John A. Libertino
Editor

Renal Cancer

Contemporary Management

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Epidemiology, Screening, and Clinical Staging

1

Michael J. Lipsky, Christopher M. Deibert, and James M. McKiernan

Epidemiology

Worldwide, kidney tumors account for 2 % of all newly diagnosed malignancies with approximately 271,000 new cases diagnosed annually. In addition, 116,000 deaths were attributed to kidney cancer globally in 2008 [1]. There is a predominance of kidney cancers in more developed areas with greater than four times the number of kidney tumors diagnosed and greater than three times the number of deaths attributed to renal malignancies when compared to less developed areas. In fact, kidney cancers are the sixth most common malignancy among males in developed countries with more than 110,000 new cases and about 43,000 deaths annually [2]. Within the United States, tumors of the kidney and renal pelvis account for about 4 % of all cancer diagnoses [3]. In 2012, there will be an estimated 64,770 new cases diagnosed with a male-to-female predominance of about 3:2 [4]. In fact, these are estimated to be the sixth and eighth most commonly diagnosed tumors in males and females, respectively. Based on data from the SEER (Surveillance, Epidemiology, and End Results) program, it has been estimated that approximately 1 in 69 males and 1 in 116 females will be diagnosed with a kidney tumor in their lifetime [5]. Additionally, about 13,500 deaths in the United States alone will be due to these cancers in 2012 [3].

The differential diagnosis of a renal mass is given in Table 1.1 and includes benign and malignant renal parenchymal tumors as well as tumors of the upper urinary tract. Renal cell carcinoma (RCC) accounts for about 85 % of all tumors of the kidney, with benign renal tumors and other malignant tumors occurring less commonly [6]. Renal cell carcinoma encompasses a variety of different histologic subtypes, each of which portends a different prognosis. Conventional or clear-cell renal cell carcinoma is the most common form of RCC, accounting for 70–85 % of all cases [7, 8]. There are reports that patients with clear-cell RCC have an increased rate of metastasis post-surgery compared to other histologic subtypes such as papillary or chromophobe, even after controlling for tumor stage [9]. This, however, is controversial, as other studies show no prognostic significance of histological subtype [8, 10]. Non-clear-cell histologic subtypes include chromophobe, papillary, and collecting duct RCC and occur in about 10–15 %, 5 %, and <1 % of all RCC cases, respectively [7].

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Table 1.1 The differential diagnosis of a renal mass (Reproduced with permission from Thieme Medical: Barbaric ZL. *Principles of genitourinary radiology*. 2nd ed. New York, NY. Thieme Medical, 1994, pg. 154 and Elsevier Saunders: Wein A, Kavoussi L, Novick A, Partin A, Peters C. *Campbell-Walsh Urology*, 10th ed., Philadelphia, PA Elsevier Saunders, 2012, pg. 141)

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	Metanephric adenoma	Tuberculosis
Urothelium based	Cystic nephroma	Rheumatic granuloma
Transitional cell carcinoma	Mixed epithelial/stromal tumor	
Squamous cell carcinoma	Reninoma (JG cell tumor)	
Adenocarcinoma	Leiomyoma	
Sarcoma	Fibroma	
Leiomyosarcoma	Hemangioma	
Liposarcoma	Vascular	
Angiosarcoma	Renal artery aneurysm	
Hemangiopericytoma	Arteriovenous malformation	
Malignant fibrous histiocytoma	Pseudotumor	
Synovial sarcoma		
Osteogenic sarcoma		
Clear cell sarcoma		
Rhabdomyosarcoma		
Wilms tumor		
Primitive neuroectodermal tumor		
Carcinoid		
Lymphoma		
Leukemia		
Metastasis		
Invasion by adjacent neoplasm		

RCC Incidence over Time

From 1999 to 2008, there was a steady increase in the incidence of malignancies of the kidney and renal pelvis in the United States [11]. These rates increased most dramatically for clinically localized tumors, likely in part due to the increased use of abdominal imaging [11]. This is supported by the fact that the number of renal masses discovered only at autopsy is decreasing, whereas the rate of occult kidney cancers per 100 autopsies did not change significantly over time in one study [12]. In conjunction with the increase in overall incidence, there has been a relative increase in stage I renal tumors with a subsequent improvement in relative survival [13]. However, other factors may be involved in the increasing incidence of renal tumors. While imaging has certainly contributed to the increasing number of asymptomatic renal tumors diagnosed, there has also been a rise in the incidence of advanced renal tumors (tumors with regional extension and distant metastases) and an increase in the kidney cancer mortality rates [14]. As the incidence of RCC increases, its prevalence is estimated to increase from 308,000 in 2010 to 426,000 in 2020 in the United States alone [15].

Demographic Factors in Renal Cell Carcinoma

Renal cell carcinoma is predominantly a cancer of the elderly. In fact, review of the SEER database from 1996 to 2000 suggests that only about 10 % of all kidney tumors are diagnosed <45 years of age, with 75 % of renal tumor diagnosed in patients

above the age of 55 [5]. Studying the age-related trend of RCC, the mean age as well as the proportion of patients diagnosed >65 years has increased from 1982 to 1997 [16]. In review of the 1996–2000 SEER database, the median age of diagnosis was 64 and 67 years for males and females, respectively [5]. While the reasons remain unclear, a recent study suggests that RCC diagnosed at a young age may in fact have different tumor biology than those diagnosed in the elderly. In a retrospective review of greater than 4,000 patients with RCC, RCC diagnosed in young patients tended to have favorable stages, grades, as well as histologic subtypes [17]. The true implications of RCC biology and patient age remain to be elucidated.

There is a male predominance of RCC incidence as well as mortality, with an approximate 3:2 ratio [3, 18]. While the incidence rates have increased in the past 40 years, the relative prevalence by gender does not seem to have changed significantly over time [19, 20]. The reasons for this discrepancy are not well understood but may be explained in that males tend to present with more aggressive forms of RCC with higher grade and higher stage, leading to a lower survival rate [18, 21].

Race is an important factor in the epidemiology of RCC. Using SEER data between 1975 and 1995, the incidence of RCC increased by 3.9 % among African American males whereas it only increased by 2.3 % among Caucasian males. Similarly, there was a 4.3 % increase in the incidence of RCC among African American females and by only 3.1 % among Caucasian females [14]. While imaging may have been a factor in the overall increase, it is only likely to have caused the discrepant increase among African Americans if an imaging bias exists in this population. Similarly, expanding the SEER data to include patients between 1975 and 1998, there was a disproportionate rise in the estimated annual percent change of RCC in the African American population relative to the Caucasian population (4.46 % vs. 2.87 % for patients 20–59 years and 4.35 % vs. 3.06 % for patients 60+ years). While the reasons for this discrepancy remain unclear, it has been suggested that perhaps it is due to exposure to RCC risk factors or inherent biologic differences between populations [22]. A review of the California Cancer Registry between 1998 and 2004 showed that African Americans not only had an increased incidence but also had a decreased survival relative to all other races. In contrast, Asians and Pacific Islanders had a lower incidence rate and a higher survival [23]. Other studies suggest that there are racial differences in the RCC subtype incidence, with African Americans more likely to have papillary tumors and less likely to have tumors of clear-cell histology [24].

In addition to the racial differences in RCC incidence, there have been reports regarding discrepancies in RCC survival. Controlling for stage and age, African Americans have a lower median disease-specific survival than Caucasians [22]. Reviewing treatment patterns of patients with RCC by race, African Americans were less likely to undergo nephrectomy (risk ratio = 0.93, $p<0.001$) for local disease or receive IL-2 for metastatic disease [25, 26]. In addition, the overall survival was worse for African American patients even after controlling for cancer-specific factors. This difference in survival, however, was negated when controlling for comorbidities as well as nephrectomy. The authors concluded that the survival discrepancy may be due to increased comorbidity rate as well as the decreased rate of nephrectomy in the African American population [25].

RCC in Children

Renal cell carcinoma is a rare entity in childhood and accounts for only 2–5 % of all renal tumors in children. The median age at diagnosis in this population is 12 years, though there have been reports of RCC occurring during infancy [27, 28]. A number of genetic abnormalities have been associated with pediatric RCC, with translocation morphologies including Xp11 and 6p21 being the most common abnormalities [29, 30]. In addition, childhood RCC has been associated with genetic syndromes such as tuberous sclerosis and Beckwith-Wiedemann syndrome [28, 31]. Prognostic variables in childhood RCC are similar to those in adult RCC with tumor stage being the strongest prognostic variable [32]. Younger patients with sporadic RCC have better survival rates following treatment when compared to adults [33].

Risk Factors for the Development of RCC

A number of factors have been reported to increase risk of the development of RCC. The most commonly cited risk factors are smoking, hypertension, and obesity, though other exposures exist (or have been linked).

Smoking

Smoking has long been associated with RCC. In one Italian case-control study, ex-smokers had a relative risk of 1.7 of having RCC compared to never-smokers. A dose-response relationship was also observed with a RR of 1.1 for moderate smokers and 2.3 for heavy smokers relative to never-smokers. Further, there was a relationship between duration of smoking, as well as age at starting to smoke and time since quitting, and the risks of RCC [34]. In a larger case-control series, Yuan et al. found that patients with RCC had a 35 % increased odds of having smoked cigarettes [35]. Further, risk increased with increasing smoking habits and decreased with increasing time from the last cigarette. In this study, they attributed 17 % of Los Angeles-based RCC to smoking.

To more directly assess the relationship between smoking and the development of RCC, McLaughlin et al. conducted a 26-year study on the smoking habits of US veterans with development of RCC as an outcome [36]. They found that smokers had a 47 % increase in the relative risk of the development of RCC compared to nonsmokers. In addition, the risk increased with the number of cigarettes smoked per day. In a recent meta-analysis of the relationship between smoking and RCC, the authors analyzed 19 case-control studies as well as 5 cohort studies. They found a 38 % increased risk in current or former smokers versus never-smokers. They confirmed the previously mentioned dose-response relationship between cigarette use and RCC development. In addition, longer time of smoking cessation (>10 years vs. 1–10 years) reduced subsequent risk of RCC [37].

Obesity

A number of studies have been conducted to investigate an association between obesity and RCC. In 1984, McLaughlin et al. conducted case-control analyses and observed that BMI seemed to be associated with RCC in women [38]. Since that point, other studies have been performed which suggested that increasing BMI puts one at an increased risk for RCC, regardless of sex [39, 40]. In fact, a quantitative analysis of all studies regarding obesity and RCC between 1966 and 1998 calculated a relative risk of 1.07 per increase in unit BMI. They conclude that 27 % of cases of RCC among men and 29 % of cases among women can be attributed to obesity [41]. A further analysis of 11 studies from 1966 to 2008 similarly concluded that increasing BMI increases the risk of renal cancer, with a stronger effect in females than males [42]. While the mechanism remains to be elucidated, there have been a number of proposed theories involving hyperinsulinemia, sex hormone dysregulation, and impaired immune function [43, 44]. Not only has obesity been associated with risk for the development of RCC, but it has also been associated with histologic subtype. Higher BMI was found to have an association with clear-cell histology [45]. The increase in the obesity rate must be considered when analyzing the increased incidence of RCC [46]. While much of the increased incidence has been attributed to increased imaging use, the relative increase in RCC risk factors such as obesity may also play a role.

Hypertension

Hypertension, smoking, and obesity are the three largest risk factors for the development of RCC. Yuan et al. have previously demonstrated an association between RCC and hypertension [39]. They found that patients with RCC had 2.2 times the odds of having a diagnosis of hypertension than the matched controls. In a prospective study from 1982 to 1989, an association was found between the rate of fatal renal cancer and presence of hypertension in females; however, this did not hold true for males [47]. This is consistent with

the results of a case-control study performed by Shapiro et al. [48]. Results from a prospective study from 1971 to 1992 demonstrate that not only is the presence of hypertension a risk factor for the development of RCC, but both increasing diastolic and/or systolic blood pressures are associated with increasing relative risks of RCC [40]. In their analysis, patients with a diastolic blood pressure 90–99 mmHg had more than double the risk of developing RCC when compared to patients with a diastolic blood pressure <70 mmHg. This association was not found for tumors of the renal pelvis. In another meta-analysis of 13 case-control studies from 1966 to 2000, hypertensive patients were found to have a pooled odds ratio of 1.75 of having RCC [49]. Further, there has been evidence that RCC risk increases with increasing time from hypertension diagnosis [50].

Medications

Antihypertensive Agents

As hypertension has been associated with RCC, there have been numerous studies to determine if drugs treating hypertension modulate RCC risk. The results of a meta-analysis of 29 prospective studies demonstrate a pooled OR of 1.54 between diuretics and RCC [51]. No other antihypertensive agents analyzed in this study, including beta-blockers, calcium channel antagonists, and angiotensin converting enzyme inhibitors, were associated with increased risk of RCC.

