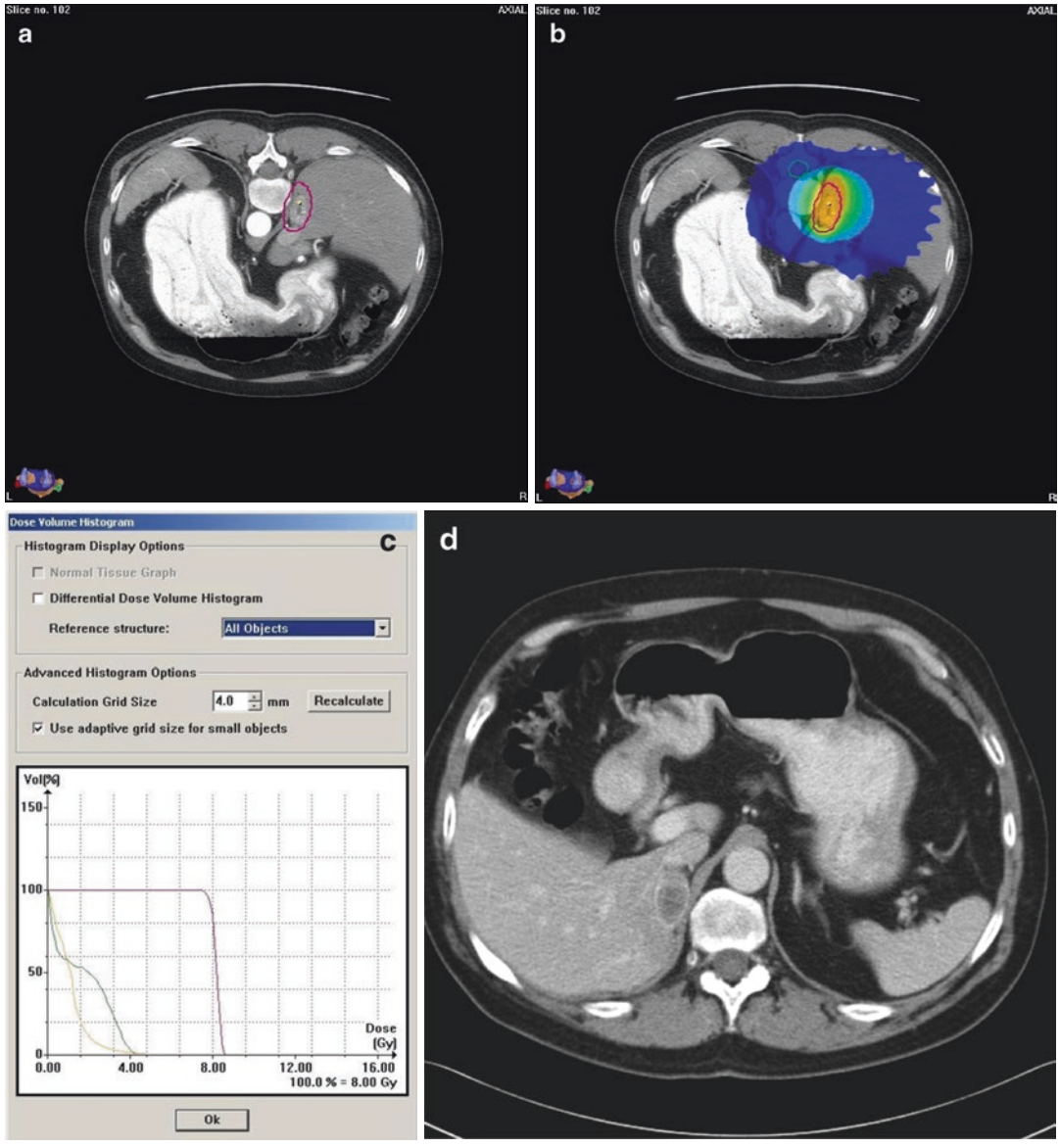

Fig. 22.2 (**a**) A 55-year-old male with history RCC s/p radical nephrectomy in 2002, s/p right lower and middle lobectomy for 1.5 cm RCC lung oligometastasis in 2004, presented in 2006 with local recurrence in right nephrectomy bed. Target delineated with 4D CT scan and treatment planning allowing for respiratory motion. (**b**) Color dose distribution. Prescription dose in *orange*, 30% dose in *dark blue*. (**c**) Dose-volume histogram (DVH) demonstrates nephrectomy bed mass (*purple*) received 32 Gy (8 Gy×4) bowel (*green*) and spinal cord (*yellow*) protected. (**d**) Posttreatment CT with increased conspicuity of treated lesion due to central hypoattenuation seen at 4 months post treatment. The patient is now 6 years post SBRT and NED

to treat 175 lesions in the spine (24%) and non-spine (76%) locations [73]. In this series, 75 of the 175 targeted lesions were treated with curative intent.

Similarly, Meyer et al. recently published a retrospective compilation of 252 tumors treated with curative intent SABR in 188 patients from 6 French referral centers [33]. Among patients treated for oligometastatic disease, the median 2-year PFS and OS were 8.6 and 23 months, respectively. For those with oligoprogressive dis-

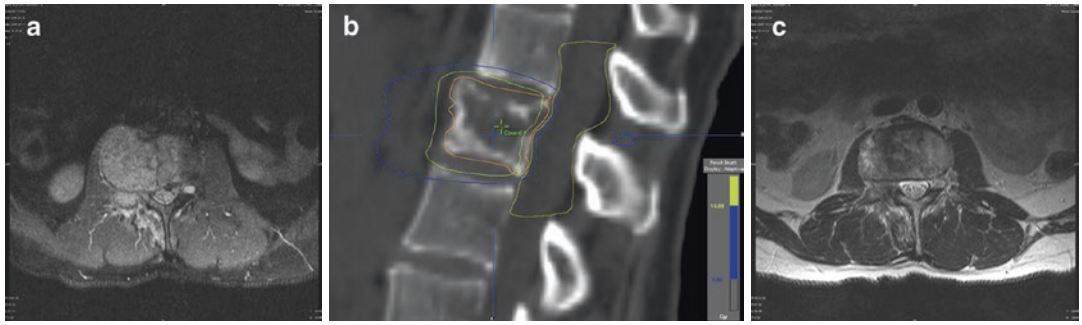

Fig. 22.3 (**a**) A 61-year-old male with severe back pain. MRI revealed spinal metastasis with paraspinal mass and mild thecal compression – biopsy metastatic RCC. (**b**) Isodose plan sagittal view. (**c**) Six months post SRS – regression of paraspinal mass and thecal compression. Patient pain-free at this site

ease, the 2-year median PFS and OS were 7.6 and 33.9 months, respectively.

High-dose ablative RT has been combined with TKI inhibitors by several investigators to treat metastatic brain and spine disease sites with no apparent increase in risk of adverse effects from RT or targeted antiangiogenic agents [35, 57].

In 2017, Dewolf et al. reported the first phase I dose escalation trial combining high-dose RT to non-CNS sites with pazopanib, a selective multi-targeted receptor tyrosine kinase inhibitor that blocks tumor growth and inhibits angiogenesis [75]. Three dose levels were evaluated (24 Gy/3 fractions, 30 Gy/3 fractions, and 36 Gy/3 fractions) in 13 patients with one patient experiencing a dose-limiting grade 4 toxicity of hypoglycemia in the 36 Gy/3 fraction dose level. The investigators concluded that SBRT in combination with pazopanib is well tolerated with good local control and response rates outside the radiation field.

Others are evaluating the efficacy of combined SBRT and anti-PD-1 antibody pembrolizumab to heighten the host immune system [63, 67] (see section "Immunoradiotherapy") through the abscopal effect. The abscopal effect refers to a rare phenomenon of tumor regression in lesions distant from the targeted site of radiotherapy, presumably through RT-induced activation of the host immune system. High-dose RT has been shown to preferentially enhance tumor-antigen presentation and later the tumor microenvironment when compared to conventionally fractionated RT [14]. Prospective trials are currently underway to better understand the outcomes of combination targeted or immune therapies with SBRT in patients with RCC [63, 65–68].

Immunoradiotherapy

Iodine-131 labeled tumor preferential monoclonal antibodies were shown to cause renal cell carcinoma xenograft regression and growth retardation in a nude mouse model [8]. The mice targeted with non-Iodine-131 labeled tumor preferential monoclonal antibodies failed to demonstrate variance from the control. Encouraging from a clinical standpoint, sequential computerized scintigraphy demonstrated that the radioisotopes were successfully targeted with high specificity for tumor tissue.

Radiation has also been postulated to enhance the antitumor response mediated by IL-2 in a murine metastatic renal adenocarcinoma model (Renca) [6]. Pulmonary metastases were induced by intravenous injection of Renca in Balb/c mice. Five days thereafter, a sublethal radiation dose (300 rads) was administered either to the whole body or left lung alone. IL-2 (5000 Cetus units) was given intraperitoneally twice daily for 5 subsequent days. The mice were either sacrificed to assess tumor burden or followed for long-term survival. Pretreatment with irradiation significantly reduced pulmonary metastases and increased survival. Local irradiation of one lung was found to be equally as effective as whole

body irradiation. Metastases in the contralateral (nonirradiated) lung were found to be reduced following local irradiation, suggesting a systemic mechanism to increased antitumor response. The study's authors surmised this systemic mechanism was synergistic with IL-2 therapy. In a follow-up study at the same institution, investigators reported that immunohistochemistry demonstrated a macrophage influx following irradiation [11]. Meanwhile, IL-2 therapy induced T-cell infiltration into tumor nodules. The investigators concluded that macrophages, mobilized by radiation-induced tissue injury, phagocytosed apoptotic tumor cells and presented tumor antigens for a systemic immune response mediated by IL-2.

In a more recent study, cells of the human renal cancer cell line R11 were transfected by interferon-alpha gene and evaluated for radiation responses in vitro by clonogenic assays [59]. Investigators found that in addition to slowing cellular growth, transfection with interferon-alpha gene increased radiosensitivity. Similar results have been reported for other cytokines, though not specifically in the context of renal cell carcinoma.

As previously discussed, clinical trials are underway to assess the role of a combination of immune modulators and radiation therapy in patients with RCC, where the immune system seems to play an important antitumor role. The University of Texas Southwestern is currently investigating the role of combination SBRT with IL-2 therapy in patients with metastatic RCC [65].

Conclusion

We have reached a far more expansive and nuanced understanding of the role of radiation therapy in the treatment of renal cell carcinoma over the course of the past decades. As radiotherapy evolves and as surgical, immunologic, and chemotherapeutic interventions evolve, this role will continue to be redefined. For the time being, the best established role for radiation therapy in RCC is undoubtedly palliative. If judiciously employed in this context, it is a safe, noninvasive, and efficacious treatment that bolsters the quality of life of patients afflicted with RCC. Further research is necessary to better understand the role radiation may play as an adjuvant therapy, a potential immune modulator, in the management of oligometastatic disease, and as a standard of care in the management of primary RCC.

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23 Systemic Therapies for the Treatment of Renal Cell Carcinoma

Eddy J. Chen

Introduction

At the time of this writing, there have been tectonic shifts in the paradigms and algorithms of renal cell cancer (RCC) treatment, and they continue to evolve as new advances in research are occurring faster in parallel to the technical advances in data management, artificial intelligence, and the dissemination of this new information. This environment will undoubtedly lead to discoveries of novel mechanisms, which in turn will deliver more candidate therapeutics that may require further trials combining older drugs with newer ones. As proof, recent successes in the immunotherapy arena has encouraged thinking on how to combine immunotherapies with the well-established anti-angiogenesis tyrosine kinase inhibitors (TKIs). There are over a dozen trials testing various permutations between these two classes of therapeutic agents [1]. A cynic might observe that this is leading to confusion in treatment planning as few validated biomarkers exist to direct care, but the optimist might point out that this is creating more options for clinicians and their patients. As such, this is the current challenge and promise of precision medicine. This chapter is an effort to highlight the recent treatment regimens and be a practical review for clinicians.

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Background

While not as common as breast, prostate, lung or colorectal cancers, there are still a notable number of new RCC cases per year, with an estimated 64,000 new diagnoses in the USA in 2017 [2]. Those with metastatic disease are not curable, with median survival usually less than 2 years [3]. However, with advances in treatments especially in immunotherapy, as will be discussed, there is optimism that for some, the disease could be managed as a chronic condition and survival rates may increase over time.

Renal cell carcinoma is a heterogeneous group of tumors, classified into clear cell (~75%), papillary (~10%), chromophobe (~5%), oncocytic (~3%), collecting duct of Bellini (1%), and other/unclassified (~6%) [4]. Most therapeutic clinical trials have focused on the clear cell phenotype given its prevalence, and while there have been some smaller trials studying non-clear cell types, some of their treatments are extrapolated from the clear cell data as will be discussed later.

A key mechanism in the development of RCCs involves the von Hippel-Lindau tumor suppressor protein and its ability to ubiquitinate proteins to target them for degradation. Dysfunction of VHL leads to stability and accumulation of hypoxia-inducible factors, subsequently promoting angio-

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genesis and cell proliferation [5]. This discovery has led to the development of effective therapies targeting angiogenesis including mediators such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These include tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (e.g., bevacizumab) that interfere with intracellular signaling and subsequent tumor growth.

Another important pathway involved in RCC proliferation is the mTOR (mammalian target of rapamycin) pathway. mTOR is a serine-threonine protein kinase within the family of phosphatidylinositol-3 kinase (PI3K)–related kinases. Its importance in renal cancer was shown when mutations were discovered in PI3K pathway proteins upstream of mTOR and in mTOR itself [6]. When mTOR inhibitors were first approved for RCC treatment, they were an important option for patient as therapies were limited to older cytokine therapies and the first-generation VEGF receptor (VEGF-R) TKIs. However, in 2018 with the advances in immunotherapy, as will be discussed, mTOR inhibitors have been relegated to later lines of therapy.

Major advances in immunotherapy and the understanding of immuno-oncology have also translated into promising therapies for RCC. While older therapies such as high-dose IL-2 and interferon-alpha (IFN-a) [7] remain as options, the extreme toxicities they possess that can resemble sepsis limit their use to the fittest cardiopulmonary patients who can endure these side effects. When compared to the newer and relatively more tolerable agents, older cytokine therapies are becoming obsolete. Understandably, the enthusiasm of using IL-2 despite its toxicities stemmed from the observations of a low but notable rate (~10%) of durable, i.e., long term, responses in some patients [7, 8]. Almost two decades later, elucidation of the checkpoint pathways in T-cell regulation has exploited the interactions of receptors involved in the PD-1 (programmed cell death 1) and CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) pathways [9]. These therapeutics used in combination or as monotherapy have shown promising results, with also a notable subset of patients who sustain durable responses, as was seen with IL-2 therapy [10]. Because of their significantly improved tolerability and efficacy, nivolumab and ipilimumab have become replacements for older cytokine therapies in the immunologics drug class in contemporary treatment.

Drug Profiles

The following is a detailed look into the major therapeutic agents in the contemporary treatment of RCC.

Immunotherapy

Ipilimumab (Yervoy)

Ipilimumab is dosed intravenously at 1 mg/kg when used in the combination regimen with nivolumab (see nivolumab information). Side effects are generally uncommon, but when they do occur, they are autoimmune in nature and generally need steroids for first-line treatment. Guidelines exist to help determine use and dosage of steroids [11]. Colitis/diarrhea, hepatitis, rash, fatigue, and myalgias are the more frequent adverse events. Rare side effects of hypophysitis, hypothyroidism, and cytopenias can also be seen [12].

Nivolumab (Opdivo)

Nivolumab is dosed intravenously 240 mg every 2 weeks or 480 mg every 4 weeks when used as monotherapy. In combination with ipilimumab, an induction period is initiated by giving nivolumab at 3 mg/kg followed by ipilimumab 1 mg/kg on the same day, once every 3 weeks (21-day cycle) for four doses, followed by maintenance dosing of nivolumab at 240 mg every 2 weeks or 480 mg every 4 weeks. Side effects are generally uncommon, but when they do occur, they are autoimmune in nature and need steroids for treatment. There appear to be more side effects with multiagent immunotherapy. Guidelines exist to help determine use and dosage of steroids [11]. Rash, hepatitis, pneumonitis, and colitis can occur. More rarely, hypophysitis, adrenal insufficiency, nephritis, and type 1 diabetes is seen [13].

VEGF-Receptor Inhibitor Therapies

Axitinib (Inlyta)

Axitinib is dosed orally at 5 mg twice a day, with or without food. It is indicated for treatment after the failure of one prior systemic therapy (AXIS) [14]. It can be used as first-line therapy [15], though other TKIs rather than axitinib are suggested for first-line use in some guidelines such as those by the National Comprehensive Cancer Network.

It can be dose reduced to 3 mg twice a day, and later 2 mg twice a day if needed. Interestingly, there are dose-intensifying modifications as it is thought that higher drug exposure could be more efficacious. If tolerated without evidence of side effects after 2 weeks, doses can be increased from 5 to 7 mg twice a day, and further to 10 mg twice a day after another 2 weeks. Common side effects include diarrhea, hypertension, fatigue, nausea, anorexia, and vomiting. Serious side effects include cardiac dysfunction, hemorrhage, arterial or venous thrombosis, gastrointestinal perforations, leukoencephalopathy, thyroid dysfunction, hepatotoxicity, and proteinuria. Wound healing complications can occur, and holding drug at least 24 hours before scheduled surgery is advised [16, 17].

Bevacizumab (Avastin)

Bevacizumab is a monoclonal antibody, unlike the other TKIs in this class, and is dosed intravenously at 10 mg/kg every 2 weeks, used with interferon alpha per the indication that received FDA approval [18]. Monotherapy is more tolerable clinically and shown to have activity [19]. Common side effects include hypertension, proteinuria, and infusion-related reactions. Serious side effects include thrombosis, viscus perforation or fistulae, encephalopathy, and hemorrhage. Wound healing complications can occur. It is advised that bevacizumab be held at least 28 days prior to elective surgery, and not restarted for at least 28 days after surgery, and until the wound is fully healed [20, 21].

Cabozantinib (Cabometyx)

Cabozantinib is dosed orally at 60 mg daily. Patients should not eat for at least 2 hours before and 1 hour after taking cabozantinib. It can be used in the first-line setting in metastatic disease for poor- and intermediate-risk disease (CABOSUN) [22], or in subsequent lines (METEOR) [23]. It can be dose reduced by 20 mg for toxicities. Common side effects include diarrhea, nausea, fatigue, hypertension, and palmar-plantar erythrodysesthesia. Serious side effects include gastrointestinal perforation and fistulas, hemorrhage, pulmonary embolism, and QT prolongation. Wound healing complications can occur, and holding drug at least 4 weeks before scheduled surgery is advised [24, 25].

Lenvatinib (Lenvima)

Lenvatinib is dosed orally at 18 mg daily, with everolimus at 5 mg daily, with or without food. It is used in the metastatic setting [26] and has a category 1 recommendation for subsequent-line therapy in the kidney cancer NCCN guidelines for 2018. It can be dose reduced to 14, 10 or 8 mg for adverse events. Common side effects include hypertension, proteinuria, diarrhea, hypocalcemia, fatigue, nausea, and arthralgia. Serious side effects include cardiac dysfunction, thrombosis, hepatotoxicity, renal failure, fistula formation and GI perforation, prolonged QT syndrome, encephalopathy, and hemorrhage. Wound healing complications can occur, and holding drug for at least 6 days prior to scheduled surgery is advised [27, 28].

Pazopanib (Votrient)

Pazopanib is dosed orally at 800 mg daily. Patients should not eat for at least 1 hour before or 2 hours after a meal. It can be used in the first-line (COMPARZ; non-inferiority trial) [29] or second-line (VEG105192) [30] settings in metastatic disease. It can be dose reduced initially by 400 mg for toxicities, but then increased or decreased by 200 mg as tolerable. Common side effects include diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting. Serious side effects include hepatotox-

icity, QT prolongation, cardiac dysfunction, hemorrhage, arterial or venous thrombosis, thrombotic microangiopathy, gastrointestinal perforations, interstitial lung disease, leukoencephalopathy, hypothyroidism, and proteinuria. Wound healing complications can occur, and holding drug at least 7 days before scheduled surgery is advised [31, 32].

Sorafenib (Nexavar)

Sorafenib is dosed orally at 400 mg twice a day, without food (at least 1 hour before or 2 hours after a meal). It can be used in the metastatic setting [33], usually not as first-line treatment in the current era of immunotherapy and recent comparison trials with other kinase inhibitors. It can be dose reduced to 400 mg daily or 400 mg every other day.

Common side effects include hypertension, rash and hand-foot syndrome, fatigue, diarrhea, nausea, and hypophosphatemia. Serious side effects include cardiac ischemia, hemorrhage/viscus perforation, prolonged QT syndrome, and hepatotoxicity. Wound healing complications can occur, and holding drug before scheduled surgery is advised (no guidance from package insert) [34, 35].

Sunitinib (Sutent)

Sunitinib is dosed orally at 50 mg daily, with or without food, on a schedule of 4 weeks on and 2 weeks off, though other schedules have been evaluated for improved tolerance, such as a 2-week-on/1-week-off schedule [36]. It can be used in the first-line or second-line setting [37–39]. It can be used in the adjuvant setting after nephrectomy for high-risk disease [40]. It can be dose reduced initially by 12.5 mg for toxicities. Common side effects include diarrhea, rash and hand-foot syndrome, fatigue, altered taste, hypertension, and myalgias. Serious side effects include hepatotoxicity, cardiac dysfunction, prolonged QT syndrome, hemorrhage/viscus perforation, tumor lysis in high tumor burden patients, thyroid dysfunction, thrombotic microangiopathy, and proteinuria. Wound healing complications can occur, and holding drug before scheduled surgery is advised (no guidance from package insert) [41, 42].

mTOR Inhibitors

Everolimus (Afinitor)

Everolimus is dosed orally at 10 mg daily, with or without food. It can be dose reduced to 5 mg once per day or every other day. It is used in the metastatic setting, usually in relapse [39], and with recent evidence supporting concurrent use with lenvatinib (at a lower dose; see lenvatinib details [26]). Its practical use has fallen down to later lines as other comparison studies of everolimus against cabozantinib and nivolumab have shown superior activity when compared against everolimus [23, 43]. Common side effects include stomatitis, diarrhea, infections, nausea, edema, fatigue, and rash. Serious side effects include myelosuppression, hyperglycemia, hypercholesterolemia, and angioedema [44, 45].

Temsirolimus (Torisel)

Temsirolimus is dosed intravenously at 25 mg daily. It can be dose reduced by 5 mg/week to a dose no lower than 15 mg/week. It is used in the metastatic setting, though in current clinical practice, it is relegated to subsequent-line therapy rather than the first line [46]. Common side effects include rash, hepatic impairment, hyperglycemia, hyperlipidemia, mucositis, fatigue, and proteinuria. Serious side effects include infection, interstitial lung disease, bowel perforation, and intracerebral hemorrhage [47, 48].

Contemporary Treatment Approaches

Neoadjuvant Systemic Therapy

There is no evidence from large randomized clinical trials to support the neoadjuvant use of systemic therapies to reduce tumor burden and improve surgical outcomes and overall survival. However, the excitement and successes of immunotherapy and targeted therapies in the metastatic stage have summoned a new wave of trials for the neoadjuvant arena [49].

Adjuvant Therapy

At this time, while there is no definitive evidence of benefit in overall survival with the use of adjuvant systemic therapy, there was benefit seen in progression-free survival for those with high-risk clear cell renal carcinoma. This was seen in the S-TRAC study [40], a multi-center, 615 patient, randomized study comparing placebo with sunitinib (50 mg po daily, 4 weeks on, 2 weeks off) in the adjuvant setting. Sunitinib provided a longer median disease-free survival of 6.8 years compared to 5.6 years with those on placebo. Overall survival medians were not reached yet at the time of study publication. Given the higher adverse event rate with sunitinib use, there is controversy on whether this should be made into a level 1 recommendation. Other therapies have been tried in the adjuvant setting, including IL-2 and interferon-alpha [50], sorafenib [51], and pazopanib [52], all failing to show any benefit in disease-free or overall survival. Given the side-effect profile of sunitinib, it remains somewhat controversial to use it as adjuvant therapy despite the evidence and some experts' recommendation.

Advanced Disease Regimens

As mentioned earlier, treatment paradigms have evolved rapidly, and there is a high likelihood guidance will change soon after this chapter is in print, as has been the case over the past several years. Here, an attempt is made to summarize the major trends on approaches to therapy. The comments here are consistent with recent NCCN (National Comprehensive Cancer Network) guidelines (Kidney Cancer, v2.2019), with additional insights via conversations with international experts.

Risk Stratification

Risk assessment is helpful in guiding treatment selection. Several models exist, including one developed by the Memorial Sloan Kettering Cancer Center (MSKCC) [53] and another by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) [54]. While there are several subtle differences in these risk models, stratification categories into favorable (0 risk factors), intermediate (1–2 risk factors) and high/poor risk (≥3 risk factors) are used. Other parameters that are also helpful include tumor grade, history of nephrectomy and metastatic disease burden, location of disease, and co-morbidities [55].

Cytoreductive Nephrectomy in the Metastatic Setting

Perhaps counterintuitively, nephrectomy is sometimes considered in the metastatic setting if only oligometastasis is seen, minimal symptoms are incurred, and the patient is an appropriate operative candidate. Two studies in the IFN-a era demonstrated improved overall survival with upfront nephrectomy followed by systemic therapy when compared with those who did not have nephrectomy [56, 57]. Conversely, no benefit was shown in the one prospective study (CARMENA) [58] evaluating sunitinib alone versus upfront nephrectomy followed by sunitinib use in the metastatic setting, though this study was designed as a non-inferiority study. Despite the lack of formal evidence of benefit from cytoreductive nephrectomy in the current immunotherapy (checkpoint blockade inhibitors) era, extrapolations of benefit can be considered in carefully selected patients. As might be suspected, clinical trials are underway studying nephrectomy with use of immunotherapeutic agents in the metastatic arena.

First-Line Therapy for Intermediate- and Poor-Risk Patients in Clear Cell Renal Carcinoma

Some experts feel that CheckMate-214 [59], which demonstrated the superiority of ipilimumab and nivolumab over sunitinib, has set a new standard for first-line treatment for intermediate- and poor-risk-group patients. The objective response rate of the immunotherapy arm was 42% versus 27% in the sunitinib arm, with 9% versus 1% complete responses seen, respectively. Median overall survival was not achieved yet at 26 months, and progression-free survival was 11.6 months versus 8.4 months, respectively.

There have also been shifts on which VEGF-R inhibitor to use first. Previously, sunitinib had been the frontrunner, followed by pazopanib replacing sunitinib due to findings from the COMPARZ trial, showing non-inferiority and better tolerance of pazopanib versus sunitinib [29]. More recently, cabozantinib was compared to sunitinib in the phase II CABOSUN trial for intermediate- and poor-risk patients as first-line therapy [22]. Some experts are swayed by these findings and feel cabozantinib should be considered as first-line VEGF-R inhibitor therapy if the patient is not a candidate for immunotherapy.

Finally, temsirolimus can also be used as a first-line therapy, though the guideline recommendation is restricted to those with poor-risk categorization. From a practical perspective, usually one of the aforementioned therapies are used in the first-line setting rather than temsirolimus, though its use is supported by level 1 evidence [46].

First-Line Therapy for Favorable-Risk Patients in Clear Cell Renal Carcinoma

Interestingly, CheckMate-214 [59] revealed that for favorable-risk patients, 18-month overall survival rates favored sunitinib over the combination of ipilimumab and nivolumab (93% vs. 88%), with objective response rates of 52% versus 29%, respectively, in subgroup analysis. As such, experts and guidelines favor the initial use of pazopanib or sunitinib in the favorable-risk population, as there is level 1 evidence of their use in the first-line setting [37, 60]. The immunotherapy combination, though, can be considered for first-line therapy if there is patient and oncologist preference, i.e., there is no overt contraindication to using immunotherapy as first-line in the favorable-risk population.

Other options in the first line in the favorable-risk population include bevacizumab + IFN-a [18] (though side effects with interferon use can make this a less desirable option for patients), high-dose IL-2 [61], and other VEGF-R inhibitors such as axitinib [15] and cabozantinib. Of note, active surveillance may also be a reasonable option in patients who have asymptomatic disease and may demonstrate indolent progression [62].

Subsequent Therapies After First Line for Recurrent Disease

The options for next-line therapy become complex to describe as it will depend on what regimen was used in the first line. For those who have used VEGF-R inhibitors, immunotherapy is recommended. Nivolumab monotherapy has been studied and has level 1 evidence for its use in the second-line setting. CheckMate-025, a phase III study, compared nivolumab to everolimus and demonstrated improvement of overall survival (25.0 months versus 19.6 months, respectively) [43] Some experts also feel that it is not wrong to try the combination therapy of ipilimumab and nivolumab despite the lack of data of its use in the second-line setting. Moving on, for those that have progressed on first-line immunotherapy, it is suggested that a TKI be used, like cabozantinib [23] or axitinib [63], which have level 1 evidence, though others like pazopanib, sunitinib, and sorafenib are also reasonable.

An interesting combination regimen of lenvatinib with everolimus was also studied and has level 1 evidence of use in the subsequent-line setting [26]. This study compared the combination against everolimus alone or lenvatinib alone in patients with prior anti-angiogenesis inhibitor therapy and showed favorable findings of the combination therapy. Median overall survival for the combination therapy was 25.5 months versus 15.4 months with everolimus monotherapy and 18.4 months with lenvatinib monotherapy.

As there are no studies that collectively cover every possible treatment sequence permutation, especially at progression after the second-line regimen, it is left to the careful, creative liberties of the patient's oncologist. As such, one can consider the use of ipilimumab with nivolumab rather than nivolumab alone for use in the second line, as mentioned earlier. Other treatments for second-line therapy not mentioned above include bevacizumab, temsirolimus, everolimus mono-

therapy, and sorafenib. Another intriguing option that is gaining favorable data is the use of another checkpoint inhibitor, atezolizumab, in combination with bevacizumab.

Systemic Therapies for Non-Clear Cell Histologies

Studies for non-clear cell renal carcinomas are rarer given the lower prevalence of this histology. Despite the low representation in clinical trials, there is some evidence to show that the therapies for clear cell have some activity in non-clear cell histology. The NCCN guidelines for kidney cancer (v2.2019) suggest the use of sunitinib as first-line therapy, with the use of many of the other aforementioned agents as possible subsequent agents. Clearly, further trials need to be performed to better study this population [64, 65] (Table 23.1).

Conclusion

It is an exciting time in the practice of oncology for kidney cancer patients. It also is a challenging one as we witness the rapid evolution of treatment options. Unfortunately, at this time, metastatic renal cell cancer remains incurable, but the treatments outlined in this chapter will give many patients meaningful time and control of their disease with a relatively good quality of life. The best may yet to come as immunotherapy treatments are in its infancy. We might dare to dream that the future will yield an even better understanding of immuno-oncology biology, with subsequent improvements in immunotherapy that may provide durations of response not measured just in a few years, but perhaps even a few decades.

Table 23.1 Summarization of important trials for renal cell cancer therapeutics

Name	Year approved	Study type/trial name	N patients	ORR	OS	Comparator
Axitinib	2012	P3/AXIS	723	23% vs. 12%	20 m vs. 19 m	Sorafenib
Cabozantinib	2016	P3/METEOR	658	17% vs. 3%	21 m vs. 16 m	Everolimus
		P2/CABOSUN	157	20% vs. 9%	27 m vs. 21 m	Sunitinib
Pazopanib	2009	P3/COMPARZ	1110	31% vs. 25%	28 m vs. 29 m	Sunitinib
Sorafenib	2005	P3/TARGET	903	10% vs. 2%	19 m vs. 16 m	Placebo
Sunitinib	2006	P3/n/a	750	47% vs. 12%	26 m vs. 22 m	IFN-a
Bevacizumab (with IFN-a)	2009	P3/AVOREN	649	30% vs. 12%	23 m vs. 21 m	IFN-a
Lenvatinib (with everolimus)	2016	P2/n/a	153	43% vs. 27% vs. 3%	25 m vs. 19 m vs. 15 m	Lenvatinib, everolimus (monotherapies)
Everolimus	2009	P2/RECORD-1	416	2% vs. 0%	15 m vs. 14 m	Placebo
Temsirolimus	2007	P3/n/a	626	9% vs. 5% vs. 8%	11 m vs. 7 m vs. 8 m	IFN-a vs. combined
Ipilimumab + nivolumab	2018	P3/ CheckMate-214	1096	42% vs. 27%	n/a vs. 26 m	Sunitinib
Nivolumab	2015	P3/ CheckMate-025	821	25% vs. 5%	25 m vs. 20 m	Everolimus

P2 phase 2, *P3* phase 3, *N* number, *ORR* objective response rate, *OS* overall survival, *m* months, *IFN-a* interferon-alpha, *n/a* not available, *Year approved* year drug was approved for renal cell cancer treatment

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24 Unified Approaches to Surgery and Systemic Therapy for Renal Cell Carcinoma

Alejandro Abello and Patrick A. Kenney

Introduction

Nearly 60,000 people in the United States were diagnosed with kidney cancer in 2010, and >13,000 died of the disease accounting for an overall 5-year survival rate of 74.5% [1]. At diagnosis, approximately 40% of patients have regionally advanced or metastatic disease, with an additional 10–28% developing recurrence or metastasis following surgery for previously localized disease [1]. This substantial percentage of patients may benefit from integrated surgical and systemic therapy. A multifaceted approach to the treatment of renal cell carcinoma (RCC) is increasingly undertaken to maximize clinical outcomes. This chapter will focus on the proper integration of surgery and systemic therapy with regard to adjuvant therapy for RCC, neoadjuvant therapy for locally advanced disease, and multimodal therapy for metastatic RCC (mRCC), including presurgical targeted therapy and cytoreductive nephrectomy.

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Adjuvant Therapy

In this chapter, the phrase adjuvant therapy will define treatment that is administered after complete surgical resection with the goal of reducing risk of recurrence [2]. Patients who develop distant metastatic disease have progressed to an incurable state, with 5-year survival rates of about 10% [1]. The consummate adjuvant therapy would have favorable toxicity, proven activity in metastatic disease, and efficacy against the standard of care (observation) in phase 3 randomized trials and could be administered to the subset of patients who are most likely to benefit, ideally on an outpatient basis [3, 4].

Contemporary Approach to Quantifying the Risk of Recurrence

An important aspect of developing effective adjuvant therapy is to define the group of patients who are at elevated risk of recurrence and who are therefore most likely to benefit from adjuvant therapy. Identifying high-risk patients will address one of the recognized disadvantages of the adjuvant approach, namely that some patients are cured with surgery alone and will be treated with adjuvant therapy that offers the potential for harm but not benefit.