Analgesics

Multiple studies implicate chronic use of analgesics in the development of RCC [52, 53]. Using prospective data from the Nurses' Health Study and the Health Professionals Follow-up Study, a longer duration of non-aspirin nonsteroidal anti-inflammatory drug use may increase the risk of RCC [53]. This trend was not observed for aspirin or acetaminophen. The authors suggest that the analgesic-mediated RCC carcinogenesis is due to inhibition of prostaglandin synthesis leading to chronic subacute renal injuries. This in turn could lead to DNA damage and uncontrolled cell proliferation.

Diet

Several theories regarding differential food intake in relation to RCC risk have been posited. Consumption of fruits and vegetables decreases the risk of RCC [54]. This finding was confirmed in a meta-analysis reviewing 13 prospective studies [55]. Similarly, there have been reports regarding increased risk in patients with high-fat, high-protein diets [56]. Benzo(a)pyrene, a polycyclic aromatic hydrocarbon present in barbecued red meats, was found to be associated with RCC in one case-control study [57]. In a prospective analysis of meat intake with the outcome of RCC, red meat consumption was found to be associated with RCC development [58]. Further, there was an association with meat intake and the papillary histologic subtype of RCC. Alcohol has been identified as a factor that decreases risk for RCC. A pooled analysis of 12 prospective studies demonstrated that those who drank slightly more than one alcoholic drink per day had a RR of 0.72 compared to nondrinkers [59]. Furthermore, this association with alcohol intake was not noted for other liquids, implying that alcohol specifically is the modifying factor [60]. While data exists regarding risk of RCC based on diet profile, mechanistic pathways must still be clarified.

Trichloroethylene Exposure

Trichloroethylene, a degreaser used for the cleaning of metal, has been identified as a risk factor for RCC. In a case-control analysis of 134 patients with RCC, trichloroethylene was found to be associated with an increased risk of RCC (OR = 5.57) [61]. In an additional case-control study, exposure to trichloroethylene was found to be associated with RCC when controlling for age, obesity, smoking, hypertension, and diuretic use [62].

Screening for Malignant Disease

Screening for the detection and treatment of malignant renal disease is enticing. An ideal screening program has several components.

The disease must have a significant impact on public health, be detectable while asymptomatic, and have improved outcomes if treated early. The disease must also be of sufficiently high prevalence in the population of interest, and if detected, patients must be willing to comply with further evaluation and treatment [63]. RCC remains a disease that is amenable to local therapy for cure, especially when the disease is discovered at an early stage.

The evolution and increased use of CT scanning has increased RCC detection. Serendipitously discovered renal tumors are smaller, lower stage, and have significantly better survival (94 % vs. 35 %) than those that present symptomatically [64]. Reviewing available SEER data, Parsons et al. discuss that early detection may not in fact decrease mortality. Rather, it may only generate a lead time bias [65]. RCC only occurs in about 1/10,000 people per year in the USA [21, 66]. With such a rare disease and the possibility of detecting benign renal neoplasms, the sensitivity and specificity of any screening test would need to be nearly 100 %. This is likely not a cost-effective strategy for malignant renal disease.

Several screening strategies have been investigated. The presence of asymptomatic microscopic hematuria was associated with a urologic malignancy, including bladder or renal cell carcinoma in only 0.2–0.5 % of screened cohorts [67]. In a contemporary cohort, RCC invaded the collecting system in only 14 % of patients. Therefore, microscopic or gross hematuria from this disease would be expected to be rare, despite the fact that it has been described as part of the classic triad of RCC presentation [64].

Renal ultrasonography (USG) has been proposed for use as a screening device. It is noninvasive, delivers no radiation, and is relatively inexpensive. With detection by CT scan as the reference, USG detects greater than 82 % of tumors larger than 2 cm [68]. In association with the large Aneurysm Detection and Management study, 6,678 adults age 50–79 self-referred for abdominal and renal ultrasound. A solid renal mass was detected in 0.33 % [69]. In the German cities of Mainz and Wuppertal, a 2-year screening program for RCC recruited 9,959 volunteers. Physicians performed renal USG, and 79 % of patients returned for a second exam a year later. Thirteen cases of renal mass (0.1 %) were detected, of which nine were RCC. In an even larger study, 219,640 Japanese adults received abdominal USG screening for any malignancy [70]. Of the total, 638 (0.3 %) had a renal mass, and RCC was identified in 192 people (0.09 %). No persons had regional or distant metastatic disease, and 35 % had T1 lesions. In their analysis, they found that USG would only be cost-effective if applied to the entire abdomen, to detect any abdominal malignancy.

Dialysis patients represent a large group of people with known increased risk of RCC [71]. Ishikawa and colleagues examined patients on dialysis who developed symptomatic renal masses compared to dialysis patients detected by USG to have a renal mass. Risk of death was reduced by 35 % in the USG-detected population [72]. For patients on dialysis, Sarasin et al. performed a decision analysis to evaluate a hypothetical screening program with USG or CT. They relate that screening for renal malignancy would only be beneficial to the youngest and healthiest patients, as others are more likely to succumb to renal failure than to renal malignancy [73]. Following renal transplantation, the risk of malignancy in the native kidneys is about 1.1–3.2 %, which is 10 times higher than the general population [66, 74, 75]. At the Brigham and Women's Hospital in Boston, transplant recipients generally undergo ipsilateral native nephrectomy at the time of transplantation. Four percent of these native kidneys contained RCC [76]. Therefore, screening of the native kidneys in both the pre- and post-renal transplant settings may be beneficial in this group.

Computed tomography (CT) is another imaging modality that can be used for screening. Fenton and Weiss performed a meta-analysis of CT screening programs [77]. These programs included screening for coronary artery disease, whole-body CT, lung carcinoma in former smokers, and 2 colon cancer case series. The pooled prevalence of preclinical renal carcinoma was 2.1 cases per 1,000 persons screened (0.21 %).

In addition to imaging modalities, urine and serum biomarkers may also provide a means of

screening or surveillance in RCC. This strategy to date has not been substantiated via any large population-based prospective trials. Recently, the detection of aberrant hypermethylation of tumor suppressor genes (including APC, p16, RAR-beta2, ARF) has shown initial viability for renal cancer detection with high sensitivity [78, 79].

Screening of Target Populations

A collaborative approach to care of the patient with a known renal syndrome is invaluable. Screening in these populations has been evaluated.

The von Hippel-Lindau gene, VHL, is a tumor suppressor gene on chromosome 3p that is normally involved in the degradation of HIF, hypoxia-inducible factor. When inactivated, VHL causes overexpression of pro-growth and angiogenic factors either directly or via loss of HIF suppression. Loss of VHL is highly penetrant and affects 1 in 36,000 live births [80]. Affected individuals may manifest disease with benign or malignant tumors or cystic lesions of the kidney, adrenal gland, pancreas, or central nervous system [80]. Annual US screening in this population for abdominal malignancy has been suggested to begin at age 8 with a switch to annual CT at age 18 [80]. Hypermethylation of the VHL gene is found in up to 80 % of RCC [81]. Choyke and colleagues followed 28 patients with VHL by yearly CT scan. With at least 1 year of follow-up, they identified 228 total renal lesions and found that they have a variable growth rate. While they note that the transition from simple cyst to solid mass is rare, complex cysts examined pathologically almost always contain RCC [82].

Tuberous sclerosis is an autosomal dominant neurocutaneous syndrome which can manifest in many organ systems [83]. While most affected patients present with dermatologic changes including hypopigmented macules, facial angiofibromas (adenoma sebaceum), and lumbosacral angiofibromas, renal lesions are seen in up to 58 % of affected patients. Angiomyolipoma is the most common lesions, seen in 85 % of cases, with cysts and RCC seen in 44 % and 4.2 % of cases, respectively [84]. Loss of the tumor suppressor features of TSC2 is related to an increase in RCC risk [83, 85]. Though no screening trials in the disease have been conducted, with the high frequency of renal involvement, periodic ultrasonographic review will help to follow the extent of renal disease.

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by multifocal renal cysts. There is no increased risk of RCC [86]. Imaging is difficult to interpret given the complexity of the cystic structures of the renal parenchyma. Contrast-enhanced CT or MRI may provide the enhanced resolution necessary to separate RCC from the other ubiquitous renal cysts, but this has not been used in any formal screening process [87, 88]. All patients with ADPKD display hemorrhagic renal cysts on imaging [87]. For children with a family history of ADPKD, USG screening has a high rate of cystic detection in a series of 420 children, but the ability to define RCC in early lesions is not discussed [89]. Transformation from simple cyst to solid mass is rare, though the solid components of complex cysts nearly always have RCC at pathologic review [82]. Given the minimal risk of RCC in ADPKD and difficulty in detecting these lesions, screening is not recommended in the population.

Families with hereditary papillary RCC may carry mutations in the c-MET proto-oncogene. Asymptomatic family members may be screened with noninvasive USG, though this only detects a small number of tumors [90].

The United States Preventive Services Task Force does not have a position statement related to kidney cancer screening. Screening for RCC in the general population cannot be endorsed at this time. However, indications to screen selected subpopulations do exist.

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. Finally, uniform staging systems allow for

the comparison of patient outcomes worldwide [91]. Flocks and Kadensky proposed one of the earliest kidney cancer staging systems in 1958, including organ confined, locally invasive, locally metastatic, and distant metastatic disease [92]. 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) [93]. This TNM staging system has had several major revisions to improve prognostic accuracy, with the most recent update published in 2010 after a structured review process with input from many experts and professional groups (Table 1.2) [91, 94]. In 1987, T1 and T2 renal lesions were divided at 2.5 cm in largest dimension by imaging, which did not differentiate well between survival for these groups [95]. In 1997, T2 disease started at 7 cm for greater differentiation from T1 [96]. The 2002 AJCC update further subdivided T1 disease, T1a: ≤4 cm and T1b: 4–7 cm [97]. Work done by the Cleveland Clinic contributed to this development [98, 99]. 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). This was confirmed in a multi-institutional study of more than 2,200 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 [99]. This outcome difference has been further substantiated irrespective of the form of surgery performed. The concept that tumor diameter greater than 4 cm leads to an adverse outcome is true in radical nephrectomy as well as partial nephrectomy [100].

Several groups have attempted to further reclassify T1 and T2 disease [101–103]. Investigators at the Mayo Clinic proposed a cutoff of 5 cm for better postoperative DFS prediction [102]. In a similar study, the group at UCLA suggested that disease-specific patient survival was more accurate if T2 started at 4.5 cm [101]. Ficarra and colleagues reported that a cut point of 5.5 cm improved cancer-related outcome stratification [103].

These same groups examined T2 patients with tumors >7 cm to gain better prognostic ability. This was supported by work by an international collaboration finding that for T2 disease, tumors larger than 11 cm have worse DFS [104]. Frank and colleagues studied an additional 544 T2 patients and proposed a 10 cm cutoff point to subclassify patients [105]. 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) [94]. The collective evidence from the multitude of these retrospective studies indicates that primary tumor size plays an important role in predicting survival.

In the most recent seventh edition TNM staging update, the T3 category changed significantly (Fig. 1.3). T3 had previously included invasion of perinephric fat, adrenal gland, renal vein, or different levels of the IVC [97]. 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 T3a tumors may not fair as poorly as larger T2 tumors [106]. Similarly, Lam et al. described 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) [107]. Siemer et al. reviewed nearly 1,800 cases and found that perinephric fat invasion did not play an independent prognostic role though tumor size did [108]. 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 %) [109, 110]. 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

Table 1.2 Revisions of TNM staging for RCC

		1987	1997	2002	2010
Extent of disease	T1	Limited to kidney, ≤2.5 cm	Limited to kidney, ≤7 cm	–	Limited to kidney, ≤7 cm
	T1a	–	–	Limited to kidney, ≤4 cm	Limited to kidney, ≤4 cm
	T1b	–	–	Limited to kidney, 4–7 cm	Limited to kidney, 4–7 cm
	T2	Limited to kidney, >2.5 cm	Limited to kidney, >7 cm	Limited to kidney, >7 cm	Limited to kidney, >7 cm
	T2a	–	–	–	Limited to kidney, 7–10 cm
	T2b	–	–	–	Limited to kidney, > 10 cm
	T3a	Invades adrenal gland or perinephric fat within Gerota's fascia	Invades adrenal gland or perinephric fat within Gerota's fascia	Invades adrenal gland or perinephric fat within Gerota's fascia	Extends into renal vein or segmental branches; invades perirenal and/or renal sinus fat
	T3b	Extends into renal vein	Extends into renal vein or IVC below diaphragm	Extends into renal vein or IVC below diaphragm	Extends into IVC below the diaphragm
	T3c	Extends into IVC below diaphragm	Extends into IVC above diaphragm	Extends into IVC above diaphragm or invades wall of IVC	Extends into IVC above diaphragm or invades wall of IVC
	T4	Extends beyond Gerota's fascia	Extends beyond Gerota's fascia	Extends beyond Gerota's fascia	Extends beyond Gerota's fascia (including contiguously into ipsilateral adrenal gland)
	T4a	Extends into IVC above diaphragm	–	–	–
Nodal status	Nx	Lymph nodes not assessed	Lymph nodes not assessed	Lymph nodes not assessed	Lymph nodes not assessed
	N0	No regional lymph node involvement	No regional lymph node involvement	No regional lymph node involvement	No regional lymph node involvement
	N1	Single lymph node involved, ≤2 cm	Single lymph node involved	Single lymph node involved	Regional lymph node involvement
	N2	Single lymph node involved, 2–5 cm	>1 regional lymph node involved	>1 regional lymph node involved	---
	N3	Single lymph node involved, >5 cm	–	–	–
Metastases	Mx	Distant metastases not assessed	Distant metastases not assessed	Distant metastases not assessed	–
	M0	No distant metastasis	No distant metastasis	No distant metastasis	No distant metastasis
	M1	Distant metastasis present	Distant metastasis present	Distant metastasis present	Distant metastasis present