Existing predictive models are based solely on preoperative variables such as gender, symptoms, and imaging findings including necrosis, lymphadenopathy, and tumor size [5–7]. These

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models may help select intervention vs. active surveillance and may prove useful for identifying patients for neoadjuvant therapy [8, 9]. On the other hand, postoperative models that incorporate pathologic variables discriminate better than preoperative models and are therefore more appropriate for selection of candidates for adjuvant therapy [9, 10].

Models Incorporating Clinical and Pathologic Data

Several models use clinical and pathologic variables to predict the risk of progression after surgery for localized RCC (Table 24.1) [11–14]. These models are useful but have shortcomings. Neither the modified UCLA Integrated Staging System (UISS) nor the MSKCC nomograms capture the nearly 20% rate of recurrence beyond 5 years [11, 14, 15–18]. In addition, since there is a known association between nuclear grade and outcome, the exclusion of nuclear grade in the 2001 MSKCC nomogram may have limited its predictive capacity [11, 13, 16]. Finally, none of these models include molecular prognostic biomarkers.

The UISS, which has been externally validated and includes all RCC subtypes, groups patients in low-, medium-, or high-risk categories [14, 19]. Instead of tailoring risk to an individual patient like a nomogram, grouping risk into categories will limit the instrument's discriminatory ability since each group will encompass a range of outcomes [9, 14]. The 2001 MSKCC nomogram and the UISS were compared with a multicenter cohort of >2400 patients [10]. The concordance index were 0.71 and 0.68 for the MSKCC and UISS models, respectively. The varied outcomes in the UISS intermediate-risk category were able to be discriminated by the MSKCC nomogram [10].

Using Molecular Markers to Improve Prognostication

In addition to using clinical and pathologic data, molecular markers may improve our ability to predict the risk of recurrence or progression. Several early efforts have demonstrated the feasibility of this approach. By incorporating expression of carbonic anhydrase IX, vimentin, and p53 with clinical variables (metastasis, T stage, performance status), investigators achieved slightly better ability to predict disease-specific survival compared to the UISS (C Index 0.79 vs. 0.75) [20]. The same group also used molecular data in a nomogram to predict disease-free survival following nephrectomy for localized ccRCC (Fig. 24.1) [21]. In addition to clinical and pathologic variables, the molecular markers included Ki-67, p53, endothelial VEGFR-1, epithelial VEGFR-1, and epithelial VEGF-D. While the molecular markers alone exceeded the predictive ability of the UISS (C Index 0.84 vs. 0.78), the accuracy of the full nomogram which incorporated clinical, pathological, and molecular data was higher still (concordance index 0.90).

Using immunohistochemistry, Mayo Clinic investigators characterized expression of B7-H1, survivin, and Ki-67 in 634 patients treated with radical or partial nephrectomy for localized or metastatic ccRCC [22]. Weighted scores were assigned to marker expression and the total score (range 0–7), termed BioScore, was able to discriminate cancer-specific survival (Fig. 24.2). The addition of BioScore improved the predictive ability of other models including TNM staging (C Index 0.82 vs. 0.79) and the UISS (0.82 vs. 0.77) [22].

The great promise of biomarker models is that they may identify the molecular characteristics that drive tumor behavior and use them to predict clinical outcome. The molecular models mentioned above are promising but need independent validation and laboratory standardization [23]. The gains in prognostication thus far appear to be modest. The added cost of the assays must be weighed versus the small incremental improvement over the user-friendly, readily available clinicopathologic models [16].

Adjuvant Trials

Radiotherapy

There are two reasons that one would expect little role for adjuvant therapy that is delivered locally. First, radical nephrectomy provides excellent

Table 24.1 Models that use clinical and pathologic variables to predict oncologic outcomes after surgery for localized RCC [11–14]

Type	Study population (n)	TNM	Histology	Nephrectomy	Years	Symptoms	Performance status	Tumor size	pT	pN	Grade	Histology	Necrosis	Vascular invasion	Outcome	Time point (years)	Concordance index
Nomogram	601	T1–3c, N0/x, M0	Papillary, chromophobe, ccRCC	Partial, radical	1989–1998	✓		✓	✓ (1997)			✓			Recurrence-free survival	5	0.74
Algorithm (low, moderate, high risk)	468	T1–4, N0, M0	Any	Partial, radical	1989–2000		✓		✓ (1997)	✓	✓				Overall survival, disease-specific survival, local recurrence-free survival, and systemic recurrence-free survival	1, 2, 3, 4, 5	NA
Algorithm (score between 0 and 11)	1671	T1–4, Nx – N2, M0	ccRCC	Radical	1970–2000			✓	✓ (2002)	✓	✓	NA	✓		Metastasis-free survival	1, 3, 5, 7, 10	0.82
Nomogram	701	T1–3c, N0/x, M0	ccRCC	Partial, radical	1989–2002	✓		✓	✓ (2002)		✓	NA	✓	✓	Recurrence-free survival	5	0.82

Adapted from Kenney and Wood [15]

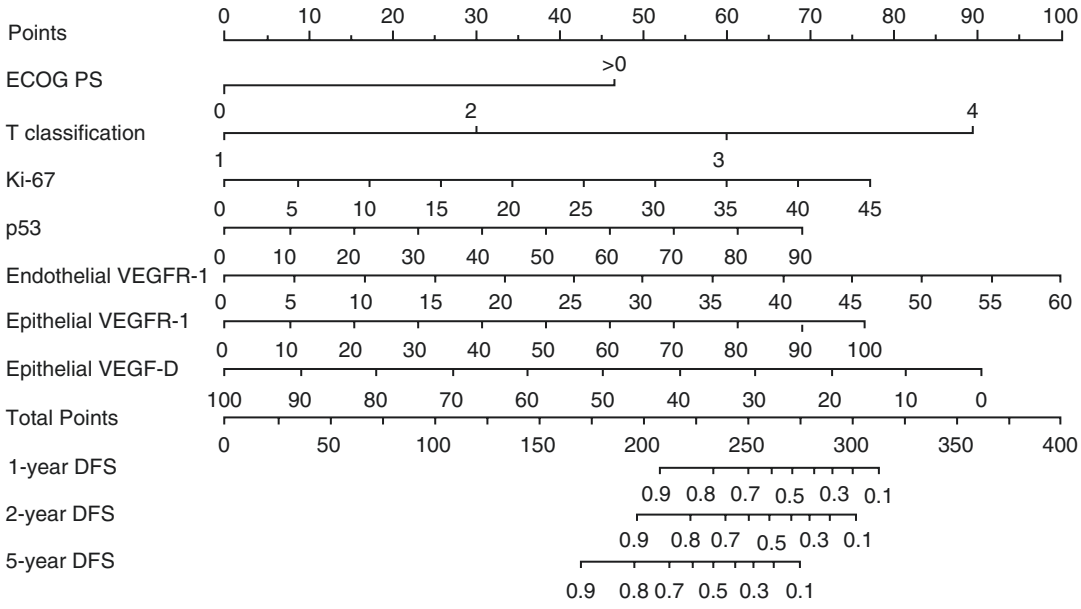

Fig. 24.1 This nomogram predicts disease-free survival using molecular data in addition to clinical and pathologic variables. The number of points assigned to each variable is determined by drawing a vertical line up to the points' axis. Total points correspond to predicted disease-free survival. (Reprinted with permission from Klatte et al. [21])

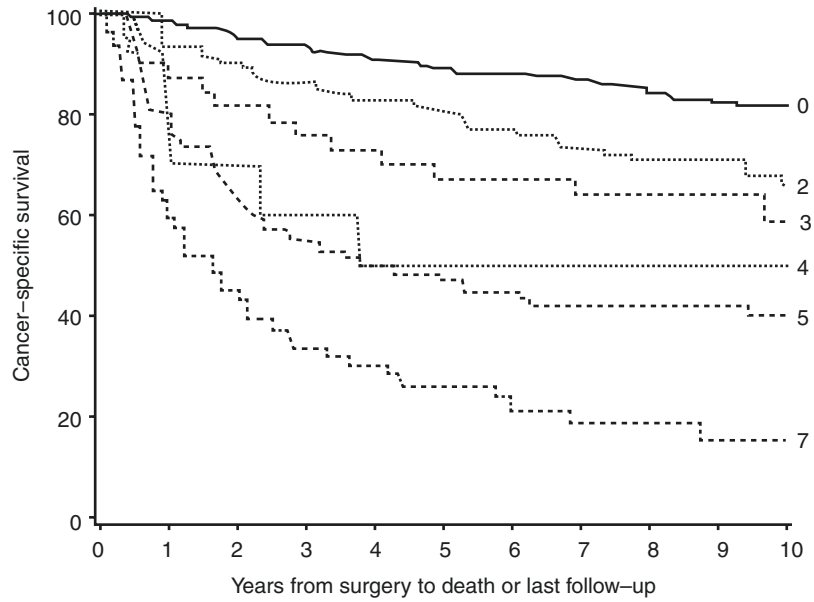

Fig. 24.2 BioScore is an algorithm that incorporates molecular markers to improve prognostication following nephrectomy for ccRCC. Total score is predictive of cancer-specific survival. (Reprinted with permission from Parker et al. [22])

local cancer control in most cases. Second, recurrence of RCC is typically distant from the primary [24]. Nonetheless, with a paucity of available systemic agents, the initial adjuvant studies in RCC used radiotherapy in an attempt to improve RCC control [4].

From 1961 to 1970, a prospective trial randomized patients with a completely resected primary tumor and no evidence of metastatic disease to adjuvant radiation to the renal bed, incision and para-aortic nodes (n = 51) or observation (n = 49) [25]. Radiotherapy was not associated

with any improvement in recurrence or survival. Most notable among the substantial side effects that were attributed to the adjuvant radiation were four deaths from liver failure. Between 1979 and 1984, a similar multicenter trial randomized patients with stage II and III RCC to 50 Gy of external beam radiotherapy in 20 fractions to the kidney bed and nodes (n = 32) or observation (n = 33). [26] Radiotherapy was associated with hepatic, gastric, and duodenal injuries, but no reduction in relapse. In nearly a fifth of patients, radiotherapy complications contributed to the patient's death. Based on these important trials, adjuvant radiotherapy is not employed for RCC.

Small retrospective studies in patients with advanced disease have shown a small benefit on 5-year survival rates after postoperative fractionated 40–50 Gy radiotherapy. However, due to the small sample size, high risk of bias from retrospective studies and absence of level 1 evidence, adjuvant radiotherapy is not currently recommended [27, 28].

Medical Therapy

Medroxyprogesterone acetate (MPA) can block glucocorticoid receptors that are expressed by some renal tumors [29]. MPA was investigated in a multicenter trial in which patients were randomized to 1 year of adjuvant MPA (n = 58) or observation (n = 62) following radical nephrectomy for non-metastatic RCC [30]. More than half of the patients had ≥T3 disease. After a median follow-up of 5 years, complications were common in the intervention arm but rates of relapse were similar in the intervention and control groups (32.7% vs. 33.9%).

Another similar trial using adjuvant tegafur and uracil after radical nephrectomy did not show any significant differences on recurrence in comparison to non-adjuvant group [31]

Immunotherapy

The primary tumor is thought to have an immunosuppressive effect [32–35]. It was proposed that once the "immune sink" was eliminated with nephrectomy, adjuvant immunotherapy could treat the remaining subclinical disease that leads to recurrence. Various adjuvant immune treatments have been evaluated including vaccines, dendritic cell therapy, cytokines, and stem-cell transplant to engender a graft-versus-tumor effect [36–38].

The impact of immune surveillance on RCC is thought to be evidenced by spontaneous regression of metastatic disease following tumor ablation or nephrectomy, as well as the infiltration of the tumor by immune cells that have anti-tumor activity [39–43]. In part, the immune system impact is thought to be mediated by interaction between CD8+ cytotoxic T lymphocytes and CD4+ helper T cells that secrete cytokines including Interleukin-2 (IL-2) and Interferon-∝ (IFN-∝) [23]. Exogenous IL-2 and IFN-∝ are effective in metastatic disease, with response rates up to 20% and a 5% durable complete response for IL-2 [37, 44–46]. IL-2 and IFN-∝ do not appear to have activity in the adjuvant setting. Randomized trials have failed to show a survival benefit to adjuvant IL-2 or IFN-∝ [47–50]. Patients who received adjuvant chemoimmunotherapy in one trial had worse 5-year overall survival when compared to control (58% vs. 76%, p = 0.028) [51]. Another recent trial comparing adjuvant 5-Fluoracil, IFN-∝, and IL-2 to placebo failed to show differences for the treatment arm in regard to disease-free survival (61% vs. 50%, p = 0.2) or overall survival at 5 years (70% vs. 63%, p = 0.4) (Table 24.2) [52].

Adjuvant active–specific immunotherapy using vaccines has also been employed with largely unfavorable results. In a trial reported in 1996, Galligioni et al. randomized patients to intradermal injection of irradiated tumor cells and BCG (n = 60) or observation (n = 60) [51]. The investigators were able to document that the vaccine induced a tumor-specific immune response by demonstrating a delayed-type cutaneous hypersensitivity reaction to autologous tumor cells in 70% of immunized patients a month after the end of therapy. This did not translate into improved outcomes with comparable 5-year disease-free survival in the vaccine and control groups (63% vs. 72%, p = NS).

The first successful adjuvant trial in RCC was reported in 2004 by Jocham and colleagues [53].

Table 24.2 No randomized trial that investigated IL-2 and IFN-∝ as adjuvant therapy

Author	Year	Eligibility	Design	*N*	Median follow-up	Primary end point (intervention vs. control)	*P* value
Pizzocaro	2001	Robson II or III	IFN-alpha vs. observation	247	NA	5-year OS: 66.5% vs. 66.0%	0.861
Messing	2003	pT3–4a or N+	IFN-alpha vs. observation	283	10.4 years	Median OS: 5.1 vs. 7.4 years	0.09
Clark	2003	pT3b-4 or N+ or M1 (resected)	High-dose IL-2 vs. observation	69	22 months	2-year DFS: 48% vs. 55%	0.431
Atzpodien	2005	pT3b-4 or N+ or M1 (resected)	IFN-alpha + IL-2 + 5-FU vs. observation	203	4.3 years	5-year OS: 58% vs. 76%	0.028
Aitchison	2014	pT3b-4 or N+ or any pT + pN1 or pN2 or positive margins or positive microvascular invasion	IFN-alpha + IL-2 + 5-FU vs. observation	309	7 years	3-year DFS	0.23

Adapted from Kenney and Wood [15]

In 1997 and 1998, the investigators enrolled 558 patients who were scheduled for radical nephrectomy at 55 German sites. Randomization took place prior to nephrectomy. An intervention consisting of six autologous tumor vaccinations at 4-week intervals was compared to observation. Following nephrectomy, only patients with pT2–3b, pN0–3, M0 RCC, and Eastern Cooperative Oncology Group (ECOG) performance status 0–2 were permitted to continue in the trial. It is important to note that patients with pT1 or pT4 disease were excluded, despite having already been randomized. The primary endpoint was tumor progression.

There was a large loss of patients from the trial. Five patients withdrew consent prior to surgery. After surgery, an additional 174 subjects were withdrawn for reasons including non-RCC histology, incorrect tumor stage, and inability to prepare the vaccine. More patients were lost from the vaccine arm than control (n = 99 vs. 75). Analyzing the remaining 379 patients, 5-year progression-free survival was higher in the vaccine group (77.4% vs. 67.8%, p = 0.02). At 5 years, the hazard ratio for progression was 1.58 (95% CI: 1.05–2.37, p = 0.02) in favor of the intervention. In the group of patients with pT3 disease, the difference in progression-free survival between intervention and control was larger (67.5% vs. 49.7%, p = 0.039).

The trial was criticized for the large loss of patients (32%) that was imbalanced between study arms [54]. Based on the study design, in which patients were randomized before pathologic diagnosis and staging, a loss of patients was assured. To address this criticism, an intention-to-treat analysis was later reported with larger vaccine (n = 233) and control (n = 244) groups [55]. The vaccine was still associated with improved progression-free survival (p = 0.048), though the magnitude of the benefit was not reported. There was no difference in overall survival (p = 0.12). The same vaccine protocol was recently evaluated with a retrospective matched-pair analysis in 495 patients [56]. At a median follow-up of 131 months, the vaccine was an independent predictor of overall survival (HR: 1.28, p = 0.030), as well as in the subset of pT3 patients (HR: 1.67, p = 0.011). Even with an improvement in progression-free survival demonstrated in a randomized trial and similar retrospective findings, the adjuvant vaccine was not widely adopted and the manufacturer became insolvent [54].

In another adjuvant vaccine trial, patients were randomized to receive Vitespen (Oncophage, Antigenics, Inc., New York, NY) (n = 409) or observation (n = 409) following nephrectomy [57]. This was the largest phase 3 adjuvant trial in RCC to date. Vitespen is a heat shock protein (HSP) vaccine, which consists of HSP-peptide complexes that are isolated from a patient's tumor. HSPs are intracellular chaperones which play a role in the loading of antigenic peptides onto MHC class I molecules, eliciting an immune response [4, 29]. After a median follow-up of 1.9 years, the rate of recurrence was comparable in the Vitespen and control groups (37.7% vs. 39.8%, p = 0.506).

Thalidomide

Thalidomide is an antiangiogenic and immunomodulatory drug that was investigated as an adjuvant therapy in a single-institution trial [58]. Thalidomide has demonstrable activity in metastatic RCC [59]. High-risk patients (high-grade T2–T4 or node-positive disease) were randomized to 2 years of thalidomide (n = 23) or observation (n = 23). Following a scheduled interim analysis, the protocol was terminated early as adjuvant thalidomide was unlikely to demonstrate any benefit. There was no difference in cancer-specific survival at 2 or 3 years, but 3-year recurrence-free survival was inferior in the thalidomide arm (28.7% vs. 69.3%, p = 0.022).

Targeted Agents

Recent adjuvant trials have evaluated VEGF receptor tyrosine kinase inhibitors. The ASSURE trial randomized patients with high-grade pT1b or greater into sunitinib, sorafenib, or placebo groups. Approximately 44% of patients in the

sunitinib group and 45% in the sorafenib group discontinued treatment because of drug-related toxicity. The trial was stopped early due to loss of power to achieve primary endpoint, and no disease-free survival differences were reported among the groups [60].

In contrast to ASSURE, the S-TRAC study comparing sunitinib to placebo in high-risk clear cell carcinoma did show a disease-free survival advantage with sunitinib (6.8 years vs. 5.6 years, $p = 0.03$). There was no difference in overall survival. Furthermore, patients in the sunitinib group were more likely to have dose reductions (34.2% vs. 2%), dose interruptions (46.4% vs. 13.2%), and dose discontinuations (28.1% vs. 5.6%) for adverse events and toxicity [61]. The main difference with ASSURE was the selection criteria of the study population (Table 24.3).

The PROTECT trial evaluated adjuvant pazopanib compared to placebo in patients with locally advanced RCC at high risk for relapse. In intention to treat analysis, the intervention group did not show significant differences in terms of disease-free survival when compared to placebo (HR: 0.69, 95% CI: 0.70–1.06; $p = 0.1$) but exhibited higher rates of grade 3–4 adverse events (60% vs. 21%, respectively) [62].

The ARISER trial assessed weekly Girentuximab, a monoclonal antibody that binds CA IX, after nephrectomy in high-risk ccRCC. The trial enrolled 864 patients randomized into Girentuximab or placebo and showed no differences in DFS (HR: 0.97, 95% CI: 0.79–1.18) or overall survival (HR: 0.99, 95% CI: 0.74–1.32) with comparable adverse events between arms [63].

Ongoing or Unreported Adjuvant Trials

Despite the demonstrated difficulty in identifying an effective adjuvant therapy, there are numerous ongoing adjuvant trials using targeted agents. Three of the trials compare agents with demonstrated activity in metastatic disease to placebo: SORCE evaluates adjuvant VEGF-targeted therapy, Keynote 564 evaluates immunotherapy with pembrolizumab, and EVEREST investigates adjuvant mammalian target of rapamycin (mTOR) inhibition (Table 24.4). All of the trials target patients with high risk of recurrence, some using the previously described predictive models. Both SORCE and EVEREST permit patients with non-clear cell histology [8].

Adjuvant Therapy: Current Status

There is no current commonly accepted evidenced-based paradigm for adjuvant therapy following nephrectomy for clinically localized disease. Adjuvant radiotherapy, MPA, Il-2, IFN-∝, and Thalidomide were evaluated in randomized controlled trials and none improved disease progression or survival [25, 26, 30, 47–50, 58]. Although an adjuvant autologous tumor vaccination was associated with a progression-free survival benefit in a randomized controlled trial, the study methodology has been criticized and the intervention was not broadly adopted [53]. No other adjuvant vaccine study had favorable results [51, 57]. Sunitinib has not been shown to improve overall survival, has had mixed results with

Table 24.3 Comparison in inclusion criteria between ASSURE and S-TRAC trials

Trial	Intervention	Inclusion criteria
ASSURE	Sorafenib vs. sunitinib vs. placebo	Selection of patients using 2002 American Joint Committee on Cancer staging: pT1b/Grade 3–4/N0/M0 pT2/any Grade/N0/M0 pT3/any Grade/N0/M0 pT4/any Grade/N0/M0 Any T/any Grade/N+/M0
S-TRAC	Sunitinib vs. placebo	Selection of patients using modified UISS criteria: pT2/N0/M0 pT3–4/N0/M0 pTx/N1/M0

Table 24.4 Ongoing trials of adjuvant therapy for clinically localized RCC

Study name	Drug(s)	Study sponsor	Drug description	Clinicaltrials.gov	Design	Population	n	Adjuvant intervention	Primary outcome	Secondary outcome	Status
SORCE	Sorafenib (Nexavar)	Medical research council	See above	NCT00492258	Randomized, double-blind, placebo-controlled phase III	Intermediate or high risk of relapse (Leibovich score 3–11)	1656	1 year of sorafenib or 3 years of sorafenib or placebo	Disease-free survival	Metastasis-free survival, overall survival, cost-effectiveness, and toxicity	Enrollment started June 2007. Final data collection anticipated in August 2012
EVEREST	Everolimus (Afinitor)	SWOG	mTOR inhibitor	NCT01120249	Randomized, double-blind, placebo-controlled, phase III	Intermediate high risk to very high risk	1218	96-week courses of everolimus or placebo	Recurrence-free survival	Toxicity and overall survival	Enrollment started in April 2011. Final data collection for primary endpoint anticipated in August 2013
Keynote 564	Pembrolizumab (Keytruda)	Keynote/ Industry	PD1 inhibitor	NCT03142334	Randomized, double-blind, placebo-controlled, phase III	Intermediate, high risk or M1 with no evidence of disease	950	3-week cycles for up to 17 cycles	Disease-free survival	Toxicity, DFS according to PD-L1 status and overall survival	Enrollment started in June 2017. Final data collection for primary endpoint anticipated in November 2022
PROSPER RCC trial	Nivolumab (Opdivo)	National Cancer Institute	PD1 inhibitor	NCT03055013	Randomized, phase III (observation vs. Nivolumab)	All patients with M0 or M1 with no evidence of disease	805	2 cycles before surgery. After nephrectomy 14-day cycles (6) followed by 28-day cycles (6)	Recurrence-free survival	Toxicity, RFS in ccRCC and overall survival	Enrollment started in February 2017. Final data collection for primary endpoint anticipated in November 2023

(continued)

Table 24.4 (continued)

Study name	Drug(s)	Study sponsor	Drug description	Clinicaltrials.gov	Design	Population	n	Adjuvant intervention	Primary outcome	Secondary outcome	Status
IMmotion 010	Atezolizumab (Tecentriq)	Industry	PD-L1 inhibitor	NCT03024996	Randomized, double-blind, placebo-controlled, phase III	All patients with M0 or M1 with no evidence of disease	664	3-week cycles for up to 16 cycles	Independent review facility disease-free survival	Toxicity and, disease-specific, metastasis-free and overall survival	Enrollment started in January 2017. Final data collection for primary endpoint anticipated in May 2022
CheckMate 914	Nivolumab (Opdivo) and Ipilimumab (Yervoy)	Industry	PD-L1 and CTLA-4 inhibitors	NCT03138512	Randomized, double-blind, placebo-controlled, phase III	High risk of relapse	800	24 weeks	Disease-free survival	Toxicity and overall survival	Enrollment started in July 2017. Final data collection for primary endpoint anticipated in September 2022

regard to DFS, and became the first FDA-approved agent for use in the adjuvant setting. It remains to be seen whether Sunitinib will play an important role given mixed results, lack of OS benefit, and toxicity.

Neoadjuvant Therapy for Locally Advanced RCC

In this chapter, we will use the term neoadjuvant therapy to designate therapy administered prior to surgical resection of clinically localized disease. The intent of neoadjuvant therapy for locally advanced RCC is not only to reduce the risk of recurrence but also to facilitate surgery by converting unresectable disease to resectable by making partial nephrectomy feasible or by simplifying resection of a venous tumor thrombus. Each of these goals continues to be theoretical, and there is little data to support the use of neoadjuvant systemic therapy in RCC.

Immunotherapy

A hallmark of immunotherapy for metastatic disease is that it appears to have little or no impact on the primary lesion. For instance, IL-2, IFN-∝, and granulocyte-macrophage colony-stimulating factor were used to treat 16 patients with metastatic RCC with the primary in situ, and no response was seen in the primary tumors [64]. Applying this concept to the neoadjuvant setting, one would not expect cytokines to shrink the primary tumor [65].

On the other hand, there is some evidence that neoadjuvant renal artery embolization, which can be used to cut off the arterial inflow to locally advanced lesions prior to nephrectomy, might engender a beneficial immune by releasing tumor-associated antigens. It is possible that angioinfarction augments the immune response to the renal tumor [66]. There are reports of regression of RCC metastases following RAE and nephrectomy [67, 68]. In addition, the common post-infarction syndrome may be cytokine mediated. Several studies have shown that RAE is immunomodulatory with documented changes in natural killer cell activity, increased cell-mediated cytotoxicity, and alteration in lymphocyte proliferation [69–71]. A single case-control study of preoperative renal artery embolization demonstrated better overall survival at 5 years (62% vs. 35%, $p = 0.01$) and 10 years (47% vs. 23%, $p = 0.01$) [72]. Nonetheless, while it may be a helpful technical adjunct to surgery, no prospective clinical evidence supports the use of neoadjuvant renal artery embolization as a means of improving survival.

Targeted Therapy

The advent of targeted therapy, which can have activity against the primary tumor, has prompted a reevaluation of neoadjuvant systemic therapy prior to surgical resection. This section will review neoadjuvant targeted therapy for locally advanced disease. Much of the data is extrapolated from the presurgical (i.e., metastatic) literature. Presurgical therapy, which we use to denote therapy prior to planned cytoreductive surgery in mRCC, will be addressed later in the chapter.

Targeted Therapy Is Active Against the Primary Tumor

Response in the primary tumor is variable and depends on the individual tumor and the systemic agent employed. Profound responses to targeted agents have been reported, including complete histologic response, but these are the exception rather than the rule (Fig. 24.3a, b) [73]. The primary tumor typically has a more modest response to targeted agents.

A number of retrospective analyses have described the impact of Sunitinib and other agents on the primary. Generally, Sunitinib has produced a more robust response in the primary tumor than any other targeted therapies [8]. Imaging for 17 patients who were treated with Sunitinib at two Dutch Centers from 2005 to 2007 was retrospectively analyzed [74]. The primary tumor was in place. Radiographic response

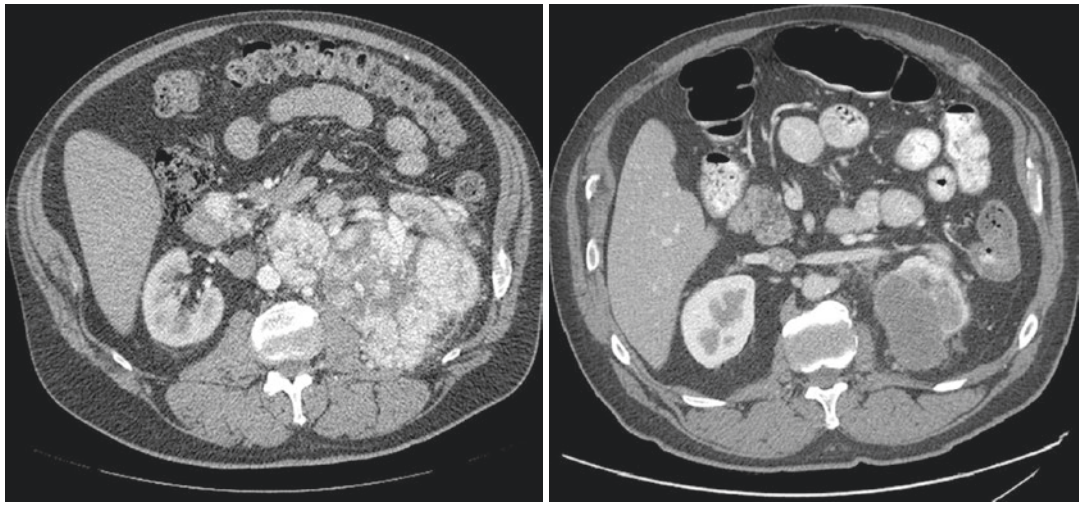

Fig. 24.3 Before therapy with Sunitinib (left), a CT scan demonstrates a large left-sided primary tumor with associated adenopathy. There was a significant decrease in both the primary tumor and nodes following treatment with Sunitinib (right). (Reprinted with permission from Abel et al. [79])

in the primary was assessed using Response Evaluation Criteria in Solid Tumors (RECIST). It is important to note that RECIST, which is based on changes in tumor size, may underestimate the impact of targeted therapy whose impact may be better judged by assessing tumor necrosis and cavitation [75]. There were 4 partial responses, 1 progression, and 12 with stable disease by RECIST. Among the patients with partial response or stable disease, there was a 31% median reduction ($p = 0.001$) in tumor volume. There was a 39% concomitant increase ($p = 0.035$) in the median volume of necrosis.

Thomas et al. also reported a retrospective series of 19 patients with locally advanced or metastatic RCC who were treated with Sunitinib with the primary tumor in place [76]. By RECIST, there were three partial responses (16%), seven with stable disease (37%), and nine (47%) with progression. Of the eight (42%) patients who had tumor shrinkage, the mean decrease was 24% (range 2–46%) (Table 24.5).

A single-arm Phase II trial of presurgical Bevacizumab ($n = 23$) or Bevacizumab plus Erlotinib ($n = 27$) was undertaken in patients with metastatic renal cell carcinoma [77]. Most patients (58%) had stable disease, with some partial responses (10%) and a single complete response (2%). 52% of patients had regression of the primary tumor, although the size reductions were generally minor: 1–10% shrinkage (29%), 11–20% shrinkage (16%), and 20–30% shrinkage (7%).

Table 24.5 In mRCC patients who were treated with systemic therapy with the primary tumor in situ, radiographic response in the primary tumor varied by drug

Agent	Number of patients	Median percentage change (IQR)	Median number days between imaging (IQR)
Sunitinib	75 (45%)	−10.2 (−21.1 to −2.8)	105 (76–201)
Bevacizumab	25 (15%)	0.1 (−4.2 to 4.6)	55 (54–56)
Bevacizumab plus erlotinib	26 (15%)	−10.1 (−17.1 to −6.0)	54.5 (54–56)
Sorafenib	16 (10%)	−6.0 (−12.3 to −0.4)	90 (61.5–124)
Temsirolimus	16 (10%)	−4.0 (−8.6 to −0.5)	56 (52–84)
Bevacizumab plus chemotherapy	7 (4%)	−6.1 (−11.9 to −0.7)	58 (43–118)
Erlotinib	2 (1%)	−5.1 (−9 to −1.3)	51.5 (41–62)
Pazopanib	1 (1%)	−11.1 (NA)	48 (NA)

Adapted from Abel et al. [79]

Similarly, Cowey and colleagues performed a single-arm Phase II trial of neoadjuvant or presurgical Sorafenib in 30 patients with ≥ Stage II RCC [78]. Nephrectomy was planned in all patients. Median treatment duration was 33 days. The vast majority (93%) of patients had stable disease by RECIST criteria. The median change in tumor size was −9.6% (range from +16% to −40%).

In 2011, Abel and colleagues reported a single-institution retrospective review of patients with mRCC who received targeted therapy with the primary tumor in situ between 2004 and 2009 [79]. Adequate imaging was available for 168 patients with a median follow-up of 15 months. Two reviewers measured the diameter of primary and metastatic lesions on pre- and post-therapy imaging. Prior to therapy, the median diameter of the primary lesion was 9.6 cm. Patients received a variety of systemic targeted therapies (Table 24.3). The median maximum change in primary tumor diameter was −7.1% after a median 62 days of treatment. The median change in primary tumor diameter was −6.5 mm.

Permitting Resection

It has been proposed that neoadjuvant therapy may render initially unresectable lesions amenable to nephrectomy. It is clear that surgical resectability is a poorly defined, subjective characteristic that is dependent upon the surgeon and patient [65, 80]. Attributes that contribute to unresectability may include tumor size, extensive hilar involvement, considerable lymphadenopathy, or adjacent organ invasion [76]. In the series reported by Thomas and colleagues, there were four patients with locally advanced disease in whom the primary tumor was judged to be unresectable due to the proximity of adjacent structures ($n = 4$), vascular involvement ($n = 2$), and substantial adenopathy ($n = 2$) [76]. The average size of the primary tumor was 11.3 cm (range 6.4–20 cm). After being treated with neoadjuvant Sunitinib, three of the four patients had tumor shrinkage (range 11–24%) and subsequently had nephrectomy. The alterations in the primary that permitted transformation to "resectable" status were not described.

In 2012, Rini and colleagues reported the results of a Phase II trial of neoadjuvant or presurgical Sunitinib in 30 patients with a primary tumor that was deemed unresectable [81]. To be considered unresectable, patients had at least one of the following characteristics: large tumor, bulky adenopathy, tumor thrombus, or proximity to vital structures. The median change in the size of the primary tumor was a 22% decrease (median: 1.2 cm). Patients with non-clear cell histology had a median 1.4% increase (0.1 cm) in primary tumor size. Thirteen patients (45%) were able to go on to nephrectomy.

Although these findings are thought provoking, it is estimated that <1% of RCC cases are characterized as unresectable [80]. In addition to being rare, unresectability is subjectively defined and may vary among surgeons. Moreover, existing drugs typically have at best a modest impact on the primary tumor. For these reasons, quantifying the impact of neoadjuvant therapy on unresectability in a reproducible manner will be a substantial challenge.