1987 [95]
1997 [137]
2002 [138]
2010 [139]

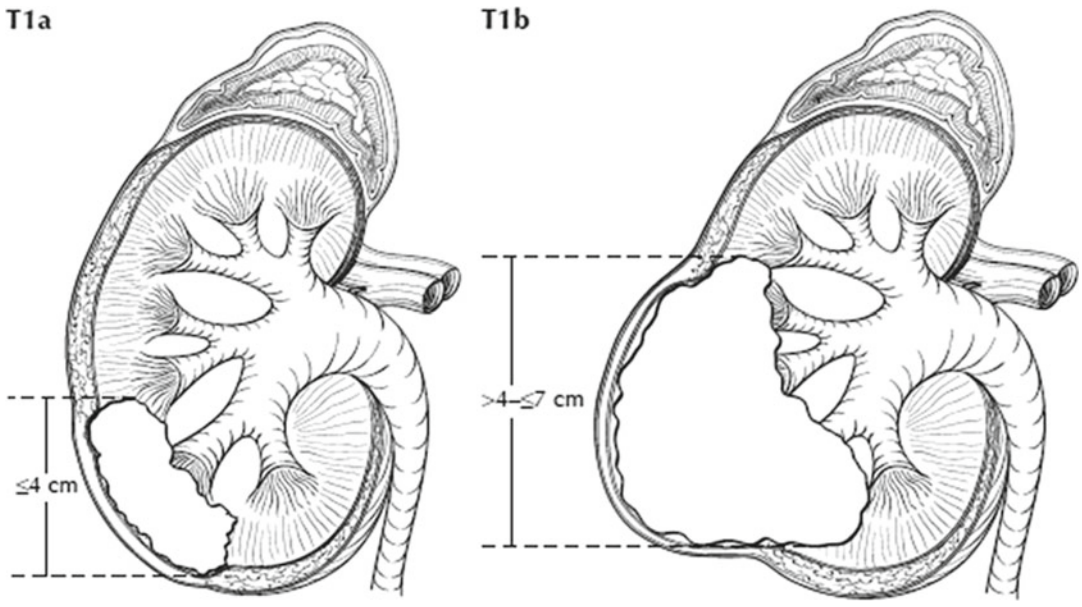

Fig. 1.1 Stage T1a – limited to kidney and ≤4 cm; T1b tumors (4–7 cm)

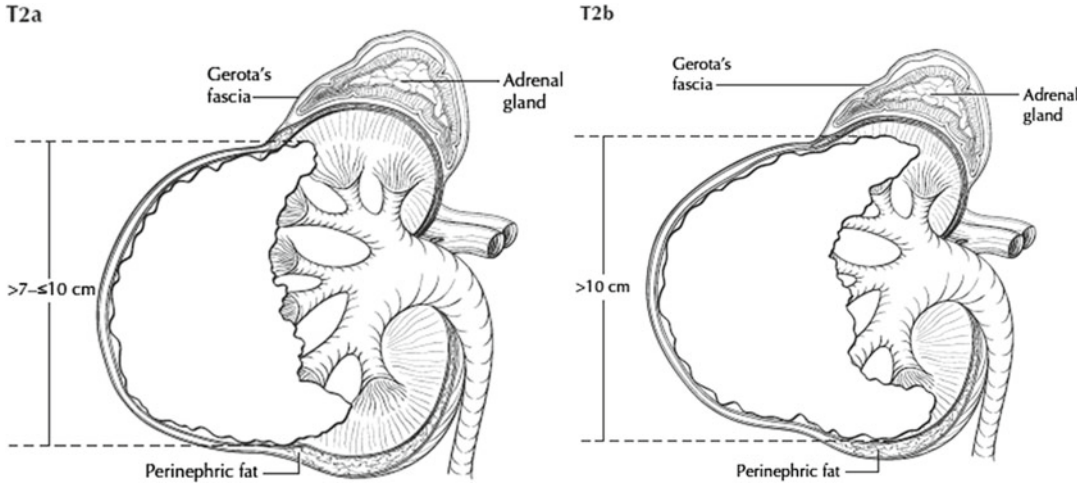

Fig. 1.2 Stage T2a – limited to kidney and 7–10 cm; T2b tumors (>10 cm)

invasion alone were more likely to die of disease than patients with renal vein thrombus alone [111, 112]. In a slightly less complex system, the group from M.D. Anderson reported on a cohort of patients with pT3N0/NxM0 disease and found that presence but not extent of venous thrombus correlated with survival. Unlike the Mayo Clinic findings, they reported that patients with extrarenal extension into fat, regardless of location, had similar DFS as those with any amount of venous thrombus alone. Subjects with both were at a greater risk of death from RCC [113]. 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 [114].

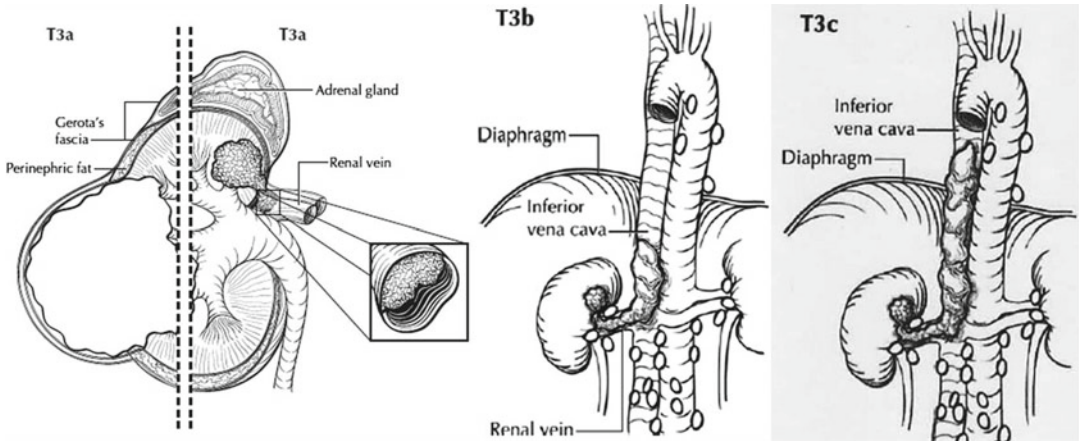

Fig. 1.3 Stage T3a – tumor thrombus extends into renal vein or invades perirenal and/or renal sinus fat; stage T3b – extends into IVC below the diaphragm; stage T3c – extends into IVC above diaphragm or invades wall of IVC

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 [115, 116]. Examining the SEER database from 2000 to 2007, Whitson et al. demonstrated that tumor thrombus extension above the diaphragm did not correlate with survival [116]. Similarly, neither renal vein nor IVC extension was associated with DFS in a cohort of 1,082 patients from Memorial Sloan-Kettering Cancer Center [117]. Other prognostic factors such as tumor size, presence of nodal or distant metastases, and IVC invasion may hold more prognostic value than level of IVC thrombus extension [118]. However, there is evidence that DFS is different between renal vein thrombus and infradiaphragmatic IVC thrombus (52 vs. 25 months) but not between infradiaphragmatic and supradiaphragmatic (25 vs. 18 months) vena caval thrombi [118]. Kim et al. reported that patients with a thrombus in the renal vein or infradiaphragmatic IVC fared better than those with supradiaphragmatic IVC thrombi [119]. Moinzadeh and Libertino compared 10-year survival of patients with renal vein involvement versus thrombus extending only 1–2 cm into the subhepatic IVC (66 % vs. 29 %, $p=0.0001$) [120]. Compared to infrahepatic IVC tumor thrombus, intra-/suprahepatic IVC tumor thrombus had poorer survival (25 vs. 13 months, $p=0.032$) [121]. A German group also confirmed this in their series of 111 patients [122]. Hence, extension of tumor thrombus 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 [123]. When compared to perinephric or renal sinus fat invasion, direct adrenal gland invasion has a worse 5-year cancer-specific survival (36 % vs. 0 %) [123]. 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) [108]. Similarly, Thompson et al. found that 2002 T3a 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, $p=0.004$) [124].

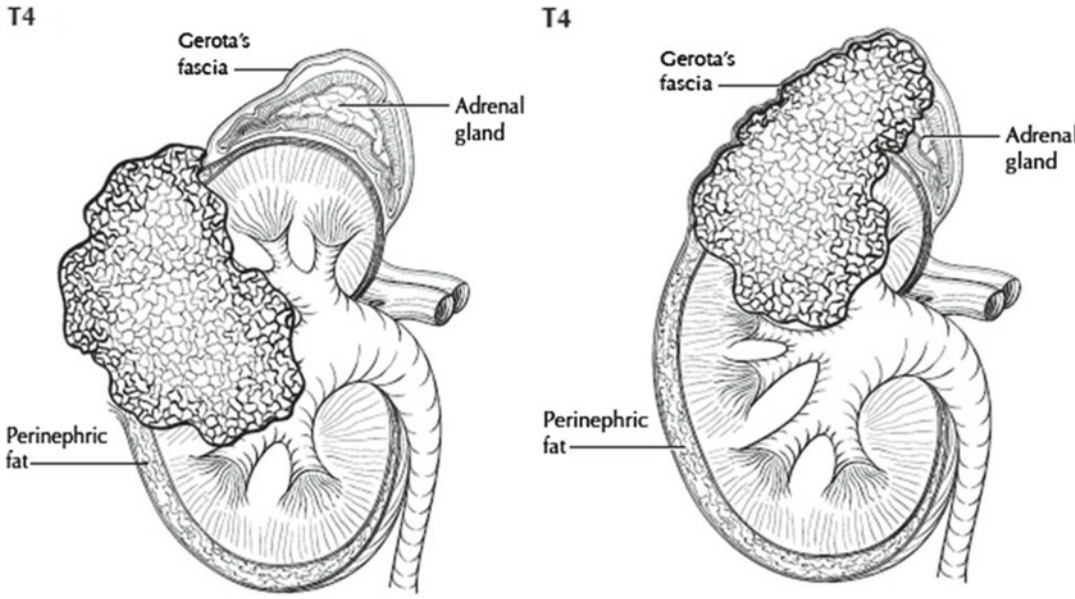

Fig. 1.4 Stage T4 tumor extends beyond Gerota's fascia or contiguously into the ipsilateral adrenal gland (Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published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

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 current seventh edition simplifies 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 [125]. In a similar study, 2,000 patients with RCC were reviewed, and survival for the 69 with nodal involvement was similar regardless of the number of lymph nodes involved [126]. These authors also suggest that poorer survival was associated with extranodal 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 [127]. The therapeutic role of lymphadenectomy is discussed further in Chap. 16.

Metastatic Disease

Patients with metastatic disease have uniformly worse survival [128]. This group has been stratified into three risk groups based on Karnofsky performance status (<80 %), high lactate dehydrogenase (>1.5 times upper limit or normal), low serum hemoglobin, high correct serum calcium (>10 mg/dL), and absence of nephrectomy. Favorable risk had no risk factors, intermediate risk had one to two, and poor risk had three or more risk factors. Median survival among all patients with metastatic disease was 10 months and for those with favorable risk was 20 months [129]. The role of surgery in metastatic disease is discussed in Chap. 18.

Other Staging Systems

Staging systems like the TNM system should be continuously reviewed and updated as necessary. Though the AJCC seventh edition improves 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 5,339 renal tumors. Some groups, such as T2b and T3a or T3c and T4, had similar disease-specific outcomes. Analyzing only the 4,848 N0/NxM0 patients, there were no differences in survival between T1a and T1b, T2b and T3a, and T3c and T4 [128]. Furthermore, a group of investigators from Korea compared the prognostic ability of the sixth and seventh TNM editions in 1,691 patients. They found a very 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 [130]. Surgeons at several institutions have found that collecting system invasion also carries prognostic strength. These tumors are often high stage, high grade, and of non-clear-cell histology. They are frequently symptomatic [101, 131]. Even for T1 or T2 disease, collecting system invasion is association with a significant increase in the likelihood of nodal and distant metastases and death [101, 132].

In an effort to further enhance staging, several academic centers also advocate 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 [133]. An integrated system was also proposed at UCLA [134]. This system includes TNM, grade, and ECOG performance status and was superior to the 1997 TNM system alone and has been externally validated [135]. The stage, size, grade, and necrosis model has also been suggested and may offer improved prognostic ability over the UCLA model [136]. Though it may be augmented, the 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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Molecular Biology and Genetics

2

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Introduction

Renal cell carcinoma (RCC) is the most common type of cancer that arises within the adult kidney, and several well-defined somatic DNA mutations are associated with the development of sporadic renal carcinomas. RCC subtypes have traditionally been defined based on the morphology of the tumor cells, and the different subtypes have distinct genetic abnormalities and gene expression characteristics [1–5]. The gene expression differences likely reflect differences in the specific cell type from which the tumor cells originate [6]. Therefore, the genetic mutations that occur may require a specific cellular context in order to lead to uncontrolled cell growth. Clear cell RCC is the most common subtype, constituting 70–80 % of renal tumors. Papillary RCC, which can be divided into type 1 and type 2, is the next most frequent subtype, representing 10–15 % of tumors. Chromophobe RCC represents about 5 % of renal tumors. Other renal cell carcinomas are either unclassifiable by conventional means or represent rare subtypes. The latter include transitional cell carcinoma of the renal pelvis, renal medullary tumor, tubulocystic carcinoma, Xp11.2 translocation-associated tumor, collecting duct tumor, adult Wilms' tumor, mixed epithelial and stromal tumor/cystic nephroma, and the usually benign renal oncocytoma and angiomyolipoma.

Though the morphologic-based subtypes have proven clinically valuable, the rapid advances in genomic technologies have begun to make it practical to classify tumors based on genetic characteristics. Therefore, through the course of this chapter, we will emphasize the molecular genetic classification of renal tumors. While this view is likely an oversimplified model of renal tumor development, it is based on the concept that a strong association of a particular genetic mutation with the development of a renal tumor would indicate a selective pressure to maintain this particular mutation in the tumor cell population.

VHL Loss-of-Function Renal Tumors

One of the most common genetic defects found in renal cell carcinomas occurs within the von Hippel-Lindau (*VHL*) gene, located on the distal tip of the short arm of chromosome 3 (3p25). *VHL* mutations exist in the majority of clear cell RCCs but are not common in other subtypes. In sporadic cases, small mutations of approximately one to three base pairs occur within one of the *VHL* exons [7–14]. The DNA-altering mechanisms that lead to these mutations are not clear

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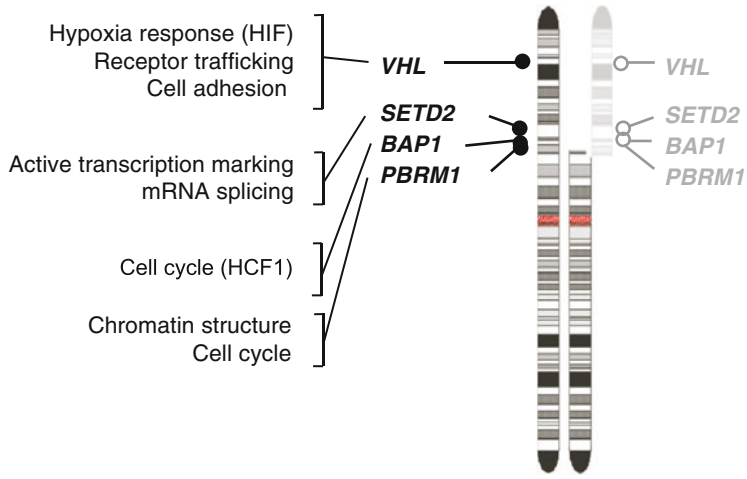

Fig. 2.1 *Chromosome 3 defects in renal cancers*. An idiogram of chromosome 3 shows the approximate location of *VHL*, *PBRM1*, *BAP1*, *SETD2*, and the breakpoint found in monosomy of 3p in clear cell RCC; monosomy is usually associated with loss of the presumed wild-type allele of these genes

but environmental, developmental, or toxicological events may be involved. Regardless of the mechanism, the majority of *VHL* mutations lead to a protein that is either partially or completely inactive [15]. It is likely that both alleles of *VHL* need to be inactivated for tumor development because one wild-type allele may produce a functional protein that compensates for the somatic mutation. Loss of the second wild-type allele of *VHL* via a chromosome deletion event is commonly observed in tumor cells. Specifically, a loss of a large section of the p-arm of chromosome 3 removes the remaining wild-type *VHL* allele along with numerous other genes (Fig. 2.1) [11, 16–23]. Interestingly, the chromosome deletion occurs at a region of the chromosome 3p that is near, but seems to be distinct from, a region that is susceptible to breakage [18, 24, 25]. As with the formation of single base-pair mutations within *VHL*, the mechanisms leading to chromosome breakage are not well understood. The combined mutation/deletion occurs in approximately 70–80 % of clear cell renal tumors. However, in some cases, *VHL* inactivation can occur by hypermethylation of the *VHL* promoter, and it is speculated that there are other mechanisms that lead to functional inactivation of *VHL* in most clear cell tumors [26–29].

The combined *VHL* mutation and deletion events result in the elimination of VHL-mediated signaling. VHL is the substrate-conferring component of an E3 ubiquitin ligase complex [30, 31]. This complex polyubiquitinates proteins for their subsequent destruction via the 26S proteasome and thus posttranslationally regulates diverse cellular functions [32]. The most-studied VHL target proteins are the hypoxia inducible transcription factors (HIFs) [33, 34]. The alpha and beta subunits of an HIF protein heterodimerize to form a transcription factor complex that coordinates the transcriptional response of cells deprived of oxygen [35–38]. As oxygen levels decrease, levels of the HIF heterodimer increase and drive the transcription of several pro-angiogenic and anaerobic metabolite genes by binding to a cis-acting sequence motif, termed the hypoxia-response element (HRE), in the gene promoter [39, 40].

In contrast, at normal oxygen levels (normoxic conditions), the HIF-alpha subunit undergoes rapid ubiquitin-mediated degradation that is mediated by the VHL protein and 26S proteasome [30, 31, 41, 42]. In this process, oxygen-sensitive prolyl hydroxylases (EGLN1-3) add a hydroxyl group to HIF proteins; this posttranslational hydroxylation is required for VHL binding [31, 43–47]. The hydroxylation reaction occurs rapidly, VHL binds and polyubiquitinates hydroxylated HIF, HIF is degraded, and transcription of hypoxia-associated genes is maintained at low levels. However, in

renal cell carcinomas with dysfunctional VHL, HIF is not properly degraded and HIF levels accumulate, inducing inappropriate transcriptional activation of metabolic and angiogenesis factors such as pyruvate dehydrogenase kinase (PDK), glucose transporter (GLUT1), erythropoietin (EPO), lysyl oxidase (LOX), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF). Molecular targeting of pro-angiogenic pathways is currently the standard of care for patients who are not surgery candidates. This targeted therapy typically includes the application of small-molecule inhibitors that target the kinase active sites of vascular endothelial growth factor receptor (VEGFR) and delay tumor progression for nearly a year [48–51].

Multiple HIF-alpha isoforms are produced from different loci that encode HIF-alpha paralogs [52]. The *HIF1A* gene is located on chromosome 14q23, the *HIF2A* gene is located on chromosome 2p, and the *HIF3A* gene is located on chromosome 10q. HIF2-alpha also dimerizes with HIF-beta to produce a functional transcription factor, but the transcriptional targets of HIF2-alpha are different from those of HIF1-alpha [53]. The role of the HIF3-alpha product is less clear, and it may function in a dominant-negative fashion [54]. Current evidence suggests that while HIF1-alpha expression is common in renal tumors, expression of the HIF2-alpha subunit is associated with aggressive renal tumor development [55]. Further, genome-wide association studies have found that a locus within the *HIF2A* gene is associated with renal tumor development [56, 57]. Inhibition of the HIF2-alpha isoform prevents renal tumor formation in cell lines that contain *VHL* loss-of-function mutations [58]. Taken together, these data suggest that HIF-related signaling, particularly the HIF2-alpha component, contributes in an important way to renal tumor development.

NF2 Loss-of-Function Renal Tumors

A small percentage (about 2 %) of clear cell renal tumors contain mutations within the exons of the neurofibromin 2 (*NF2*) gene, which is located on the long arm of chromosome 22 [29, 59]. However, *NF2* mutations are prevalent in cell lines commonly used to model renal tumor cell biology, and it is suspected that this mutation may delineate an important subtype of renal cancer. As with VHL, inactivation of NF2 signaling likely requires disruption of both alleles of *NF2*, although bi-allelic inactivation in renal tumors is not well described [60]. Missense mutations in *NF2* are thought to produce loss of function of the protein product due to reduced protein half-life [60].

The protein product of the *NF2* gene is often referred to as Merlin, an acronym for "moesin-ezrin-radixin-like." Moesin, ezrin, and radixin possess highly similar protein sequences, and the Merlin acronym reflects their similarity to NF2. NF2/Merlin serves a scaffolding function that links actin filaments to either the cell membrane or membrane-associated glycoproteins [61, 62]. NF2/Merlin may be involved in regulating cell-to-cell adhesion, cytoskeletal architecture, and membrane protein organization. Preliminary analysis of sporadic tumors suggests that the mechanism of *NF2*-mediated tumor development is distinct from that of *VHL*-mediated tumor development. *NF2* mutant cell lines and tumor samples do not express high levels of the classical HIF target genes common to tumors with inactivating *VHL* mutations [29]. Moreover, renal tumor cells that arise in *NF2* knockout mice activate signaling pathways (such as epidermal growth factor receptor (EGFR) signaling) that are not commonly reported in tumors with *VHL* inactivation [63].

Germline mutations in the *NF2* gene predispose individuals to a disease known as neurofibromatosis type 2. Interestingly, patients afflicted with this disease develop various nervous system tumors, including schwannomas, meningiomas, ependymomas, and astrocytomas, but they do not develop renal tumors [64–66]. Due to the distinct signaling mechanisms of neurofibromatosis type 2-associated tumors, the application of small-molecule inhibitors that target the VEGF family of receptor tyrosine kinases (e.g., sunitinib, sorafinib, and pazopanib) may not be effective. The identification of both *NF2* and *VHL* mutations in the clear cell subtype of renal tumors shows that these tumors can arise

due to distinct genetic mechanisms. An interesting and open question is whether these tumors also contain distinct morphologic features when subjected to sophisticated analysis.

MET Gain-of-Function Renal Tumors

Activation of the MET receptor tyrosine kinase (RTK) is often associated with the development of the papillary type 1 subtype of renal cancer. Two types of genetic changes are thought to result in abnormal MET signaling in papillary tumors. In the first case, development of a single-nucleotide mutation within an exon of the *MET* gene leads to the formation of a hyperactive protein. Approximately 10 % of papillary type 1 tumors (about 1 % of renal tumors overall) contain somatic gain-of-function mutations in MET [67–71]. Further supporting a role for MET activation in renal tumor development are rare individuals that develop hereditary papillary renal carcinoma (HPRC). These individuals possess germline missense mutations within the *MET* gene that are associated with increased receptor signaling [69]. In the second case, the genetic change is an increased DNA copy number of the *MET* locus. A high proportion of papillary type 1 renal tumors contain three or more copies of chromosome 7, which contains the *MET* gene [71–75]. Amplification of chromosome 7 leads to increased transcription of *MET*, and most papillary type 1 tumors display high expression of the *MET* transcript [4]. Although this expression pattern could be an effect of the cell type in which papillary type 1 tumors arise, the increased expression is thought to be pathogenic. However, it is not clear whether increased expression alone is sufficient to hyperactivate MET signaling. Recent data has suggested that a kinase located on chromosome 12, the leucine-rich repeat kinase 2 (LRRK2), is associated with MET hyperactivation in papillary type 1 cancers. In this model, both *MET* and *LRRK2* are amplified and overexpressed in type 1 papillary tumors, and *LRRK2* amplification facilitates MET activation [76]. RTKs can be activated by crosstalk between kinase signaling pathways which physically intersect within specific membrane microdomains such as focal

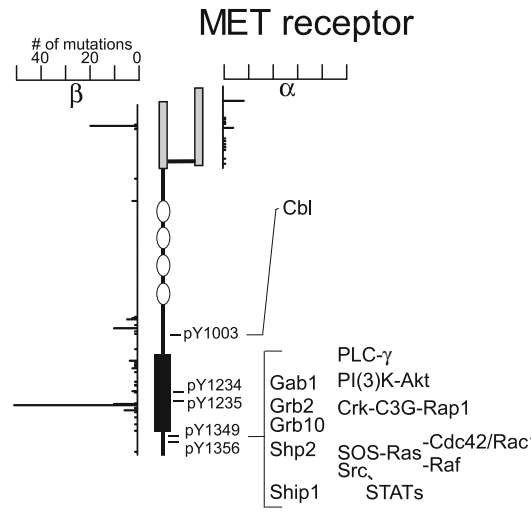

Fig. 2.2 *Activating mutations in the MET receptor tyrosine kinase*. A schematic of the MET receptor tyrosine kinase in which the semaphorin, IPT, and kinase domains are highlighted as *grey bars*, *open ovals*, and a *black box*, respectively. Tyrosine residues that become phosphorylated (pY) and proteins that bind to the C-terminal domain of MET following receptor activation are also shown. The locations of somatic mutations have been identified according to the COSMIC mutation database (http://www.sanger.ac.uk/genetics/CGP/cosmic/) – most are in the kinase domain and are associated with sustained kinase activation

adhesions and lipid rafts to form key signaling nodes [77]. LRRK2 associates with lipid rafts, which are known to play important roles in cellular functions such as signal transduction, membrane trafficking, and cytoskeletal organization [78]. In vitro studies suggest that co-expression of *LRRK2* with *MET* facilitates an activation of MET that is independent of HGF stimulation.