Enabling Nephron-Sparing Surgery

There is a growing body of evidence favoring nephron-sparing surgery over radical nephrectomy. There is a higher probability of renal insufficiency following radical nephrectomy compared to partial nephrectomy [82, 83]. It is presumed that the higher rate of chronic kidney disease following radical nephrectomy may place patients at higher risk of atherosclerotic disease and death. In a population-based analysis, radical nephrectomy was associated with a 1.4 fold higher number of cardiovascular events ($p < 0.05$) and a higher risk of overall mortality (HR: 1.38, $p < 0.01$) compared to partial nephrectomy [84]. Another population-based study that compared partial and radical nephrectomy for T1a RCC demonstrated comparable kidney cancer–specific survival (HR: 0.82; 95% CI: 0.19–3.49) but substantially lower risk of death with partial nephrectomy (HR: 0.54; 95% CI: 0.34–0.85) [85]. With

partial nephrectomy, survival at 2, 5, and 8 years increased by 5.6%, 11.8%, and 15.5%, respectively ($p < 0.001$). It should be noted that these findings were not supported by a controversial and methodologically problematic prospective European Organization for the Research and Treatment of Cancer (EORTC) study that demonstrated improved overall survival with radical compared to partial nephrectomy [86].

Given the apparent benefits of partial nephrectomy, it has been proposed that one could employ neoadjuvant systemic therapy for large or locally advanced lesions to permit partial nephrectomy where it would otherwise not be feasible [65, 87]. There are reports of Sunitinib being utilized in the neoadjuvant setting to facilitate imperative partial nephrectomy, including a patient with two tumors in a solitary kidney after prior radical nephrectomy [88]. It was thought that partial nephrectomy of these centrally located lesions would not be possible. The patients were treated with neoadjuvant Sunitinib which resulted in 20% decrease in size of the tumors. Subsequent partial nephrectomy was successful. Similarly, Thomas et al. described two cases of bilateral tumors in which neoadjuvant Sunitinib was followed by successful partial nephrectomy [89].

Sunitinib was also used in 12 patients, 5 of whom had metastatic disease, prior to partial nephrectomy as reported by Silberstein et al. in 2010 [90]. Each patient had an imperative indication for partial nephrectomy including chronic kidney disease ($n = 9$), solitary kidney ($n = 7$), or bilateral tumors ($n = 2$). In response to Sunitinib, all patients had measurable tumor shrinkage with the mean tumor diameter decreasing from 7.1 to 5.6 cm (21%). All patients underwent partial nephrectomy. There were three urine leaks. Follow-up was 23.9 months. Limitations of the study include lack of a control group and brief follow-up. In addition, the impact of Sunitinib on surgical complexity was not reported. It would have been valuable to quantify change in the surgical complexity of the tumor using anatomic or morphometric data (e.g., centrality index or nephrometry score) [91, 92]. A fundamental shortcoming of this study is that the indication for neoadjuvant or presurgical Sunitinib was not reported. It is unclear if Sunitinib had any impact on the feasibility, technical complexity, or oncologic outcome of partial nephrectomy.

A similar study was reported by Hellenthal et al., who performed a single-arm prospective study of neoadjuvant or presurgical Sunitinib in 20 patients with localized or metastatic ccRCC [87]. After 2 months of Sunitinib, 17 out of 20 (85%) patients had tumor shrinkage with a mean decrease of 11.8%. Eight patients had partial nephrectomy for pT1b–pT3a N0 M0 disease, and the remainder had radical nephrectomy. No complications were attributed to the upfront drug. These series provide evidence that partial nephrectomy following Sunitinib is feasible. Unfortunately, they do not provide efficacy data to support the use of systemic therapy prior to partial nephrectomy.

Downsizing Caval Tumor Thrombus

The data supporting the use of neoadjuvant targeted therapy to downsize caval tumor thrombus has similar problems. There are case reports in which neoadjuvant Sunitinib permitted a less morbid surgical approach for venous tumor thrombi. Karakiewicz and colleagues reported a patient who refused sternotomy for an 11 cm renal tumor with an atrial thrombus [93]. Following 12 weeks of neoadjuvant Sunitinib, the tumor thrombus had regressed to the infrahepatic IVC (Fig. 24.4a, b). In another report, presurgical Sunitinib was used to shrink a caval thrombus which permitted laparoscopic rather than open cytoreductive nephrectomy [94].

These dramatic responses are not likely typical, and it is clear that not all caval tumor thrombi have gratifying responses to neoadjuvant therapy. Bex et al. described two patients with metastatic disease who were enrolled in a phase II trial of presurgical Sunitinib [95]. Despite treatment with Sunitinib, one patient developed a new caval tumor thrombus despite Sunitinib and the second had growth of an existing infrahepatic thrombus up to the atrium.

In a larger retrospective series, Cost et al. described 25 patients with an RCC tumor thrombus who were treated with targeted therapy [96]. The majority of the patients (76%) had

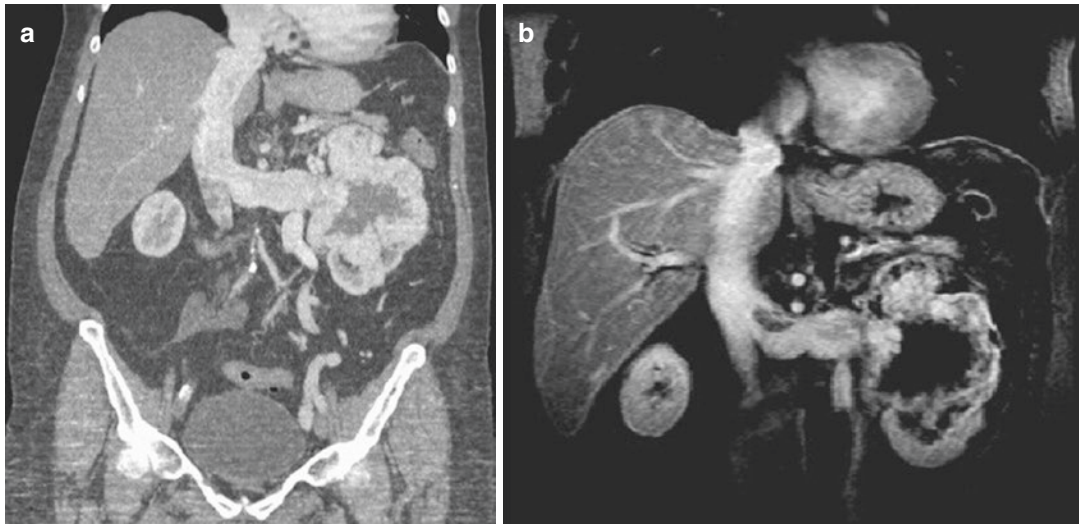

Fig. 24.4 CT scan demonstrating a left-sided RCC with an associated tumor thrombus extending into the right atrium (**a**). The thrombus substantially regressed in response to two cycles of Sunitinib. Following therapy, it is visible as a dark filling defect at the junction of the renal vein and cava (**b**). (Reprinted with permission from Karakiewicz et al. [93])

ccRCC. Not all of the patients were considered surgical candidates. The tumor thrombus was level 2 ($n = 18$), level 3 ($n = 5$), or level 4 ($n = 2$). Systemic therapies were Sunitinib ($n = 12$), Bevacizumab ($n = 9$), Temsirolimus ($n = 3$), and Sorafenib ($n = 1$). In response to systemic therapy, the thrombus regressed in 44% of patients and expanded in 28%. In most patients, the thrombus level did not change. In one patient, the thrombus level increased (level 2–3). The thrombus level decreased in three patients, including one patient with a level 4 thrombus that became level 3. This was the only patient in whom the surgical approach would have been affected. A minority of the patients (36%) went on to radical nephrectomy and tumor thrombectomy. In addition to the retrospective design, other limitations are the heterogeneous patient population and drugs, and that not all patients were surgical candidates.

Neoadjuvant Therapy: Current Status

In summary, rigorous research is needed to determine what role neoadjuvant approaches may have in the management of locally advanced RCC. Little role is anticipated for systemic immunotherapy, which to date has had little impact on the primary tumor [64]. Targeted therapies can affect the primary tumor, but overall the impact with these agents is not robust. The impact of neoadjuvant therapy on resectability, feasibility of partial nephrectomy, and regression of tumor thrombus remains unclear, and this application is investigational.

Integrated Therapy for Metastatic Disease

While treatment of the primary tumor in other metastatic malignancies is usually limited to a palliative role, radical nephrectomy with therapeutic intent has been a core component of the treatment of metastatic RCC [4]. Cytoreductive nephrectomy was established as a treatment paradigm during the immunotherapy era. With the advent of targeted therapy, the ongoing role of cytoreductive nephrectomy remains to be elucidated and has been called into question by the results of CARMENA. In addition, the proper sequence of surgery and systemic therapy is not yet known. Advantages to presurgical systemic therapy in metastatic disease have been proposed and may significantly alter the existing integrated therapy archetype.

Cytoreductive Nephrectomy

During the first immunotherapy era, several findings prompted consideration of cytoreductive nephrectomy as a therapeutic adjunct to systemic therapy. First, immunotherapy appeared to have little or no impact on the primary tumor. Second, it was thought that the primary tumor inhibited immunosurveillance and could act as a source for further metastatic progression [97]. Further, nephrectomy was a favorable, independent prognostic factor in several retrospective immunotherapy series [98–102]. In particular, Motzer et al. created a multivariate model to predict survival by analyzing 670 patients with advanced RCC who were treated from 1975 to 1996. In addition to Karnofsky performance status <80%, lactate dehydrogenase (LDH) >1.5 fold normal, low hemoglobin, and corrected serum calcium >10 mg/dL, absence of nephrectomy was an independent predictor of shorter survival [102].

In 2001, two randomized trials from SWOG and the EORTC firmly established the role of cytoreductive nephrectomy prior to systemic treatment with IFN-∝ in patients with metastatic RCC [103, 104]. In both trials, patients were randomized to cytoreductive nephrectomy followed by IFN-∝ vs. IFN-∝ alone. In both trials, cytoreduction was associated with improved overall survival. In a combined analysis of the two similarly designed trials, cytoreductive nephrectomy followed by IFN-∝ was associated with longer median survival than IFN-∝ alone (13.6 months vs. 7.8 months, $p = 0.002$) [105]. Based on this considerable survival benefit, cytoreductive surgery followed by systemic therapy was confirmed as the principal treatment algorithm for mRCC.

In the combined analysis, there were 253 patients with measurable disease, and the objective response rates in the nephrectomy plus IFN and IFN alone groups were similarly low (6.9% vs. 5.7%, $p = 0.60$) [105]. Without a measurable improvement in metastatic disease, the mechanism of improved survival is unclear. Possibilities include tumoristasis induced by post-nephrectomy azotemia and metabolic acidosis, improved immune surveillance following removal of the immunologic sink, and elimination of a source of growth factors [2, 97].

The Importance of Proper Patient Selection

Cytoreductive nephrectomy is not without risks. Some patients may experience cancer progression during recovery from surgery. In addition, the morbidity of surgery may prevent a subset of patients from receiving the necessary systemic therapy. In addition, surgical convalescence may delay administration of systemic therapy.

Cytoreductive nephrectomy should clearly not be applied to all patients with metastatic RCC. It is essential to note the selection criteria of the SWOG and EORTC trials. In both trials, patients were excluded for ECOG performance status 2 or worse, prior systemic therapy, high-level tumor thrombus, or a primary tumor that was deemed unresectable. Patients with brain metastases were not eligible for the EORTC trial. The results of these trials should not be generalized to all patients with metastatic RCC, such as those with poor performance status.

Retrospective analyses identified clinical variables that were predictive of surgical benefit [4, 97, 106–110]. Good performance status, lack of central nervous system, liver or extensive bone metastases, absence of sarcomatoid or other poor prognosis histology, and debulking of a high fraction of disease were all associated with a favorable response to surgery [4].

In 2010, Culp et al. identified preoperative factors that were prognostic of a favorable response to cytoreductive nephrectomy [111]. In a retrospective analysis, the authors compared cytoreductive nephrectomy patients ($n = 566$) to those managed without cytoreduction ($n = 110$) from 1991 to 2007. The cohort of patients was similar to the ECOG and SWOG studies in that fewer than 3% had ECOG performance status 2 and none had performance status ≥3. There were brain metastases in 3.5%. The authors determined that cytoreductive nephrectomy patients who died within 8.5 months of surgery did not receive a survival benefit from surgery ($p < 0.05$). Independent predictors of inferior overall survival among cytoreductive nephrectomy patients included elevated LDH (HR: 1.66, $p < 0.001$), hypoalbuminemia (HR: 1.59, $p = 0.001$), symptomatic metastases (HR: 1.35, $p = 0.028$), liver

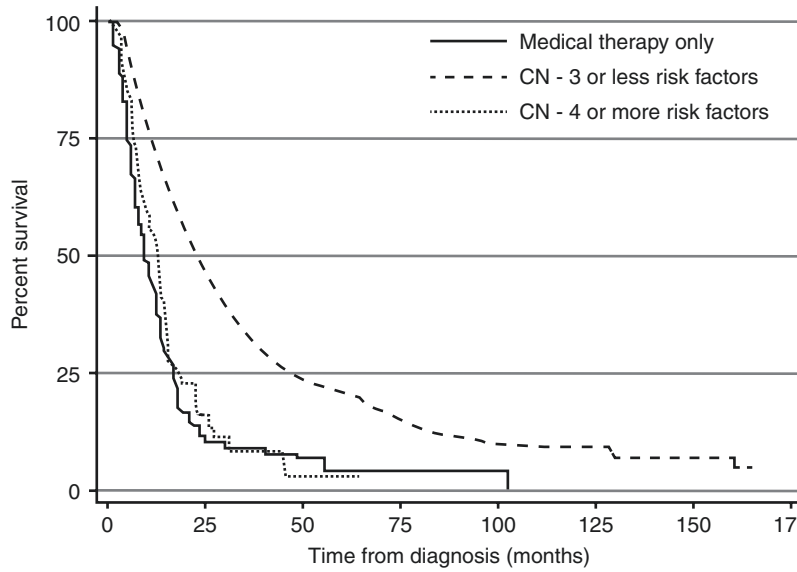

Fig. 24.5 In this Kaplan-Meier curve of overall survival after cytoreductive nephrectomy, survival of patients with four or more risk factors approximates that of patients treated with medical therapy alone. (Reprinted with permission from Culp et al. [111])

metastases (HR: 1.47, $p = 0.039$), retroperitoneal adenopathy (HR: 1.29, $p = 0.040$), supradiaphragmatic adenopathy (HR: 1.48, $p = 0.001$), and clinical T3 (HR: 1.37, $p = 0.045$) or T4 (HR: 2.05, $p = 0.019$) disease. The survival curve of cytoreductive nephrectomy patients with ≥4 of these risk factors overlapped that of patients treated with medical therapy alone (Fig. 24.5). Even in a patient population that largely mirrored that of the SWOG and EORTC trials, not all candidates benefited from cytoreduction.

Targeted Therapy and Cytoreductive Nephrectomy

The benefit observed with cytoreductive nephrectomy may not be intrinsic to the operation but may due to an interaction between the operation and the particular systemic agent employed thereafter. Cytoreductive surgery was established as a pillar of mRCC treatment in concert with early immunotherapy. It is not a foregone conclusion that there should continue to be a role for cytoreduction with targeted therapy or checkpoint inhibition.

Despite a paucity of data, cytoreduction has retained its place in the treatment paradigm in the targeted therapy era. In the Phase III trials demonstrating progression-free or overall survival advantages for Sunitinib, Sorafenib, Temsirolimus, Everolimus, Bevacizumab/IFN-∝-2b, and Bevacizumab/IFN-∝-2a compared to control, the rates of prior nephrectomy in the intervention arms were 91%, 94%, 66%, 96%, 85%, and 100%, respectively [112–117]. The lower rate of nephrectomy in the Temsirolimus trial is explained by the proportion of high-risk patients in that trial [112]. Although commonly employed, the uncertain benefit and potential adverse consequences of surgery have prompted a reevaluation of the paradigm of integrated therapy.

Retrospective studies and subgroup analyses suggest that cytoreductive nephrectomy does provide a survival advantage when followed by targeted therapy [118–120]. A multicenter collaboration reported a retrospective review of 645 patients who were treated with Sunitinib, Sorafenib, or Bevacizumab [119]. Patients who had a nephrectomy for clinically localized disease who later developed metastasis were excluded ($n = 331$). Patients who were treated with a cytoreductive nephrectomy ($n = 201$) were compared to those who were managed without nephrectomy ($n = 113$). Patients who had surgery were younger ($p < 0.01$), less often had poor performance status ($p < 0.01$), more often had >1 metastatic site ($p = 0.04$), less often received targeted therapy within a year of diagnosis ($p < 0.01$), and less often had hypercalcemia ($p < 0.01$). Cytoreductive nephrectomy was

independently associated with better overall survival (HR: 0.68, $p = 0.04$), although the survival benefit was modest in patients with poor performance status and high-risk disease. These results support the continued use of cytoreduction in selected patients [121].

In summary, the Phase III trials that demonstrated the effectiveness of targeted therapeutics largely enrolled patients with prior cytoreductive nephrectomy. Second, while our highest quality data to date is retrospective, it suggests that the addition of cytoreductive nephrectomy to targeted therapy improves survival.