MET contains an extracellular ligand-binding region with semaphorin domains, a hydrophobic membrane-spanning region near the IPT domain, and an intracellular region that contains both a tyrosine kinase domain and a C-terminal segment that mediates interactions with several signal transduction pathways upon receptor activation [79] (Fig. 2.2). In normal tissues, the activation of RTKs results from binding a protein growth factor. The growth factor that activates MET is hepatocyte growth factor/scatter factor (HGF/SF), which was identified independently as both a growth factor for hepatocytes (HGF) and as a fibroblast-derived cell motility/scatter factor

(SF). HGF/SF-MET signaling can induce different biological effects depending on the cell context, including proliferation, motility, invasion, chemotaxis, and morphogenic differentiation. Normal MET activation by HGF/SF is believed to occur through receptor dimerization and transphosphorylation of tyrosine residues, which are critical for growth factor-mediated signal transduction. Phosphorylation of two tyrosine residues located within the activation loop of the tyrosine kinase domain greatly enhances the intrinsic kinase activity of the receptor and generates a multisubstrate docking site to which several adaptor proteins, including Gab1, Grb2, Shp2, and Shc, can bind (Fig. 2.2). In turn, these adaptors recruit numerous signal transduction proteins – including phosphotidylinositol-3-OH kinase (PI3K); phospholipase C-gamma (PLC-g); the GTPases Ras, Rac1/Cdc42, and Rap1; and others – that meditate cell proliferation, cell scattering, and branching morphogenesis, depending on the cell and tissue subtype. Unlike the case of VHL where data implicates the activation of HIF as a significant event in tumor development, it is not clear which of the MET downstream signaling events is required for tumor development [79]. However, the somatic MET mutation profile and the high expression of the *MET* transcript provide the motivation for using inhibitors of MET signaling as treatments for papillary RCC [80] even though type 1 papillary tumors are relatively benign [71, 72, 81, 82].

NRF2 Gain-of-Function Renal Tumors

Emerging evidence indicates that activation of the nuclear factor (erythroid-derived 2)-like 2 protein (NRF2/NFE2L2) is common in type 2 papillary RCC. The evidence is primarily based on the high expression of downstream targets of NRF2 that are prominent in the type 2 subtype (Fig. 2.3). The genetic mechanisms that lead to activation of NRF2 in papillary type 2 RCC are

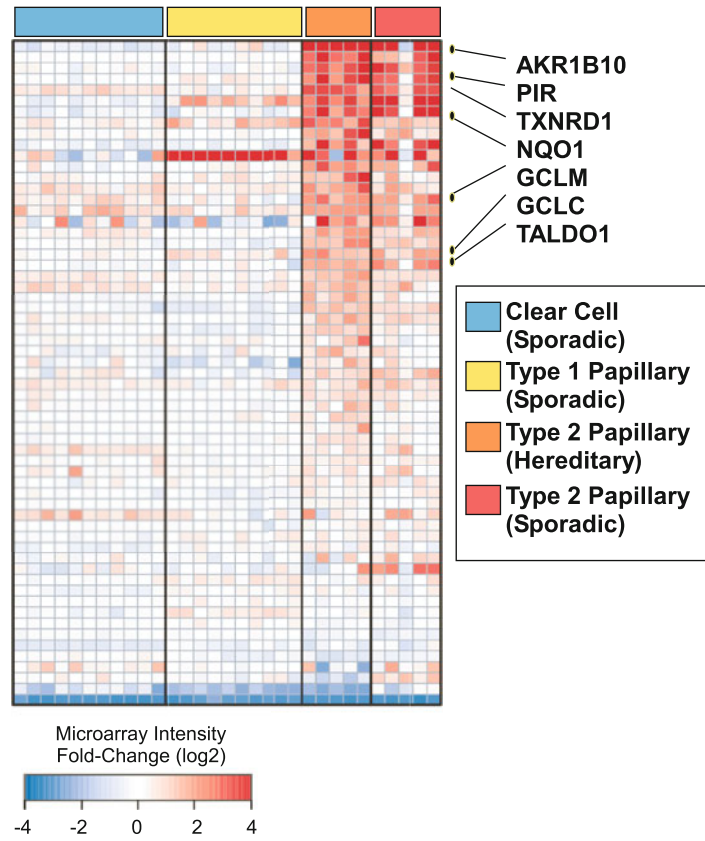

Fig. 2.3 *Activation of NRF2 in renal cancers.* Genes regulated by the KEAP1-NRF2 complex were isolated [200] and examined in representative clear cell RCCs, type 1 papillary RCCs, type 2 papillary RCCs that arose in the general population (sporadic), and type 2 papillary RCCs that arose due to germline mutations in the fumarate hydratase gene (hereditary). Each column represents an individual tumor sample, and each row represents a KEAP1-NRF2-regulated gene. *Red*, *white*, and *blue* indicate increased expression, no apparent change in expression, or decreased expression, respectively, relative to non-diseased renal tissue. Genes commonly reported to be activated by NRF2 are labeled [118]

not as well described as those for MET activation in papillary type 1 RCC.

The best described mechanism for NRF2 activation in papillary type 2 RCC involves a loss-of-function mutation in the fumarate hydratase (*FH*) gene. *FH* is located on the long arm of chromosome 1 and encodes a mitochondrial enzyme that is crucial for the generation of ATP during the citric acid cycle (oxidative phosphorylation). Single base-pair mutations in the *FH* gene occur in type 2 papillary renal tumors [83, 84]. The presence of *FH* mutations prevents FH enzymatic activity and results in a large increase in cellular fumarate levels [85]. Fumarate is a reactive chemical that covalently modifies a negative regulator of NRF2, the Kelch-like ECH-associated protein 1 (KEAP1) [86–88]. When KEAP1 no longer degrades NRF2, NRF2 accumulates and presumably activates cellular survival pathways [89, 90]. Excessive fumarate can react with proteins in addition to KEAP1 and potentially influence other signaling events as well [91–93].

NRF2 is a key transcription factor that regulates the cellular response following exposure to reactive molecules that can damage cellular proteins and lipids [94–103]. These reactive compounds can either be exogenous (such as compounds found in cigarette smoke) or endogenous (such as reactive intermediates found in metabolic cycles). NRF2 binds to a cis-acting element, termed the antioxidant response element (ARE). NRF2 binding causes the transcriptional upregulation of genes that code for aldose ketose reductases (e.g., *AKR1B10*), cytochrome P-450 mixed function oxidases (e.g., *CYP4F11*), enzymes involved in glutathione synthesis (e.g., *GCLM*, *GCLC*), and enzymes involved in glucoronidation (e.g., *UGT1A*), among others. The ARE consensus sequence also controls the expression of a large number of genes that regulate cellular antioxidative molecules, including the NAD(P)H dehydrogenase quinone 1 (*NQO1*) and thioredoxin reductase 1 (*TXNRD1*) [104].

In the canonical model, NRF2 is sequestered in the cytoplasm by the Kelch-like ECH-associated protein 1 (KEAP1). KEAP1 functions as an electrophile sensor within cells: its exposed cysteine residues, including Cys 151, are sensitive to oxidative and electrophilic modification. Chemical adduction of Cys 151 (and other cysteines) causes a conformational change that prevents KEAP1 from binding to NRF2 [105–109]. When released from KEAP1, NRF2 translocates to the nucleus and increases expression of NRF2 target genes. The NRF2-KEAP1 interactions are highly dynamic and transient, and they occur in multiple nuclear and cytoplasmic compartments [reviewed in 110]. KEAP1 adduction ultimately results in activation of NRF2-associated pathways that confer protection against cellular damage. This protection benefits both cancer and normal cells [111]; NRF2 induction in normal cells has been reported to provide longevity and anticancer properties, while in cancer cells it promotes cell survival and drug resistance [112–115].

The contribution of NRF2 to cancer cell survival can be clearly seen in lung cancer, where gain-of-function mutations in NRF2 and loss-of-function mutations in KEAP1 are frequent [113, 116–118]. For example, *NRF2* mutations are found in about 16 % of squamous cell lung carcinomas, most of which occur within exon 2, the region of the gene that encodes the DLG and ETGE motifs that interact with KEAP1 [119]. These mutations suggest that chronic activation of NRF2 provides a selective advantage to tumor cells. However, it remains to be seen whether targeted therapies that modulate NRF2 activity can prevent or limit papillary type 2 tumor growth.

CCND1 Gain-of-Function Renal Tumors

Beyond small nucleotide mutations, several other classes of somatic aberrations can affect protein functions. Chromosomal translocations were once thought to be rare in solid tumors, but they have been known to occur in renal tumors for several years [120]. A translocation involving chromosome 11q13 is found in approximately 50 % of renal oncocytomas [121], which are largely benign renal neoplasias composed of oncocytes, cells that possess mitochondria-rich cytoplasm [122]. The cyclin D1 (*CCND1*) gene

is located proximal to the 11q13 breakpoint and was thus identified as a candidate gene contributing to the oncocytoma etiology. Consistent with this finding, a subgroup of renal oncocytomas shows high levels of *CCND1* mRNA [123]. Whole-genome sequencing of renal oncocytomas has confirmed that high levels of CCND1 are associated with 11q13 translocations and earlier cytogenetic studies that mapped the breakpoint near the *CCND1* gene (B.T. and K.F., unpublished data). These translocations are analogous to those reported in B-cell lymphomas and leukemias [124–126].

The cyclin family of proteins is synthesized and degraded in a cyclical pattern closely tracking the phases of the mitotic cell cycle. Following synthesis of a cyclin protein, it binds to a cyclin-dependent kinase (CDK). Sequential binding of cyclins to cyclin-dependent kinases coordinates the completion of DNA replication and cell division. Thus, CDK activation serves as an important point of regulation, allowing cell cycle progression to proceed regardless of defects in DNA replication or mitotic spindle assembly. Although cyclin D1 activation has been associated with several diverse functions, one of its well-known effects is to promote cell proliferation through activation of CDK4 or CDK6 [127]. In renal oncocytomas, one compelling model posits that the presence of sustained levels of cyclin D1 due to the translocation event drives CDK4-/CDK6-dependent proliferation. While renal oncocytomas are mostly benign, a potential strategy to manage these tumors independent of surgery is the application of CDK inhibitors that have been tested in other tumor subtypes [127].

MiTF-TFE3 Gain-of-Function Renal Tumors

A subtype of renal tumors that occurs in pediatric patients shows a papillary histology [128, 129]. These early-onset tumors were initially described as aggressive tumors displaying papillary or alveolar patterns. Subsequent cytogenetic studies showed that the tumors contained translocations involving the X chromosome at the breakpoint Xp11.2. Now recognized as a distinct subtype of RCC, Xp11.2-translocation renal cell carcinomas often possess a rearrangement of the *TFE3* gene on the X chromosome with the *PRCC* gene on chromosome 1 [130]; *TFE3* can also be involved in chromosomal rearrangements involving other genes [130–135]. The *TFE3* gene encodes a member of the helix-loop-helix transcription factor family. Many, if not all, of the *TFE3* gene fusions result in the formation of a chimeric transcription factor with deregulated transcriptional activity. In the same gene family as *TFE3* is *TFEB*, and analogous *TFEB* translocations have been described in tumors having a papillary phenotype. In either case, inappropriate regulation of the TFE3 or TFEB protein is likely involved in tumor development. A third member of helix-loop-helix transcription factor family is encoded by the *MITF* gene. Germline mutations within the *MITF* gene, located on chromosome 3p14, predispose individuals to develop renal tumors and melanomas, further supporting a tumorigenic role for this gene family [136].