More recently, results of the Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) were reported. CARMENA was a phase III non-inferiority trial comparing cytoreductive therapy and targeted therapy in intermediate to poor-risk patients with metastatic ccRCC and absence of brain metastases. The study randomized 450 patients to Sunitinib alone or cytoreductive nephrectomy followed by Sunitinib. The primary endpoint was overall survival, with secondary endpoints including objective response, progression-free survival, and postoperative morbidity. [122]

After a median follow-up of approximately 50.9 months, sunitinib alone was non-inferior to sunitinib + cytoreductive nephrectomy in regard to overall survival, response rate, or progression-free survival [122]. CARMENA has been criticized for alterations in the study protocol and differences between the study groups. For example, the initial recruitment goal was 576 patients, and the study closed after 450 participants had been included over a period of 8 years for poor accrual. Moreover, 70.1% of the patients in the cytoreductive nephrectomy + sunitinib group had T3 and T4 tumors in comparison to 51% in the sunitinib alone cohort, possibly creating imbalances between the groups.

Similarly, SURTIME trial evaluated immediate vs. deferred cytoreductive nephrectomy in metastatic ccRCC patients receiving sunitinib. The study intended to recruit 458 patients to have adequate power for progression-free survival estimation. However, due to poor accrual, ITT 28-week progression-free rate was assessed for 99 recruited patients showing no difference in immediate vs. deferred cytoreductive nephrectomy (42% vs. 43%, respectively, $p = 0.61$). Considering secondary endpoints in exploratory analysis, deferred cytoreductive nephrectomy group showed an advantage of approximately 17 months in overall survival when compared to immediate surgery (32.4 months for deferred arm vs. 15 months for immediate arm). Of note, 98% of the patients in the deferred arm received sunitinib while only 80% received this medication in the deferred arm. Moreover, 29% of the patients in the deferred arm did not undergo cytoreductive nephrectomy due to disease progression indicating a possible role for presurgical therapy to selecting the right patients who could benefit from the surgical procedure after sunitinib therapy [123].

Treatment Chronology: Upfront Nephrectomy Versus Presurgical Targeted Therapy

The Argument for Presurgical Targeted Therapy

While surgery prior to immunotherapy was accepted as the proper order of therapy, it is not clear that upfront surgery followed by targeted therapy is the best sequence [4, 124]. Investigators have proposed several reasons that presurgical targeted therapy might be beneficial. First, presurgical therapy may decrease RCC-related morbidity prior to surgery [124]. Second, molecular evaluations of post-treatment nephrectomy specimens may elucidate markers of response and resistance [2, 4].

Third, the primary tumor may be more amenable to excision following presurgical targeted therapy. In a retrospective review by van der Veldt et al., three patients with mRCC had unresectable primaries due to suspected liver invasion [74]. Presurgical Sunitinib reduced primary tumor volume by 30–46%, and all were able to have subsequent cytoreductive surgery. Another retrospective analysis included ten patients with mRCC who received Sunitinib with the primary tumor in situ due to uncertain resectability, which

was defined as adjacent organ invasion or involvement of essential vascular structures such as the great vessels, celiac axis, or superior mesenteric artery [125]. There were two partial responses by RECIST. The median change in primary tumor size was −10% (range from −20% to +11%). The tumor site that prohibited surgery shrank in six patients. This happened after 2–4 months of therapy and permitted cytoreductive nephrectomy in three patients. The ability of current agents to downsize complex primary tumors in mRCC patients is limited [2]. Barring the emergence of future therapies that are substantially more effective at downsizing the primary, other benefits will have to be recognized for presurgical therapy to be embraced.

Fourth, presurgical targeted therapy may have a role as a "litmus test" to identify a subset of patients with stable or responsive disease who will most benefit from cytoreductive nephrectomy [4]. Patients with rapidly progressive disease in the face of targeted therapy may not benefit from surgery. Rather than surgery, these patients with an aggressive phenotype would be selected for another systemic therapy [4]. At present, there is only limited data to support the "litmus test" concept. The long-term SWOG trial results demonstrate that disease progression within 90 days independently predicts worse overall survival (HR: 2.1, $p < 0.0001$) [126]. Additionally, there were six patients (12%) in the presurgical Bevacizumab trial who had progressive disease despite presurgical systemic therapy and did not go on to nephrectomy [77]. Despite being switched to alternative systemic therapies, none achieved disease stabilization or response, and it appears that they were spared unnecessary surgery.

The Supporting Evidence

The feasibility of presurgical targeted therapy has been demonstrated in case reports and retrospective series [76, 89, 94, 125, 127–131]. Additionally, the safety and efficacy of presurgical targeted agents has been addressed in several prospective single-arm studies [77, 78, 125, 132].

In the single-arm Phase II presurgical Bevacizumab (with or without Erlotinib) trial, outcomes appeared similar to postsurgical treatment with median progression-free survival of 11.0 months and with median overall survival of 25.4 months. In 2011, results from two single-arm Phase II trials of presurgical Sunitinib in metastatic ccRCC were published by Powles et al., a total of 17 patients (33%) had MSKCC poor-risk disease [132]. The rest had intermediate-risk disease. Patients received two or three cycles of Sunitinib prior to nephrectomy. Median decrease in the primary was 12%. Cytoreductive nephrectomy was undertaken in 37 out of 53 (70%) patients. Patients with disease progression ($n = 9$) did not have surgery. In addition, surgery was not employed in some due to patient preference ($n = 3$) or being unfit for surgery ($n = 2$). It is important to note that no patients became ineligible for surgery due to local progression. At a median of 21 days after surgery, Sunitinib was resumed. Among the 27% rate of complications was a case of postoperative respiratory failure leading to death. The median progression-free survival was 8 months (95% CI: 5–15).

Is Presurgical Therapy Safe?

One argument against presurgical therapy is that it might adversely affect disease biology by increasing invasion, metastasis and resistance [2, 133–135]. Another concern is that wound healing could be impaired by presurgical therapy leading a higher complication rate after cytoreductive nephrectomy [2]. Chapin et al. retrospectively evaluated cytoreductive nephrectomy patients at a single-center from 2004 to 2010 [136]. Patients had received a variety of presurgical targeted agents such as bevacizumab, bevacizumab plus erlotinib, sunitinib, sorafenib, erlotinib, and temsirolimus. Clavien-Dindo complications within 1 year of surgery were assessed for patients who received presurgical systemic therapy ($n = 70$) and those who had immediate cytoreductive nephrectomy ($n = 103$). A total of 99 out of 173 (57%) patients had 232 complications. No increased risk of overall or severe complications (Grade 3 or higher) was noted on multivariable analysis. On the other hand, presurgical targeted therapy was associated with a higher rate of wound complications such as superficial wound dehiscence or infection (HR: 4.14, $p = 0.003$).

Determining the Proper Duration of Presurgical Therapy

The correct duration of presurgical therapy will likely be determined by factors including the particular drug and demonstrated response to therapy. Abel and colleagues retrospectively reviewed a single institution's experience with treating mRCC patients with Sunitinib without prior nephrectomy from 2004 to 2009 [79]. The median maximum change in the size of the primary tumor was −10.2%. The maximum size change was noted after a median of 120 days of therapy. Early tumor response was defined as a ≥10% decrease in size within 60 days. This independently predicted improved overall survival (HR: 0.26, p = 0.031). Since the maximal response in the primary tumor occurs in the first 2–4 months, some have logically concluded that three cycles of presurgical Sunitinib would be adequate [2, 74]. It is nevertheless important to consider that the correct duration of presurgical therapy ultimately may not be dictated by the radiographic response in the primary tumor.

Ongoing or Unreported Presurgical Trials

Presurgical targeted therapy in advanced or metastatic RCC is an active area of research with more than a dozen Phase II trials underway, including evaluations of presurgical Sorafenib, Sunitinib, Everolimus, Pazopanib, and Axitinib [2, 8]. The proper sequence of cytoreduction and systemic targeted has been evaluated by SURTIME. While SURTIME was limited by poor accrual, exploratory analysis could be viewed as supporting deferred cytoreduction.

Integration of Cytoreductive Nephrectomy and Systemic Therapy: Current Status

Clinical data should be used to select the patients most likely to benefit from extirpative surgery. Despite the fact that we have not prospectively demonstrated a survival benefit for cytoreductive nephrectomy in the targeted therapy era, it is likely to remain a standard component of the treatment paradigm, especially for those without poor-risk disease, pending the results of ongoing studies [114–116].

Conclusion

It will be essential to rationally integrate surgery and systemic therapy to improve outcomes in RCC. Despite substantial efforts to date, there is no commonly accepted role for adjuvant therapy following nephrectomy for clinically localized disease, but studies of checkpoint agents are promising. For locally advanced disease, it has been proposed that neoadjuvant therapy may make unresectable disease resectable, enable partial nephrectomy, or shrink venous tumor thrombus. These theoretical goals remain in need of further study. For patients with metastatic RCC, the correct paradigm remains to be elucidated. The role of cytoreductive nephrectomy in the immune checkpoint era will need to be evaluated.

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25 Defining an Individualized Treatment Strategy for Metastatic Renal Cancer

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Over a quarter of renal cell carcinoma (RCC) patients are diagnosed with metastases at the time of initial presentation [1]. Once RCC has metastasized, the chance of durable complete response is low, despite many advances in treatment. Because RCC is traditionally viewed as chemotherapy resistant and radiotherapy resistant, early treatments relied on cytokine therapy, which had low response rates and high levels of treatment-related toxicity. Over the past decade, the armamentarium for treating metastatic RCC (mRCC) has increased greatly with the emergence of targeted therapy directed against angiogenesis, mammalian target of rapamycin (mTOR) pathways, and more recently immune checkpoint pathways.

There are several factors that make treatment of mRCC well suited for an individualized approach. The first is the biologic diversity of the disease. The variability in response rates exemplifies differences in both tumor biology and host response to the tumor and therapy. Second, improvements are being made in the ability to recognize individual clinical and molecular differences in mRCC. Lastly, therapies against mRCC are numerous, allowing for individualized variations in treatment.

This chapter serves to update our previous understanding of RCC biology and the molecular pathways involved in tumorigenesis. Available surgical and systemic therapies as well as risk stratification tools and biomarkers that assist in prognostication and prediction of response are updated. The available data are summarized to guide the selection of systemic therapy and role for surgery toward a more individualized strategy.

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Relevant Biologic Pathways in RCC

Tumor hypoxia is a common feature in solid tumors such as RCC and is associated with poor patient outcomes. Hypoxia is important to tumor progression because it has the potential to limit cell proliferation and differentiation while promoting necrosis and apoptosis [2]. Its presence can also lead to more aggressive tumors with abundant angiogenesis. RCC is a tumor that is

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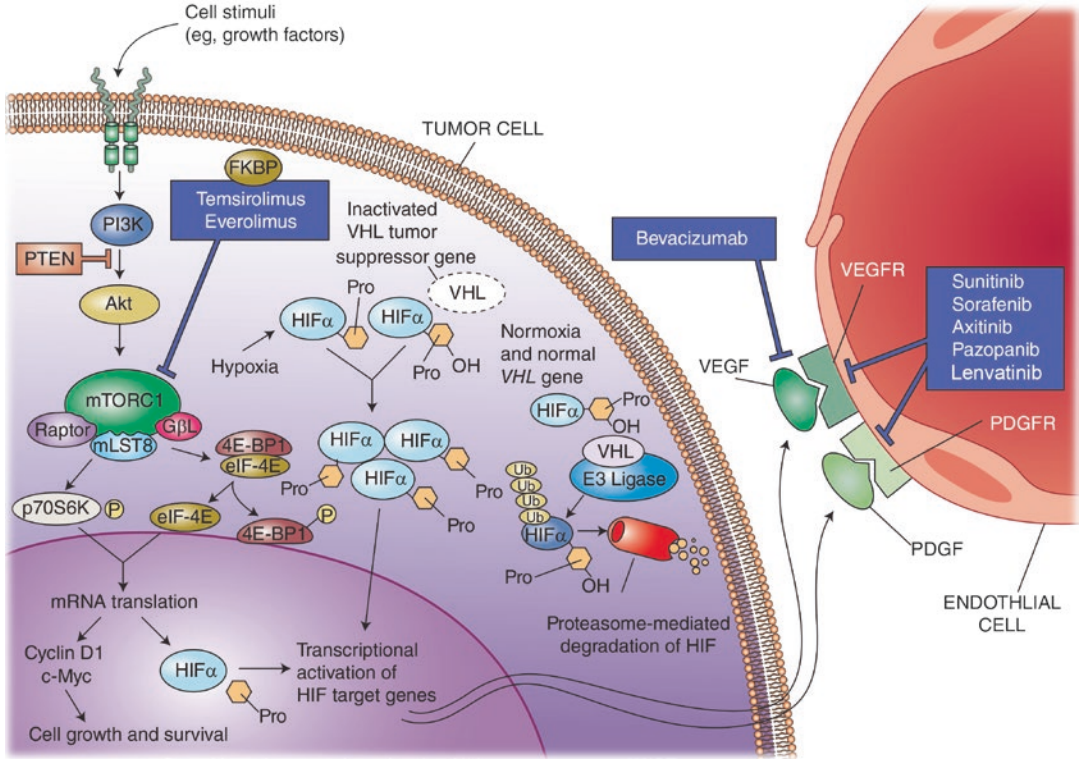

Fig. 25.1 Biologic pathways and therapeutic targets in RCC. (Modified from Rini et al. [3])

known for its marked vascularity, and investigation into its biology has uncovered hypoxia-induced signaling as a main element in tumorigenesis and progression. Figure 25.1 provides an overview of the biologic pathways in RCC [3].

Important in understanding the angiogenesis pathway for RCC is the identification of the von Hippel-Lindau (VHL) gene as a critical modulator of hypoxia-responsive gene elements. VHL is a tumor suppressor gene that encodes for the VHL protein. This protein complexes with cullin 2, elongin B, and elongin C to form the E3 ubiquitin-ligase complex, which targets hypoxia-inducible factors (HIF-1a and HIF-2a) for ubiquitin-mediated degradation by hydroxylation [4–6]. In hypoxic conditions, HIF-1a and HIF-2a do not undergo hydroxylation and act as transcription factors for more than 200 genes [7]. Proteins regulated by HIF include vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) . Mutation of both VHL alleles causes defective complex formation. With an ineffective ubiquitin-ligase complex, HIF levels accumulate and facilitate the transcription of genes involved in angiogenesis, cell survival, and cell proliferation [8].

HIF can receive input from another key cellular pathway: mTOR. This pathway is established as important in the regulation of multiple oncologic processes, such as cell survival and angiogenesis. mTOR is a serine/threonine kinase involved in cell response to energy depletion and hypoxia. mTOR upregulation is implicated in both chemotherapy and radiotherapy resistance [9]. Through immunohistochemical analysis, mTOR has been found upregulated in RCC compared with normal renal tissue [10]. After binding of VEGF, PDGF, or other growth factors to a receptor tyrosine kinase, phosphatidylinositol 3-kinase

(PI3K) is activated. Protein kinase B (Akt) is recruited and able to activate mTOR. mTOR can also activate Akt by phosphorylation. Akt can then inhibit cell apoptosis by inactivating proteins, such as procaspase-9 and AKD1 [8]. mTOR is also able to activate ribosomal protein S6 kinase, which has broad effects on cell physiology and survival. Increased S6 kinase expression is associated with more aggressive RCC [11].

While it has long been known that VHL is a key gene implicated in RCC, recently three other tumor suppressor genes have been found to be frequently mutated in ccRCC, namely polybromo-1 (PBRM1) , BRCA1-associated protein-1 (BAP1), and SET domain-containing 2 (SETD2), all of which are located on the same region of chromosome 3p which also includes VHL [12, 13]. PBRM1 is a chromatin remodeling complex gene, while SETD2 plays a role in chromatic structure and transcriptional control, suggesting that chromatin regulation may play a vital role in tumorigenesis in RCC.

Another recent insight in the pathophysiology of RCC involves a better understanding of the tumor immunity. It has long been appreciated that RCC can dysregulate host antitumor immunity [14, 15]. In more recent years, specific T-cell costimulatory molecules have been discovered to be negative regulators of antitumor immunity [16]. These costimulatory molecules include programmed death protein 1 (PD-1) and programmed death ligand 1 (PD-L1) as well as cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and are currently classified together as immune checkpoints. Both CTLA4 and PD1 are expressed on T cells, while PD-L1 is expressed on antigen-presenting cells, including tumor cells [17]. CTLA4 regulates T-cell activation, while PD1 primarily appears to regulate T-cell activity in the tumor microenvironment. PD-L1 is a ligand for PD-1 and has demonstrated aberrant expression in RCC [18]. Further, the overexpression of PD-L1 has been demonstrated an association with poor prognosis [18].

Prognostication

Risk stratification has emerged as an important clinical instrument for prognostication, designing of clinical trials, and selecting appropriate therapies. Risk criteria for mRCC were developed by Motzer and colleagues at Memorial Sloan Kettering Cancer Center (MSKCC) [19]. Five risk factors were identified as most prognostic in survival: low performance status, high lactate dehydrogenase, low serum hemoglobin, high corrected serum calcium, and time from initial RCC diagnosis to start of systemic therapy of less than 1 year. Patients with none of these risk factors are categorized as good risk, those with one or two risk factors have intermediate risk, and those with three or more risk factors are categorized as poor risk. In a study examining these criteria in patients undergoing treatment with interferon-α, median survival was 30 months in the good-risk group, 14 months in the intermediate-risk group, and 5 months in the poor-risk group.

The MSKCC criteria have been externally validated and additional predictors of survival elucidated [20]. A study of treatment-naïve patients with mRCC enrolled in clinical trials found prior radiotherapy and presence of liver, lung, and retroperitoneal nodal metastases as independent predictors of survival [20]. Another notable clinical prognostic approach, the University of California Los Angeles (UCLA) Integrated Staging System, uses TNM staging, ECOG performance status, and Fuhrman grade. This system has also been validated as associated with survival [21].

In the modern therapeutic era, prognostic factors for OS in patients treated with VEGF-targeted therapy were examined by Heng and colleagues which ultimately led to the development of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria [22]. There was agreement with four MSKCC criteria associated with worse survival: anemia, hypercalcemia, Karnofsky performance scale status (KPS) less than 80%, and time from diagnosis to treatment of less than 1 year. However, neutrophilia and thrombocytosis were identified

as additional adverse prognostic factors. Of these six factors, patients were divided into risk categories: good (no prognostic factors), intermediate (1–2 prognostic factors), and poor (3–6 prognostic factors). Two-year OS rate was 75%, 53%, and 7%, respectively. These findings were externally validated in a separate cohort. Median overall survival was 35.3, 16.6, and 5.4 months, respectively. Similar trends were seen in prognosis when receiving second-line targeted therapy [23]. As such, the IMDC criteria have largely supplanted former models and are now used in the design of prospective clinical trials.

Overview of Treatments of mRCC

Surgery

Despite mRCC being a systemic disease, surgery continues to play a role in its optimal treatment. Traditionally, nephrectomy was reserved for palliation in patients with symptoms of pain or bleeding. Given the lack of effective systemic therapy, many patients underwent cytoreductive nephrectomy (CN) with the presumption that removing a large portion of the tumor burden would improve response to systemic therapy. Although rare, spontaneous regression of metastases was seen after CN, indicating a beneficial biologic response to the surgery [24]. This most commonly occurred in patients with limited pulmonary metastases. There are hypotheses for CN improving survival, the most prominent that the primary tumor suppresses the activation of T cells [25]. By removing this suppression, the immune system has greater activity against sites of metastasis. Another possible mechanism is the beneficial removal of cells that produce tumor-related growth factors that result in abnormal signaling pathways [26].

Early experience with CN showed that morbidity from surgery precluded many patients from receiving immunotherapy. One study found that in patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ranging from 0 to 2, only 23% were able to undergo immunotherapy after CN [27]. This pattern of treatment called into question the benefit of CN. Subsequently, two randomized trials have compared survival after CN plus interferon-α versus interferon-α alone. The Southwest Oncology Group (SWOG) trial, which included 120 patients from 1991 to 1998, found that CN was associated with a statistically significant 3-month survival advantage (11.1 vs. 8.1 months) [28]. The European Organisation for Research and Treatment of Cancer (EORTC) study, which randomized 85 patients from 1995 and 1998, reported a median survival benefit of 10 months associated with CN (17 vs. 7 months) [29]. A combined analysis of the two trials found CN was associated with a 6-month median survival benefit (13.6 vs. 7.8 months) [30]. The benefit of CN was more pronounced in patients with PS0 (17.6 vs. 11.7 months) as compared with PS1 (6.9 vs. 4.8 months).

Since there were previously no randomized data that evaluated CN with systemic targeted therapy, two important trials have led to a reevaluation of the role of CN in that context. The first trial, the EORTC SURTIME, compared treating patients with sunitinib followed by CN to CN followed by sunitinib. The trial closed early in 2016 due to poor accrual, and though it was underpowered, the intention-to-treat (ITT) analysis did favor deferral of CN [31]. The other recent non-inferiority trial, CARMENA, which was conducted in France, randomized patients with intermediate- or poor-risk disease per MSKCC criteria to either CN followed by sunitinib or sunitinib alone [32]. This trial also did not meet its accrual goal but did meet non-inferiority criteria statistically for the ITT cohort (but not for the per-protocol cohort of patients who received the actual treatment assignment; in that analysis, results were inconclusive). In the ITT population, overall survival favored the sunitinib-only group compared to CN followed by sunitinib (18.4 vs. 13.9 months). Seventeen percent of patients in the sunitinib-only arm did go on to receive a palliative nephrectomy. Of note, 44% of patients in the CN followed by sunitinib arm and 42% of patients in the sunitinib-only arm were poor-risk patients. For these patients, delay of systemic therapy is generally held to

portend poor outcomes. The results of these trials should not exclude nephrectomy as a crucial part of mRCC treatment but rather highlight the importance of careful patient selection to identify those most likely to benefit from CN.

Metastasectomy for RCC was described in 1939 in a patient who lived 23 years after surgery, ultimately dying of coronary artery disease [33]. In the absence of effective systemic therapy, metastasectomy was thought a reasonable approach to controlling systemic disease in select patients. Multiple studies have demonstrated favorable survival in select patients after judicious metastasectomy, with 5-year survival rates ranging from 35% to 60% [34–36]. There are important caveats, however, to metastasectomy. First, it is unclear what extent indolent cancer biology contributes to improved survival. Also, the role of metastasectomy in the targeted therapy era has yet to be clearly defined. There are no prospective or randomized data that can accurately determine the survival impact of metastasectomy. However, systematic reviews and meta-analyses on the current data regarding metastasectomy suggest that complete metastasectomy has better OS and cancer-specific survival as well as local control benefits than those treated with either incomplete or no metastasectomy [37, 38]. Beneficial considerations include longer time from diagnosis to presentation of metastasis, low-volume metastatic burden, and pulmonary-only metastatic spread. Despite limitations in available data and the potential for additional morbidity with surgery, metastasectomy remains a viable option in highly selected patients with mRCC.

Systemic Therapy

The first therapies that showed promise in the treatment of mRCC were cytokines. The cytokines interferon-α and interleukin (IL)-2 are generally associated with low rates of response and high levels of toxicity. Interferon-α has a complete response (CR) rate of 2.5% and a partial response (PR) rate of 26% [34, 35]. IL-2 has a CR rate of approximately 5–7% and a 15–20% overall response rate (ORR) [39]. In the past, high-dose IL-2 has been associated with treatment mortality as high as 4%. Better patient selection and supportive care have helped mitigate many of these toxicities, but these treatment modalities must be employed by practitioners who are well-versed in managing the often serious adverse effects of therapy. A retrospective evaluation of data from 89 patients from UCLA who had been treated with IL-2 after undergoing CN and 120 patients from SWOG8949 who received interferon-α after CN found median OS of CN with IL-2 to be 16.7 months, 5 months longer than CN plus interferon-α. The 5-year survival rates were 19.6% for CN plus IL-2 compared to 10% for CN plus interferon-α. Survival in the control arms were similar [40]. This along with higher complete response rates led to the uptake of IL-2 as the cytokine of choice in this setting.

Unlike cytokine approaches, targeted therapy was developed to offer more specific sites of action and less toxicity (see Fig. 25.1). Tyrosine kinase inhibitors (TKI) that target angiogenesis pathways include sunitinib, sorafenib, pazopanib, axitinib, lenvatinib, and cabozantinib; they have shown an improvement in either overall survival (OS) or progression-free survival (PFS) in various mRCC patient contexts (see Table 25.1).

In a randomized Phase 3 study, sunitinib improved PFS compared to interferon-α in treatment-naïve patients (11 vs. 5 months) [41]. Sorafenib as first-line therapy was found to have similar PFS compared with interferon-α in a Phase 2 study. Sorafenib, however, had superior tumor control compared with interferon-α as well as a benefit in PFS in those who underwent dose escalation or crossover from interferon-α [42, 43]. Sorafenib as second-line therapy has been shown to significantly improve PFS compared with placebo (5.5 vs. 2.8 months) [44]. Pazopanib has been shown to improve PFS in treatment-naïve and cytokine-treated patients compared with placebo in a Phase 3 trial (9.2 vs. 4.2 months) [45]. Axitinib, a second-generation TKI with more potent VEGF inhibition, has been evaluated as a second-line treatment of mRCC with longer PFS compared with sorafenib (8.5 vs. 5.7 months) [46, 47]. Cabozantinib, a multikinase inhibitor

Table 25.1 Key VEGF therapy clinical trials

Investigational therapy	Prior treatment	Phase/trial name	Comparator	Primary outcome	Comments
Sunitinib	Treatment-naïve	3	Interferon-α	PFS: 11 vs. 5 months	
Sorafenib	Treatment-naïve	2	Interferon-α	PFS: no statistical benefit (5.7 vs. 5.6 months)	Superior tumor reduction and PFS benefit in dose-escalation and interferon-α crossover cohort
Sorafenib	1 prior cytokine	3/TARGET	Placebo	PFS: 5.5 vs. 2.8 months	In further follow-up, OS benefit not seen in ITT analysis, but was seen in per-protocol analysis (17.8 vs. 14.3 months)
Pazopanib	1 prior cytokine	3/VEG105192	Placebo	PFS: 9.2 vs. 4.2 months	
Pazopanib	Treatment-naïve	3/COMPARZ	Sunitinib	PFS: non-inferior	Suggestion of better QOL in pazopanib
Axitinib	1 prior VEGF, MTOR or cytokine therapy	3/AXIS	Sorafenib	PFS: 8.3 vs. 5.7 months	No OS benefit seen in follow-up though PFS maintained
Cabozantinib	At least 1 prior VEGF TKI; no prior mTOR or cabozantinib	3/METEOR	Everolimus	PFS: 7.4 vs. 3.8 months	In follow-up, OS benefit (21.4 vs. 16.5 months) also seen
Cabozantinib	Treatment-naïve	2/CABOSUN	Sunitinib	PFS: 8.2 vs. 5.6 months	Studied only IMDC intermediate- and poor-risk patients only
Lenvatinib, lenvatinib plus everolimus	Prior VEGF therapy (no prior lenvatinib or mTOR), cytokine therapy allowed	2	Everolimus	PFS: lenvatinib alone 7.4 vs. 5.5 months. Lenvatinib plus everolimus 14.6 vs. 5.5 months	Did not meet statistically significant benefit when lenvatinib plus everolimus compared to lenvatinib alone
Bevacizumab plus interferon-α	Treatment-naïve	3/AVOREN	Placebo plus interferon-α	OS: not superior (23.3 vs. 21.3 months)	Study stopped early with plan for PFS to be sufficient endpoint which was superior: 10.2 vs. 5.4 months
Bevacizumab plus interferon-α	Treatment-naïve	3/ CALGB90206	Placebo plus interferon-α	OS: not superior (18.3 vs. 17.4 months)	PFS was superior: 8.5 vs. 5.2 months

targeting VEGFR, MET, and AXL, demonstrated longer PFS compared to everolimus in previously treated patients (7.4 vs. 3.8 months) and ultimately an OS benefit (21.4 vs. 16.5 months) in a Phase 3 trial called METEOR [48, 49]. In a randomized Phase 2 study of patients with treatment-naïve intermediate to poor-risk mRCC, with risk defined by the IMDC, cabozantinib significantly prolonged PFS compared to sunitinib (8.2 vs. 5.6 months) [50]. Lenvatinib, a multikinase inhibitor with targets including VEGFR, demonstrated an improved PFS benefit alone or when combined with everolimus as compared to everolimus alone (7.4 vs. 14.6 vs. 5.5 months) in patients with previously treated mRCC in a randomized Phase 2 trial [51].

Another type of therapy targeting the VEGF receptor is bevacizumab, a monoclonal antibody against VEGF. One randomized, double-blind, Phase 3 trial compared bevacizumab plus interferon-α to interferon-α plus placebo in treatment-naïve patients. This study reported that bevacizumab plus interferon-α significantly improved PFS compared with the control group (10.2 vs. 5.4 months) but did not significantly improve OS in later follow-up [52, 53]. Another similar Phase 3 study resulted in the same outcome [54].

Temsirolimus and everolimus act by inhibiting mTOR and are approved for the treatment of mRCC after the results of large Phase 3 registration studies. Temsirolimus was evaluated in a multicenter, Phase 3, randomized trial of temsirolimus plus interferon-α in treatment-naïve, poor-risk patients that included 20% with non-clear cell histology [55]. The trial reported that temsirolimus significantly improved PFS (5.5 vs. 3.1 months) and OS (10.9 vs. 7.3 months) compared with interferon-α. Everolimus was tested in a randomized, double-blind, placebo-controlled crossover trial as second-line therapy in patients who had progressed on tyrosine kinase inhibitors of VEGF receptor, such as sunitinib and/or sorafenib [56, 57]. Everolimus was shown to significantly prolong PFS (4.0 vs. 1.9 months).

Immune checkpoint inhibitor therapy now has proven efficacy in mRCC. In a Phase 3 study, nivolumab, an inhibitor of PD-1, was compared to everolimus in patients who had previously received TKI therapy, and extended OS (25 vs. 19.6 months) though PFS was similar [58]. Subsequently, a great deal of interest has developed in combination immune therapy. Most notably, nivolumab combined with ipilimumab, an antibody targeting CTLA4, demonstrated superior PFS (11.6 vs. 8.4 months) and OS (not reached vs. 26 months) compared to sunitinibin a Phase 3 study of treatment naïve patients of intermediate or poor risk by IMDC criteria [59]. Another promising combination has been that of bevacizumab with atezolizumab, a PD-L1 inhibitor, compared to sunitinib in the Phase 3 IMmotion 151 study, demonstrating a significantly prolonged PFS (11.2 vs. 8.4 months) in the intention-to-treat therapy-naïve patients, and demonstrated an even better PFS in the primary endpoint population of patients whose tumors have positive PD-L1 expression (11.2 vs. 7.7 months) [60]. While currently nivolumab and the combination of nivolumab plus ipilimumab have been approved by the FDA, a number of other combination studies are currently ongoing, which may provide further options for treatment.

Molecular Biomarkers

Immune Checkpoint Inhibitor Therapy

While PBRM1 mutations have been shown to potentially correlate to lower grade tumors, a recent study examined whole-exome sequencing in the tumors of 35 patients with metastatic ccRCC [61]. PBRM1 mutations, which were found in about 40% of tumors, were significantly associated with a response to nivolumab. These results were validated in an independent cohort of 63 patients treated with either nivolumab or atezolizumab.

In addition, another study utilized tumor xenografts to evaluate the tumor microenvironment, determining by RNA-sequencing data two distinct immune signatures, an inflamed subtype and a non-inflamed subtype [62]. The inflamed subtype correlated with thrombocytosis, anemia, and poor survival. The inflamed subtype was also seen more frequently in tumors with BAP1 mutations as well as papillary type 2 subtypes. Further investigation may lead to identifying a correlation to systemic responses to immune checkpoint inhibitor therapy based on the tumor microenvironment.

The most developed predictive marker at this point remains PD-L1 status by immunohistochemical (IHC) stain, but its role in individualized management is not yet established in mRCC. In the IMmotion 150 Phase 2 trial that compared the combination of atezolizumab plus bevacizumab to atezolizumab

alone or to sunitinib alone, PD-L1 status was scored as positive if ≥1%, negative if <1% [63]. In that study, no difference was seen in PFS in an intention-to-treat analysis, but PD-L1+ patients had a trend toward better PFS when treated with atezolizumab plus bevacizumab or atezolizumab. The subsequent IMmotion 151 Phase 3 study evaluated the combination of atezolizumab plus bevacizumab versus sunitinib in mRCC and showed a higher PFS in patients whose tumor specimens had positive PD-L1 expression [60].

The role of PD-L1 as a biomarker for nivolumab therapy has been explored. The Checkmate-025 trial evaluating nivolumab versus everolimus assessed PD-L1 expression as ≥1% vs. <1%, or as ≥5% vs. <5% [58]. With either of these definitions of PD-L1 status, positive status did not predict response in that study. The Checkmate-214 trial testing nivolumab plus ipilimumab versus sunitinib did show that, among intermediate- to poor-risk patients, PD-L1 expression ≥1% correlated to a longer OS with immune checkpoint inhibitor therapy [59]. More recently, the Keynote-427 study, a single arm study evaluating pembrolizumab in therapy-naïve mRCC patients, demonstrated a higher ORR based on PD-L1 expression – 50% for those with ≥1% expression and 26% for those without PD-L1 expression [64].

mTOR Inhibitors

While there remain no validated predictive biomarkers insofar as response to mTOR inhibitors is concerned, recently tumor DNA from a cohort of mRCC patients treated with mTOR inhibitors was analyzed using next-generation sequencing [65]. In this study, MTOR, TSC1, and TSC2 mutations were more commonly seen in responders. Still, about half of the patients who did respond to mTOR therapy had no mTOR pathway mutation identified. Thus, more work remains to identify correlates to this therapy.

Treatment Paradigm Based on Individualized Factors

Metastatic RCC is a complex disease with increasing treatment options and stages of presentation. This discussion assists in developing a treatment paradigm for mRCC based on individual clinical factors. Figures 25.2, 25.3, and 25.4 provide algorithms for selecting treatment in patients with mRCC with a primary tumor, systemic treatment naïve, and failed first-line therapy.