Renal Tumors with Inactivation of Chromatin-Modifying Proteins

The associations of VHL, MET, NRF2, CCND1, and TFE3 with the various subtypes of renal cancer, while important, represent an overly simplified model of renal tumor development. Early genetic mapping studies performed to identify tumor susceptibility loci indicated that regions in addition to the *VHL* locus on chromosome 3p were involved in renal tumor development. Further, both low- and high-resolution cytogenetic studies have indicated there is not a clearly defined minimal region of loss of chromosome 3p (Fig. 2.1). Rather, large sections of the chromosome 3p arm are frequently deleted in clear cell RCC tumor cells, suggesting the presence of additional tumor suppressor genes and also that mutations in *VHL* are necessary but not sufficient for development of such tumors. Resequencing approaches have uncovered new classes of mutations related to the development of clear cell RCC; one such mutation is in the

polybromo-1 gene (*PBRM1*) [137]. Approximately 35 % of clear cell RCC cases harbor *PBRM1* mutations, most of which are insertion/deletion or nonsense mutations. The identification of these somatic variants implicates *PBRM1* as a tumor suppressor lost in renal tumor development. Similar to VHL, loss of the p-arm of chromosome 3 is consistent with a two-hit mutation model for *PBRM1* alleles.

PBRM1 encodes a 180-kDa subunit of the SWI/SNF chromatin-remodeling complex [138]. This complex was first described in independent genetic screens that discovered yeast mutants incapable of switching between mating types (SWI) or incapable of shifting between high- and low-glucose media for growth (SNF). Decades of subsequent studies have shown that the SWI/SNF complexes are conserved in humans and that multiple, distinct SWI/SNF complexes can be formed. The SWI/SNF protein subunits fit into three categories: enzymatic, core, and accessory. SWI/SNF complexes are formed from a central ATP-dependent DNA helicase enzyme with core subunits and a set of accessory proteins. PBRM1 was co-purified with the BRG1 helicase and is also known as BAF180, for "BRG1-associated protein of 180 kDa" [139]. BRG1 is the enzymatic component of this particular SWI/SNF complex, and PBRM1 is an accessory protein.

It is thought that the accessory proteins dictate the specificity of the SWI/SNF nucleosome remodeling and of tissue-specific regulation of cellular development and differentiation [140–142]. Increasing evidence suggests that the SWI/SNF chromatin-remodeling components have an important role in tumor formation and various subunits have been implicated in modulation of the cell cycle and DNA repair [143–149]. PBRM1 has been associated with inhibition of the cell cycle by activation of the p21 cyclin-dependent kinase inhibitor and by induction of G(1) arrest following radiation exposure [150]. PBRM1 also regulates p53 activity and activates cellular senescence following exposure to activated RAS (i.e., oncogenic stress) [151]. These activities are comparable to mutations in *SMARCB1* (also termed BAF47) that are found in rhabdoid tumors and lead to inactivation of the cyclin-dependent kinase inhibitors p21 and p16 [149, 152]. Another accessory protein, ARID1A (also termed BAF250), was recently found mutated in a large fraction of clear cell ovarian carcinomas [153, 154], and an imbalance of other subunits has been observed in human cancers [155, 156]. Functional studies of *PBRM1* mutations are ongoing in an attempt to identify its role in clear cell RCC initiation and progression [157].

Another mutation that may affect chromatin structure occurs within the *BAP1* gene. *BAP1* (BRCA1-associated protein-1) is located on the short arm of chromosome 3 very near the *PBRM1* gene; as such, most clear cell renal tumor cells are haploinsufficient at this locus. Putative loss-of-function mutations in this gene were identified in several cases of renal cell carcinoma [158]. BAP1 is a deubiquitinating enzyme that removes ubiquitin marks on nuclear proteins, and both germline and somatic mutations in this gene are associated with tumor development [159–162]. Like VHL, this enzyme activity can affect multiple cellular processes. Some of the best-studied roles of BAP1 in tumor development are through its regulation of the chromatin-associated human factor HCF1 [163], which is a dimer that regulates transcription through the modulation of chromatin structure and is required for the recruitment of the methyltransferases Set1 and MLL1 to histones [164, 165]. This activity has been associated with deregulation of multiple aspects of the cell cycle, including entry into G1 and later in cytokinesis [166]. This is associated with, but distinct from, the role of *PBRM1* in regulating the cell cycle.

Several genes associated with histone modification – including the histone methylases *SETD2*, *MLL*, *MLL2*, and *MLL4* and the histone demethylases *JARID1C*, *JARID1D*, and *UTX* – have also been implicated in the development of clear cell RCC, although the frequency of these mutations (1–4 % of tumors) is much lower than that of *PBRM1* or *VHL* mutations [29, 167, 168]. The *MLL*, *MLL2*, and *MLL4* gene loci are large, and it is possible that mutations in these genes are "passenger" mutations that arise due to random background mutation. On the other hand, the

family of *MLL* genes is frequently mutated in other tumor subtypes [169], including *ARID1A* mutations in ovarian clear cell carcinoma [153, 154, 170]. Interestingly, *SETD2* encodes a histone H3 lysine methyltransferase that maps to chromosome 3p21.3, a region noted in loss-of-heterozygosity studies as associated with development of clear cell RCC. However, the role of *SETD2* and other histone-modifying genes in promoting tumor development remains unclear [168, 171].

Renal Tumors with Inactivation of Electron Transport Proteins

In addition to the nuclear genome, each mitochondrion of a cell contains DNA (mtDNA) that codes for several proteins that are part of the electron transport pathway (Fig. 2.4). Mutations in mitochondrial DNA have a particularly strong association with mitochondria-rich tumors, termed oncocytic tumors. Mitochondria-rich cells also occur in a small subset of clear cell RCCs, termed granular clear cell RCC. Gene expression studies have revealed high expression of electron transport-related genes in these tumors [172–174]. Somatic defects in the mitochondrial genome are also strongly associated with the development of renal neoplasias, although this is complicated by the fact that renal tumor cells contain hundreds of copies of the mitochondrial genome [175].

Oncocytic tumors have been characterized by granular, eosinophilic cytoplasm due to an overabundance of defective mitochondria. Sporadic oncocytic tumors, renal oncocytomas in particular, have been shown to accumulate mutations within the mitochondrial genome [172, 173]. Two types of mtDNA mutations have been identified. The first type is somatic mtDNA mutations that inactivate subunits of the mitochondrial complex I [172–174, 176, 177]. In renal oncocytomas, frameshift mutations in the genes of either subunit ND1, ND4, or ND5 of complex I occur at high frequency, and the activity of complex I is undetectable or greatly reduced in renal oncocytomas. Somatic mutations found in chromophobe RCC also tend to be associated with mitochondrial mutations, including complex I mutations [178]. In chromophobe renal cancer, mtDNA mutations in the D-loop and in the mitochondrially encoded ribosomal RNA have also been reported [178]. The role of these mutations in regulating mitochondrial function is not clear.

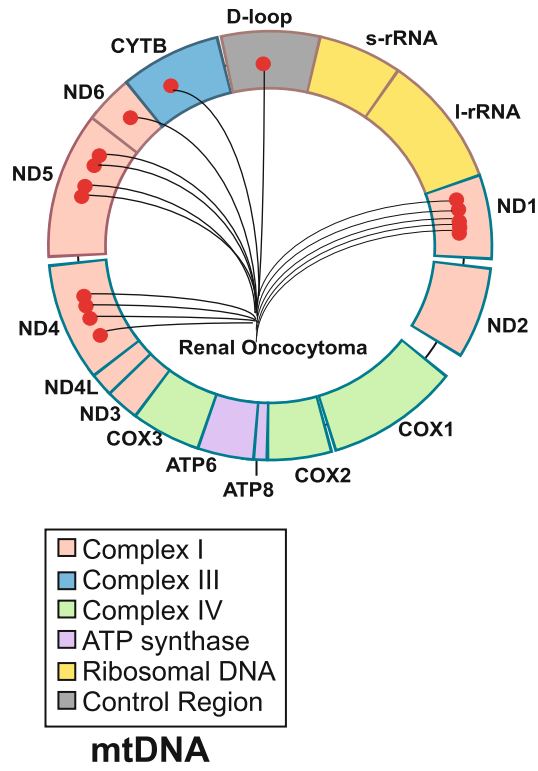

Fig. 2.4 *Somatic mitochondrial mutations in renal oncocytoma*. Mitochondrial gene organization and the location of the somatic mutations that have been reported in renal oncocytoma. The majority of mutations affect genes encoding proteins that are part of complex I

Both sporadic renal oncocytoma and chromophobe RCC have mitochondria-dense cytoplasm and high expression of genes associated with oxidative phosphorylation [172, 174, 179]. The gene expression and cellular phenotypes observed are thought to represent feedback mechanisms to compensate for mitochondrial impairment by increasing the number of mitochondria. Further work is required to understand how the defects in mitochondria are associated with renal tumor development [180].

Cytogenetic Variants Within Renal Tumors

In addition to small mutations and specific structural variants, some of the most dramatic genetic abnormalities in sporadic RCC are defects in chromosome number [181]. The chromosome content of renal cell carcinomas has been well scrutinized using comparative genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) [17, 21, 71, 182–188]. Just as specific single-nucleotide defects are associated with different histological subtypes of RCC, the common subtypes also have characteristic sets of chromosomal abnormalities [3], and quantification of these chromosomal defects can assist in classification of the tumors [11, 19, 23, 72].

Sixty to seventy percent of clear cell RCCs are characterized by loss of chromosome 3p. Losses of chromosomes 14q, 8p, 6q, or 9p occur at frequencies ranging from 15 % to 25 %. A gain of chromosome 5q occurs in about 50 % of renal tumors and a gain of chromosome 7 in approximately 15 % [21]. An unbalanced chromosomal translocation between the p-arm of chromosome 3 and another chromosome is fairly common. One early insight into the genetic regulator on chromosome 3p and its link to clear cell RCC was based on finding a translocation between chromosome 3 and chromosome 8 [16]. Subsequent studies have revealed that the most common translocation partner of chromosome 3p is the q-arm of chromosome 5. The formation of the t(3;5) derivative chromosome results in a net loss of one copy of chromosome 3p and a net gain of one copy of chromosome 5q [21]. While gain of chromosome 5q is the second most common cytogenetic abnormality in ccRCC, tumor cells that harbor this abnormality tend to be less aggressive than tumor cells that lack it [9, 21].

One interpretation of the frequent appearance of specific cytogenetic abnormalities is that tumor-modifying genes located within a region of frequent amplification or deletion become deregulated. Many genes within that region of chromosome 5q become overexpressed [74]; the colony-stimulating factor 1 receptor (*CSF1R*) gene on chromosome 5q32 is an example of a candidate mediator of tumor formation [11, 48, 189, 190]. Signaling through CSF1R prevents cellular apoptosis, and CSF1R is part of a complex signaling interaction between the tumor cells and the tumor microenvironment. CSF1R is also inhibited by the RTK inhibitor sunitinib, although the dose required for CSF1R inhibition is five to ten times higher than the dose required to inhibit the VEGF receptor [191]. How CSF1R and other genes in its region contribute to renal tumor formation remains an active area of investigation.

In clear cell RCC, several chromosomal abnormalities are associated with increased renal tumor cell aggressiveness. For nearly 15 years, deletions of chromosome 14q have been associated with aggressive tumors [2, 11, 23, 192, 193]. Emerging data suggests that shifts within the isoforms of the HIF transcription factor may be one of the biochemical mechanisms for loss of 14q [194, 195]. The *HIF1A* gene is located on chromosome 14q23. Given the dramatic upregulation of the HIF transcription factor complex as a result of *VHL* mutation in clear cell RCC and the influence of activation of angiogenic pathways in tumor development, it was somewhat surprising that a somatic mutation screen revealed loss-of-function mutations in the HIF1A isoform in this tumor subtype [29, 195]. In addition, expression of the HIF2A isoform, which is located on chromosome 2p, has been strongly linked to renal tumor development and aggressive renal tumors [55, 58, 196]. Loss of chromosome 14q is associated with decreased expression of HIF1A mRNA and decreased HIF1A protein levels in clear cell RCC. A compelling model is that loss of the *HIF1A* gene locus disrupts the balance of HIF1A and HIF2A isoform expression within the cell, leading to disproportional expression of HIF2A and the formation of HIF2A-driven tumors.

Another region of chromosome loss that is frequently associated with more aggressive renal tumors is on chromosome 9 [21, 188, 197]. Recent high-resolution mapping studies have highlighted a minimal region of deletion and predict that cyclin-dependent kinase inhibitors (CDKIs) are likely candidate tumor suppressor genes from that chromosome 9q region [22].

The cyclin-dependent kinases are regulated by a family of CDKIs, which are expressed in a highly regulated manner to prevent inappropriate activation of CDKs. Two related CDKIs, CDKN2A and CDKN2B, both inhibitors of CDK4, reside in the 9q deletion region. However, more robust analysis of the region suggests that other genes proximal to the CDKIs are also associated with the 9q deletion [198].

In addition to histological distinctions between clear cell and papillary renal tumors, there are also distinctions in chromosomal abnormalities. For instance, loss of chromosome 3p and gain of chromosome 5q are uncommon in papillary RCC. Type 1 papillary RCCs are instead characterized by gains of chromosomes 3q, 7, 12, 16, 17, and 20 [71–74] in about 70–80 % of cases. As previously mentioned, *MET* and *LRRK2* are located on chromosomes 7 and 12, respectively, but many other candidate genes map to these chromosomes as well. Although type 2 papillary RCCs share some abnormalities with papillary type 1, gains of chromosome 7, 12, and 17p are less frequent, and losses of chromosome 9/9p and gains of chromosome 8q are more frequent in type 2 papillary RCC. Moreover, the amount of cytogenetic variability also differs between type 1 and type 2 tumors. In type 1 papillary RCC, the tumor cells are cytogenetically homogenous, and it is rare to find cells that contain abnormalities other than the common ones described above. Type 2 tumor cells often contain additional cytogenetic abnormalities involving a more chaotic assortment of chromosomes that do not seem to follow a particular pattern [71–75]. This increased complexity may be a reflection of the advanced stage that is typically associated with type 2 tumors. Interestingly, gains of chromosome 17 were found in a large fraction of type 1 and type 2 papillary tumors. When taken as a whole, it seems as though a tumor-modifying gene that maps to chromosome 17 is a common occurrence in papillary tumors.

Chromophobe renal cell carcinomas contain different chromosomal abnormalities than either clear cell or papillary RCC. Chromophobe RCCs contain frequent losses of chromosomes 1, 2, 6, 10, 13, and 17; the tumor cells have lost so much genetic material that they are considered severely hypoploid. There are two variants of chromophobe RCC, typical and eosinophilic [187], and genetic differences between these variants have not yet been reported. While renal oncocytoma and chromophobe RCC share gene expression and morphological characteristics, these tumors differ in their cytogenetic abnormalities [123]. Renal oncocytoma cells are either karyotypically normal or contain a limited number of abnormalities that may include loss of chromosome Y [199], loss of chromosome 1 [186, 199], or translocations involving chromosome 11. Interestingly, tumor cells that harbor loss of chromosome 1 are mutually exclusive to tumor cells that contain translocations of chromosome 11, suggesting two genetically distinct subtypes of renal oncocytoma. The fact that loss of chromosome 1p is shared between renal oncocytoma and chromophobe RCC suggests that a tumor-modifying gene is located in this interval. However, nearly 1,500 genes are thought to map to this region, so identifying the candidate gene(s) by traditional mapping studies is daunting.

Summary

The developments of rapid sequencing and high-resolution cytogenetic approaches have led to a continued reexamination of the genetic defects that occur in RCC. In many cases, these new studies have confirmed a variety of small nucleotide mutations, structural mutations, and large chromosomal abnormalities. However, application of these new technologies has also identified new molecular pathways that were previously unappreciated in RCC, such as mutations in genes that interact with chromatin structure and the activation of NRF2 in type 2 papillary RCC. Between 5 and 70 small somatic mutations can be found in individual tumor cells of the clear cell histology [137, 158] and several other histologies (B.T. and K.F, data not shown), in addition to large and small cytogenetic abnormalities reported in this chapter. How these mutations interact with and modify the HIF, NRF2, MET, and CCND1 signaling pathways will be an important area of study in order to develop a more complete picture

of the molecular pathways that are deregulated in RCC. Moreover, continued study of the molecular genetic defects may also provide opportunities for new targeted therapies that may prevent tumor cell growth.

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Familial and Hereditary Syndromes

3

Brian Shuch and Peter Pinto

Introduction

While most cancers are believed to occur sporadically, there is increasing recognition that cancers can cluster in families [1]. Currently it is believed that up to 10 % of cancers have a hereditary cause, and several dozen cancer susceptibility syndromes are now recognized [2]. Of the 60,000 new cases of RCC diagnosed in the United States each year, hereditary RCC is estimated to account up to 4 % of these cases [3, 4]. As with other cancers, familial clustering has been observed with RCC, and the risk nearly doubles when a parent or sibling has a history of RCC [4]. Previous studies suggest over half of kidney cancers could have a hereditary predisposition with RCC segregating in specific lineages [5]. Many of these hereditary syndromes are related to a single alteration in a tumor suppressor gene or a proto-oncogene and therefore are testable with genetic testing. However, many presumed hereditary cancers are currently impossible to diagnose with existing technology. In these cases, risk can be associated with inherited predisposition loci rather than specific gene alterations [6, 7].

The study of hereditary kidney cancer has led to much of the current understanding of kidney cancer. Efforts to better understand the genes responsible for hereditary RCC and their function are expected to lead to the development of novel therapeutic agents [3]. Similar cytogenetic and molecular alterations are shared between sporadic and hereditary forms of kidney cancer. The study of the molecular biology of clear hereditary RCC has lead to the development and the approval of seven new targeted cancer agents. Other therapeutic strategies developed from the study of hereditary papillary kidney cancers and now form the basis of current clinical trials for sporadic forms of kidney cancer.

Several kidney cancer syndromes are related to metabolic alterations converging on similar pathways involved in dysregulated oxygen sensing, iron metabolism, and energy/nutrient sensing [8]. While well-characterized RCC syndromes exist including von Hippel-Lindau (VHL), hereditary papillary RCC (HPRC), hereditary leiomyomatosis and RCC (HLRCC), and Birt-Hogg-Dubé (BHD), less common syndromes have also been described in recent years. While many of the RCC syndromes share common dysregulated metabolic pathways, there are variations associated with tumor histology, aggressiveness, and renal penetrance.

Clinicians treating patients must recognize the hereditary syndromes as their management can differ from those with sporadic kidney cancer. Specific management strategies have been developed to provide oncologic control and maximize kidney function in this population. It is not uncommon that patients have clear signs of a known hereditary syndrome and are managed similarly to sporadically occurring cancers. While

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some management strategies are similar, often they are not and patients can be managed inappropriately. While many urologic oncology physicians recognize the existence of familial cancer syndromes, incomplete penetrance, poor family history, and the development of de novo mutations often mislead clinicians with limited experience with these syndromes.

In this chapter, we will discuss the multiple hereditary RCC syndromes. The specific features and guidelines that should trigger referral for genetic testing will also be reviewed. The genetics and management strategies for the individual syndromes will be outlined.

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 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 exon 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.

Table 3.1 Features suggestive of hereditary kidney cancer

Features suggestive of hereditary RCC syndrome
Bilateral renal tumors
Multifocal renal tumors
Associated renal cysts
Early age of onset
Strong family RCC history
Unusual histologic types
Related malignant cancers
Dermatologic manifestations
Benign clinical features

Description of Hereditary Syndromes

Von Hippel-Lindau

Von Hippel-Lindau (VHL) was first described in the early twentieth century when two physicians von Hippel and Lindau described manifestations of the disease. The syndrome is characterized by the development of multiple highly vascular tumors including clear cell RCC, retinal angiomas, hemangioblastomas of the spine and cerebellum, pancreatic cysts and neuroendocrine tumors, pheochromocytomas, and cystadenomas of the ovary and epididymis (Fig. 3.1). The disease affects 1:35,000 individuals and is inherited in an autosomal dominant pattern.

Determination that a single gene was responsible VHL came from the study of RCC where

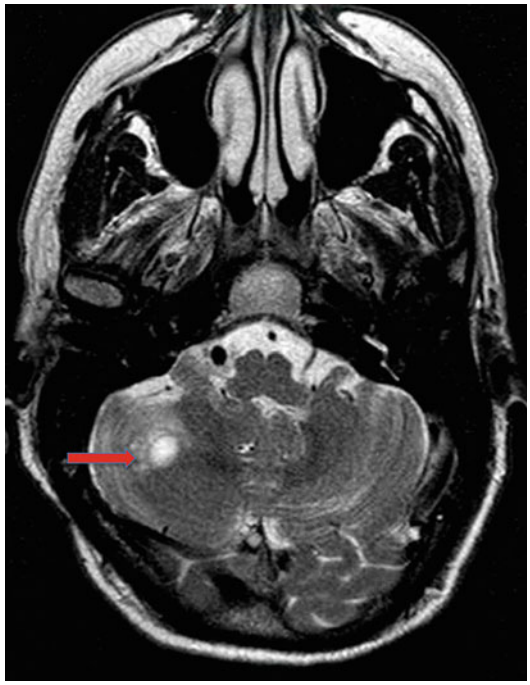

Fig. 3.1 Cerebellar hemangioblastoma in a patient with VHL (*red arrow* showing lesion)

loss of 3p was consistently observed [9, 10]. Affected individuals were believed to have secondary somatic events leading to the loss of the wild-type allele. Further linkage analyses of affected individuals confirmed the gene to be located around 3p25 [11].

Later work at the National Cancer Institute located the *VHL* gene to 3p25.1 and determined it behaved like a classic tumor suppressor gene [12]. Different mutation types have been described which divide the disease into two types based on the occurrence of pheochromocytoma [13]. Type I VHL is not associated with pheochromocytoma and is caused by germline deletions, insertions, and nonsense mutations. Type II VHL is cause by missense mutations and can further be divided by the development of RCC and hemangioblastoma.

Approximately 25–60 % of patients with VHL develop bilateral, multifocal renal lesions consisting of cysts and clear cell RCC [14]. 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 [15]. Prior to the current management recommendations, a third of patients died of metastatic RCC [14, 16]. With proper screening, recommended with ultrasounds beginning in childhood, renal lesions are identified early and treatment can prevent the development of metastatic disease [14]. The historic management of those with multifocal RCC included bilateral radical nephrectomy with hemodialysis. The past two decades have seen the emergence of patients having been managed with repeat partial nephrectomy.

Hereditary Papillary Renal Cell

Hereditary papillary renal cell carcinoma (HPRC) is a very rare syndrome with approximately a dozen families reported in the literature. HPRC was the second hereditary RCC syndrome described, first defined in 1994 in a lineage demonstrating papillary renal cell cancer in three generations. Analysis of affected individuals found no evidence of linkage to the VHL loci, and tumors consistently did not show loss of 3p [17]. The germline mutation associated with HPRC was linked to chromosome 7q31 and identified as *MET* [18]. MET is an important tyrosine kinase receptor with hepatocyte growth factor as its ligand [19]. As this proto-oncogene is present in every cell in the body, highly activating mutations are not observed except in sporadically occurring tumors with somatic *MET* alterations [20]. While the *MET* activation alone may be insufficient for transformation, trisomy 7 is common in HPRC and it preferentially amplifies the mutant copy [21].

Unlike the other hereditary RCC syndromes, the only manifestation of this disease is kidney cancer. The syndrome behaves in an autosomal dominant fashion and is highly penetrant with 67 % of individuals developing RCC by age 60 [22]. Renal tumors associated with papillary RCC generally appear after the age of 30; however, an early-onset genotype has been described [22, 23]. Tumors associated with HPRC routinely demonstrate a papillary type I pattern [24].

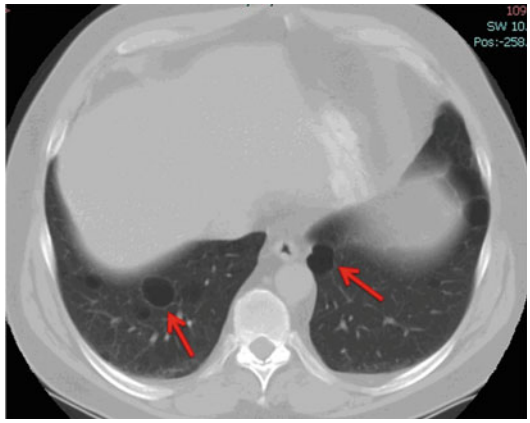

Fig. 3.2 Lung cysts in a patient with BHD (*red arrows* showing cysts)

Several thousand small papillary tumors are estimated to be present in the normal parenchyma of patients with HPRC [25].

Birt-Hogg-Dubé

Birt-Hogg-Dubé syndrome (BHD) is hereditary cancer syndrome first discovered by a team of Canadian dermatologists whom described a large family with dermatologic lesions demonstrating abnormal hair follicles associated with fibrous tissue. Associated skin manifestations also included trichodiscomas and acrochordons [26]. Patients with BHD were later found to have a 50-fold increased incidence of pneumothoraces (Fig. 3.2) [27]. The final manifestation of BHD is bilateral, multifocal solid renal neoplasms [28–30].

The incidence of BHD is believed to be around 1:200,000 and is passed in an autosomal dominant manner. Linkage analysis of kindreds with BHD located the gene to chromosome 17p11.2 [31]. Later, the gene for BHD was determined to be *folliculin* (*FLCN*), which behaves like a classic tumor suppressor syndrome [32]. FLCN is part of a complex that is believed to be a downstream effector of AMPK and mTOR [33]. Preclinical models demonstrate that both mTORC1 and mTORC2 become activated with loss of FLCN [34].