Patient Selection for Cytoreductive Nephrectomy

It is now clear that not all patients with mRCC benefit from CN. Poor patient selection can result in overtreatment and limit patients' candidacy for systemic therapy, which the CARMENA and SURTIME studies reiterate [31, 32]. Performance status is perhaps the most important factor when considering a patient's candidacy for CN. The earlier SWOG and EORTC studies found that favorable performance status was an independent predictor of survival [28, 29]. Benefit to CN was seen in patients with an ECOG performance status of 0 or 1. Considering that no randomized CN studies have included those with performance status of 2 or 3, it is unclear if this population receives benefit from CN. It is generally regarded that patients with poor performance status have limited survival based more on cancer biology. This is illustrated by 20–25% of patients in all arms of the earlier SWOG and EORTC trials experiencing rapid progression and death within 4 months. Additionally, a subgroup analysis of patients treated with temsirolimus versus interferon-α found that survival in poor-risk patients was not associated with nephrectomy status [66]. These findings indicate that CN should be used judiciously, if at all, in patients with poor performance status.

Besides performance status, clinical factors to consider when judging candidacy for CN include the amount of metastatic disease, organs of

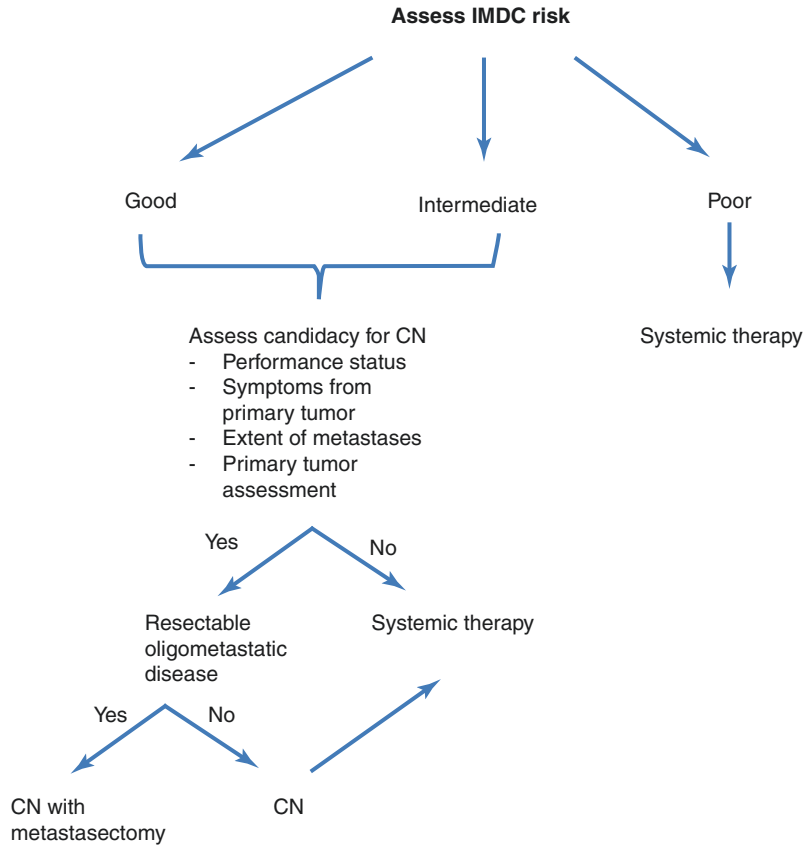

Fig. 25.2 Approach to newly diagnosed patient with metastatic RCC

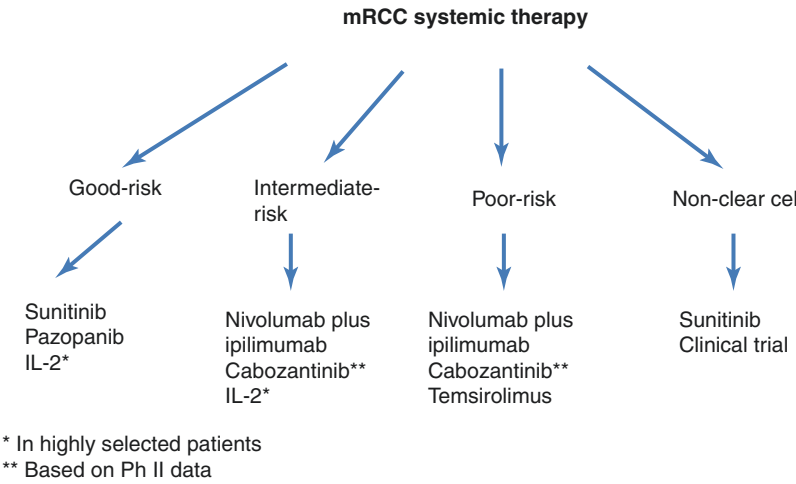

Fig. 25.3 2018 Algorithm for systemic treatment of newly diagnosed metastatic RCC

metastasis, and symptoms from the primary tumor. Minimal disease burden and lung-only metastases have been thought to portend a better prognosis. The SWOG study found lung-only metastases significantly associated with improved survival. The combined analysis of the randomized trials, however, did not find disease burden or sites of metastases predictive of survival [30]. Symptoms from the primary tumor, such as bleeding or pain, are important to consider

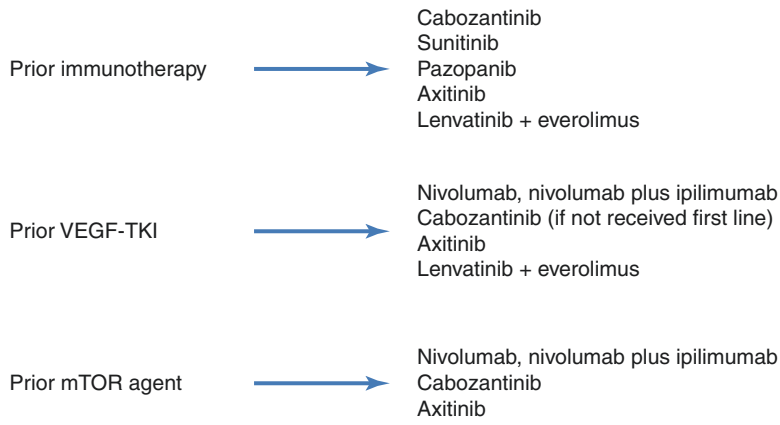

Fig. 25.4 2018 Algorithm for second-line treatment of metastatic RCC

		Nephrectomy: immunotherapy planned		Nephrectomy: targeted therapy planned	
		Metastatic burden		Metastatic burden	
		Limited	Extensive	Limited	Extensive
Good surgical risk	With symptoms related to primary tumor	Appropriate	Appropriate		Uncertain
	Without symptoms related to primary tumor		Uncertain		
Poor surgical risk	With symptoms related to primary tumor	Uncertain			
	Without symptoms related to primary tumor		Inappropriate		

Fig. 25.5 Appropriateness ratings are shown for CN in patients with mRCC with primary tumor in situ who did not receive primary immunotherapy. The boxes are labeled as an appropriate rating, uncertain rating (disagreement among panelists), and inappropriate rating. (Modified from Halbert et al. [67])

because surgery can alleviate these. Paraneoplastic syndromes can be treated with nephrectomy, though it is unclear if CN without metastasectomy is effective in mRCC.

Given the often difficult decision of selecting patients for CN, consensus opinions have been drawn from medical oncologists and urologists regarding its appropriateness [67]. After an extensive literature review, an expert panel rated CN as appropriate, uncertain, and inappropriate in different clinical settings (Fig. 25.5). In patients with good surgical risk, symptoms related to the primary tumor and limited metastatic burden, the panel thought that CN is appropriate if targeted therapy is planned. If cytokine therapy is planned, the appropriateness of CN is extended to symptomatic patients with extensive metastasis or asymptomatic patients with limited disease. In patients who are poor surgical risk and asymptomatic from the primary tumor, CN is thought inappropriate in most cases. While these criteria have not recently been updated, they do provide a useful framework. In a patient with good performance status and good surgical risk, CN may, for example, still be considered prior to the initiation of targeted therapy, though the recent results of CARMENA or SURTIME must inform the decision as well. The most recently updated guidelines from the EAU recommend CN for patients with good ECOG PS (0–1), large primary tumors, and low metastatic volume, but recommend against CN for patients with poor PS or intermediate- to poor-risk disease, small primary tumors, large metastatic burden, or sarcomatoid tumors [68].

Another useful paradigm involves the identification of preoperative risk factors predictive of better outcomes. A retrospective evaluation of 666 patients who had received either CN and medical therapy or medical therapy alone identified seven preoperative factors that correlate to OS: elevated LDH, decreased albumin, symp-

tomatic metastases, liver metastases, retroperitoneal metastases, supradiaphragmatic metastases, and stage T3 or above [69]. Patients with ≥4 of these factors did not benefit from CN when compared to patients with ≤3 factors.

Timing of Cytoreductive Nephrectomy

The knowledge that certain patients experience rapid progression despite surgery led to the use of up-front systemic therapy to determine patients who will benefit from CN. Bex and colleagues examined 16 patients with mRCC treated initially with two courses of IL-2 and interferon-α [70]. Five of the patients progressed and were not offered surgery. The remaining underwent CN followed by additional immunotherapy with a mean OS of 11.5 months, results comparable to the survival in the CN arms in the SWOG and EORTC trials. This demonstrated that cytokine therapy may safely be used to select the subset of patients unlikely to benefit from surgery, saving them the morbidity of surgery.

The results of SURTIME and CARMENA trials indicate that, for patients with intermediate- and poor-risk disease, CN can be safely deferred if a patients' candidacy is questionable. In the CARMENA trial, 17% of patients did go on to have a nephrectomy after initial sunitinib therapy, indicating that a patient could still benefit from nephrectomy after initial targeted therapy. In the SURTIME trial, in which deferred CN was part of the study design, 83% of patients in the arm treated first with sunitinib went on to have CN, with fewer patients having surgical complications than in the arm of patients undergoing CN first.

Patient Selection for Metastasectomy

The main factor that portends favorable outcomes after metastasectomy is a disease-free interval greater than 12 months from treatment of the primary tumor to metastasis. Other important factors are number of metastases, the ability of complete resection, and the sites of metastases. Thus, these are the most important considerations in determining whether a patient should undergo metastasectomy. The importance of complete resection is shown in a retrospective study of 887 patients [71]. All patients had multiples sites of metastasis and 14% were able to undergo complete surgical resection of all metastases. Complete resection was associated with a longer cancer-specific survival (4.8 vs. 1.3 years) and was particularly beneficial in patients with lung-only metastases. Patients with multiple metastases involving organs other than the lung still benefited from complete resection. Additionally, the benefit of metastasectomy was seen for both synchronous and metachronous metastases.

A study by Kavolius and colleagues reported lung metastases, solitary metastases, and age less than 60 independently predictive of improved survival with metastasectomy [72]. Another study found good-risk stratification by MSKCC criteria and undergoing metastasectomy independently associated with improved survival [73]. Metastasectomy was found beneficial to patients in all risk categories.

Patient Selection for Systemic Therapy

In recent years, it has become increasingly clear that clinical risk characterization as well as histologic subtype plays a role in optimizing systemic mRCC therapy. Thus, this discussion proposes an individualized approach accordingly.

Treatment-Naïve Good-Risk Patients

IL-2 and interferon-α, although largely supplanted by targeted therapy and immune checkpoint inhibitor therapy due to the potential toxicity associated with these cytokine-based treatments, still have a role in the treatment of mRCC in highly selected patients. In particular, in the studies establishing IL-2 as a treatment, patients were largely limited to those with excellent performance status, and thus it could be proposed that IL-2 could still be considered in the treatment of mRCC patients with good-risk disease characterized by either MSKCC or IMDC criteria. Based on the results of the Checkmate-214 trial, sunitinib (or perhaps more

broadly, VEGF-R TKI) use is favored in patients with good-risk disease compared to nivolumab plus ipilimumab. Given previous data that indicate pazopanib is non-inferior to sunitinib, good-risk patients could be reasonably treated with either sunitinib or pazopanib [70]. If a patient does have PD-L1 positive staining tumor, the combination of atezolizumab plus bevacizumab could be considered based on IMmotion 151 trial results, although it should be noted that this regimen has not yet been approved by the FDA.

Treatment-Naïve Intermediate-Risk and Poor-Risk Patients

The results of the Checkmate-214 trial indicate an overall survival advantage to the use of nivolumab plus ipilimumab in treatment-naïve patients with intermediate- and poor-risk mRCC, and thus it should be considered as first-line therapy for these patients. As noted among good-risk patients, patients with PD-L1 positivity can be considered for treatment with atezolizumab plus bevacizumab. The results of the CABOSUN trial, albeit a randomized Phase 2 trial, indicate superiority of cabozantinib to sunitinib in treatment-naive intermediate- and poor-risk mRCC patients [50]. Thus cabozantinib can be considered in the first-line setting as well.

The Phase 3 trial establishing the efficacy of temsirolimus in the first-line setting primarily enrolled patients with poor-risk mRCC [55]. Thus, temsirolimus can be considered, although based on most recent data, this would be an option utilized more in patients who might have a contraindication to the use of combination immune checkpoint inhibitor therapy, such as an active autoimmune disease.

Patient Selection for Second-Line Therapy and Beyond

After progression on first-line therapy, clinical risk stratification becomes less important in decision-making; rather, prior systemic therapy is the most important factor. Patients who have only been treated with IL-2 should be treated with a similar paradigm to those who are therapy naive. Because the use of nivolumab combined with ipilimumab has only recently been adopted, little is known regarding the sequence of therapies subsequent to exposure to immune checkpoint inhibitor therapy. However, small retrospective studies indicate that VEGF TKIs can have efficacy after exposure to anti-PD-1 therapy [74]. Thus, for patients who have progressed on nivolumab plus ipilimumab, VEGF TKIs that would be considered in first-line treatment should be utilized.

For patients who have progressed after TKI therapy, axitinib has demonstrated improved PFS compared with sorafenib [47]. Cabozantinib is associated with improved PFS and OS compared to everolimus in VEGF-TKI pre-treated patients, as well [48]. The combination of lenvatinib with everolimus was also found to improve PFS when compared to everolimus alone in this patient population [51]. Nivolumab was also studied in patients who had progressed on VEGF-TKI and demonstrated an OS benefit compared to everolimus, and thus it should also be strongly considered for treatment in the second-line setting [58]. An argument can be made for using combined nivolumab and ipilimumab due to its efficacy in the first-line setting, but this regimen has yet to be formally examined in the Phase 3 context after progression on initial therapy.

Experience is limited regarding the optimal second-line treatment after temsirolimus in the first-line setting, but currently, patients are treated with second-line VEGF TKIs such as cabozantinib or axitinib or with nivolumab. Again, nivolumab and ipilimumab in combination may be considered.

As a result of the trials establishing superior efficacy of cabozantinib and nivolumab, everolimus has largely been relegated to the third-line (and beyond) setting but remains an option for patients who had not received an mTOR inhibitor previously.

Systemic Treatment Considerations Based on Histology

Non-clear cell RCC (nccRCC) represents far fewer cases than clear cell subtype and represents a heterogeneous collection of histologic subtypes with distinct molecular characteristics. These

patients have largely been excluded or underrepresented in clinical trials evaluating systemic therapy, leading to challenges in developing a management strategy. Because of emerging data that molecular drivers such as MET mutations may play a role in treatment, clinical trial enrollment is by far the best choice for therapy for these patients if one is available to them.

There were two small, randomized Phase 2 trials comparing sunitinib to everolimus in patients with nccRCC, one studying nccRCC patients specifically while the other enrolled all patients with mRCC and performed a post hoc subgroup analysis of nccRCC patients [75, 76]. Both suggested an OS and PFS benefit to sunitinib compared to everolimus in these patients. Thus, sunitinib should be strongly considered as initial therapy in patients with nccRCC, while mTOR inhibitors do appear to have activity and thus can be utilized in the TKI-refractory setting. The trials establishing the efficacy of nivolumab and nivolumab plus ipilimumab in mRCC excluded nccRCC patients [58, 59]. However, a small retrospective evaluation did show that patients with nccRCC who received nivolumab did have responses to therapy on par with clear cell disease [77]. Thus, more studies are required to establish the use of nivolumab (with or without ipilimumab) in nccRCC patients.

Future of Individualized Therapy

As the biology of mRCC is better understood and more therapies are developed, identifying patients based mainly on histology is shifting to focus on other factors. Our current understanding of mRCC indicates that patients respond differently to some therapies based on their clinical risk stratification. More clinical data are expected evaluating the combination of immune checkpoint inhibition therapy with other agents, and thus treatment paradigms are likely to continue to shift in the near future. Emerging data indicate that the tumor immune microenvironment, namely PD-L1 status, plays a role in predicting response to immune checkpoint inhibitor therapy. The field remains on the brink of identifying other molecular biomarkers that are validated to correlate to response. Given the complexity and heterogeneous nature of mRCC, individualized care continues to hold promise for selecting the therapy most likely to translate to clinical benefit.

Summary

Treatment of mRCC has changed dramatically and is moving toward a more individualized strategy. This strategy relies on multiple factors for prognostication and prediction of response that include clinical, pathologic, and molecular markers. Great strides have been made in identifying types of therapies that have good efficacy in certain subsets of patients. A validated marker that accurately predicts treatment failure or success, however, is still lacking. Further research to elucidate the molecular changes of mRCC induced by treatment and the host is necessary.

mRCC exhibits tremendous genetic, biologic, and clinical diversity:

- The goal of individualized care is to provide the potential for optimal efficacy while limiting morbidity.
- Better understanding of molecular pathways can lead to diagnosing the key aberrant pathways in patients with mRCC.
- Some biomarkers may help in prognostication and may soon predict response to treatment.
- Currently, there are no validated markers that can accurately predict treatment success or failure.
- An individualized treatment strategy of RCC is approaching, although further research is required to validate biomarkers and further elucidate the molecular changes induced by treatment and host immune responses.

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