Renal tumors occur in approximately 20 % of patients affected with BHD with mean age around 50 years of age [28–30]. The renal prognosis is favorable with <5 % of affected individuals developing metastatic disease [35]. Those that have proceeded to develop metastatic had large primary tumors that were not managed with modern screening practices [35]. Renal tumor histology is variable with hybrid oncocytic (mixture of oncocytoma and chromophobe RCC) and chromophobe tumors occurring in 50 % and 35 %, respectively [36]. Both clear cell and papillary RCC rarely occur in BHD, but when they do, tumors can behave very aggressively [35].

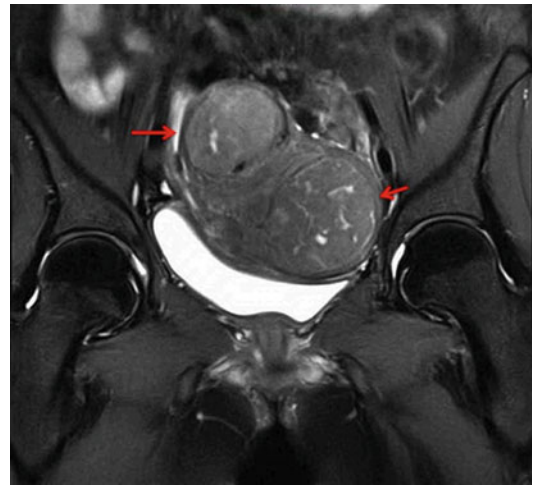

Fig. 3.3 Large uterine fibroids in a 24-year-old female with HLRCC

Hereditary Leiomyomatosis and Renal Cell

Hereditary cutaneous leiomyomas were first noted in the dermatology literature in 1958 [37]. This condition was associated with early-onset uterine fibroids and renal cell carcinoma, leading to the new name, hereditary leiomyomatosis and renal cell cancer (HLRCC) (Fig. 3.3) [38–40]. Recently, a fourth manifestation of HLRCC, macronodular adrenal hyperplasia, has also been described [41]. Genetic linkage localized the chromosomal region to 1p42.3–43 and later identified the gene as *fumarate hydratase* (*FH*) [42, 43]. FH is a key Krebs cycle enzyme responsible for the conversion of fumarate to malate.

HLRCC-associated tumors demonstrate loss of heterozygosity of wild-type *FH*, leading to an impairment in the Krebs cycle shifting metabolism towards aerobic glycolysis [43–45]. Approximately 15–30 % of patients with HLRCC develop renal tumors [39, 46]. While these tumors were initially described as papillary type II, other morphologies can be observed [47]. The unifying features are eosinophilic nucleoli with a clear, perinuclear halo [44]. The initial experience with these tumors was much different than the other hereditary RCC syndromes with patients having an extremely aggressive disease. Over half the patients in the initial series demonstrated regional or distant disease even when associated with small renal primaries [46]. 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.

Succinate Dehydrogenase Deficiency B, C, and D

Classically, only 10 % of pheochromocytomas have been considered to have a hereditary component. However, in recent years, multiple genes have been identified that predispose to the development of pheochromocytoma and paraganglioma, and now, over 25 % of non-syndromic cases are believed hereditary [48]. Several of these syndromes are associated with germline mutations in different members of the succinate dehydrogenase (SDH) complex, an inner mitochondrial enzyme critical to the electron transport system and the Krebs cycle. The inheritance patterns of these syndromes behave in an autosomal dominant pattern. The development of kidney cancer was first linked to SDHB nearly in 2004 with approximately 10 % of individuals affected with RCC [49]. Subsequent studies demonstrate that nearly 5 % of familial RCC cases with no associated manifestations are associated with *SDHB* germline mutation [49, 50]. The other SDH subunits have been suspected of increasing risk of kidney cancer, and recently, several individuals with SDHC and SDHD have been found to have RCC [51, 52]. Besides RCC and pheochromocytoma, recent evidence suggests that patients with SDH mutations may be at risk for gastrointestinal stromal tumors [53].

Little is known about the SDH family of renal tumors except they can present with an early-onset disease and appear to have an aggressive phenotype. Similar to HLRCC, the loss of SDH function leads to failure of the Krebs cycle, aerobic glycolysis, and upregulation in hypoxia pathways [54]. As many patients may present without a family history of a pheochromocytoma, early-onset and pathologic features may be the only suggestion of SDHB. A recent report describes SDHB tumors as having characteristic features including indistinct cell borders and eosinophilic cytoplasm [55].

Bilateral, Multifocal, and Familial Renal Oncocytoma

Oncocytomas are the most common benign renal neoplasms and represent approximately 5 % of overall kidney tumors. Oncocytomas have an enhancement pattern similar to malignant tumors on imaging, and renal mass biopsy often cannot distinguish them from other eosinophilic tumors. These tumors look similar to chromophobe tumors and have a nested pattern with abundant mitochondria. As with malignant neoplasms, oncocytomas can grow during periods of observation [56]. Tumors are generally small and asymptomatic, but large tumors can produce local symptoms.

Oncocytomas are found in roughly 1 in 1,000 autopsy cases, and approximately 10 % of oncocytomas are bilateral [57–59]. Pathologic concordance of a contralateral renal tumor in a patient with a known oncocytoma is over 70 % [60, 61]. Patients with bilateral, multifocal oncocytomas should have genetic testing for BHD. When negative, these patients are considered bilateral, multifocal oncocytoma (BMF-O). A familial form has been named familial renal oncocytoma (FRO) with affected individuals developing bilateral and multifocal oncocytomas [62]. While several families in the initial series were later found to have

intron mutations in the *FLCN* gene, the remaining families are still considered to have FRO. Generally patients can be observed with imaging studies, and if a lesion demonstrates rapid growth, it can be biopsied to confirm histology. Reasons for intervention include palliation of local symptoms or if a tumor is demonstrating rapid growth, allowing surgery while still amenable to partial nephrectomy. The etiology of this tumors in unknown; however, sporadic forms demonstrate loss of chromosome 1p, and Y occurs in approximately 50 % of tumors [63]. Patients with BMF-O and FRO have been undergoing whole genome sequencing to determine if there is a common gene responsible for this syndrome.

A specific group of individuals have a variant syndrome, called renal oncocytosis. Diffuse oncocytic nodules are dispersed throughout the renal parenchyma [64]. Specific care must be performed to maintain renal function as progression towards chronic kidney disease is believed related to the disease process. As metastatic progression has not been demonstrated, patients should be managed conservatively when possible.

Cowden's Syndrome

Cowden's syndrome is an autosomal dominant hereditary cancer syndrome recently linked to the development of kidney cancer. The prevalence of Cowden's syndrome is believed to be around 1:200,000 individuals; however, many experts believe this is an underestimation [65]. The gene for Cowden's was first localized to 10q22 by linkage analyses and later identified as the tumor suppressor gene *PTEN* [66, 67].

Cowden's is characterized by multiple cutaneous and mucocutaneous hamartomas. Trichilemmomas are benign hair follicle tumors considered a pathognomonic characteristic and were first recognized 50 years ago in the dermatologic literature [68]. Benign characteristics include macrocephaly and central nervous system hamartomas, called Lhermitte-Duclos disease. The neurologic manifestations can include ataxia, tremor, and mental retardation. Epithelial neoplasms are a hallmark of Cowden's syndrome with breast, uterine, thyroid, colon, and prostate cancers the most frequent malignancies. Recently a large cohort of Cowden's patients was analyzed, and there was a 4 % incidence of papillary and chromophobe renal neoplasms. This represented nearly a 30-fold increase in the risk of developing kidney cancer. There is an estimated 34 % lifetime risk of developing kidney cancer and therefore screening for kidney cancer is suggested [69].

Microphthalmia-Associated Transcription Factor RCC

Approximately half of young individuals (age <20) with RCC have a specific type of kidney cancer called "translocation renal cell carcinoma." This papillary tumor behaves extremely aggressively, and when metastatic, patients have poor prognosis. Most forms of this tumor type occur sporadically and are associated with unbalanced chromosomal translocations similar to that observed with alveolar soft part sarcoma [70]. Translocations of t(X;11) and t(6;11) lead to dysregulation of TFE3 and TFEB, respectively, both members of the microphthalmia-associated transcription factor (MITF) family [70, 71]. A third member of the family, MITF, has no fusion partner leading to renal malignancy. However, a germline mutation in this gene has been identified affecting posttranslational modification and transcription factor activation. This germline *MITF* mutation leads to dysregulated cell signaling and is associated with the development of melanoma and renal cell carcinoma [72].

Tuberous Sclerosis 1 and 2 (TSC1 and 2)

Tuberous sclerosis complex (TSC) is an autosomal dominant condition characterized by tumors in the brain, eye, and kidney. Dermatologic manifestations include both ash leaf and shagreen patches. Neurologic conditions are quite common and include epilepsy and mental retardation. Germline mutations can be found in two tumor suppressor genes, *TSC1* (hamartin) and *TSC2* (tuberin) [73, 74]. Renal manifestations are highly penetrant and include angiomyolipomas, cysts, and clear cell RCC (Fig. 3.4). Chronic kid-

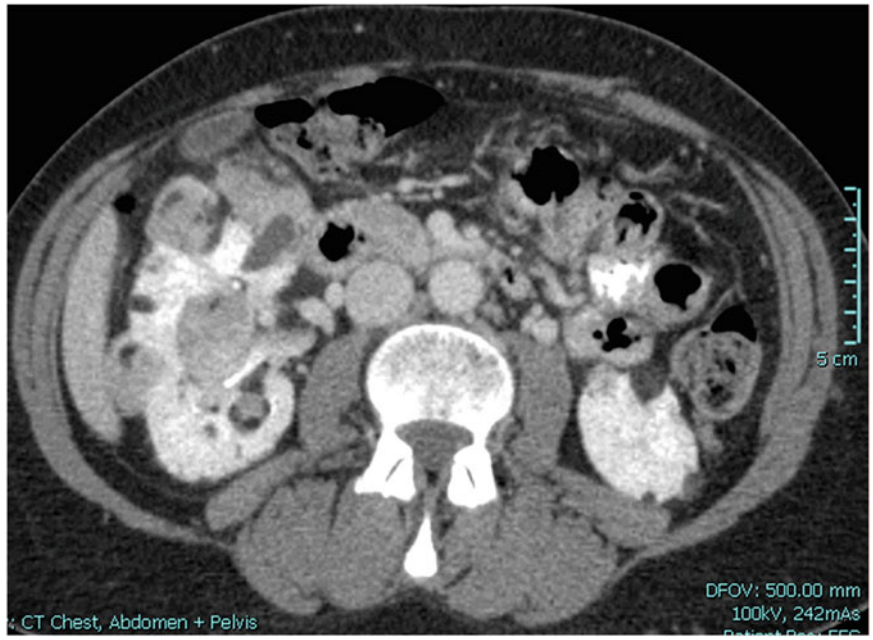

Fig. 3.4 Bilateral, multifocal angiomyolipoma in a patient with TSC

ney disease is also common in these patients, but the etiology is unknown. Clear cell RCC is not common, but when it occurs, it can behave aggressively [75]. Angiomyolipomas can become quite large and cause local symptoms. The risk of hemorrhage increases with size and can be life-threatening. Loss of TSC2 in animal models has demonstrated upregulation of HIF and mTORC1, similar to VHL-related clear cell RCC [76, 77].

Chromosome 3 Translocation Kidney Cancer

In 1979, Cohen and colleagues reported a family with hereditary kidney cancer demonstrating an abnormal karyotype, a balanced translocation involving chromosome 3. Since that time, a dozen chromosome 3 translocations have been associated with hereditary clear cell RCC, each involving different break points on various chromosomes [78]. These individuals do not have other nonrenal manifestations and appear to develop kidney cancer at a later age than patients affected with VHL. Patients with this entity appear to have a three-hit model of renal carcinogenesis (Fig. 3.5). First, they are born with an abnormal karyotype with translocation of chromosome 3p to a different chromosome. Second, they have loss of the derivative 3p fusion chromosome. Finally, the remaining VHL allele undergoes a somatic mutation [79, 80].

Familial Renal Cancer (FRC) of Unknown Etiology

Our institution considers affected individuals with a first- or second-degree relative with kidney cancer to have familial renal cancer (FRC). Many patients with FRC will present with bilateral and multifocal RCC. Frequently despite genetic counseling, a germline mutation may not be identified. In the future, these individuals may be identified with a cancer syndrome as each year additional syndromes are characterized. Currently around 50 cancer syndromes are recognized and are related to monogenic germline mutations [2]. As cancer susceptibility may be more complicated than a single gene, failure to identify a hereditary syndrome with the current testing modalities cannot rule out a more complex genetic component involved in familial predisposition.

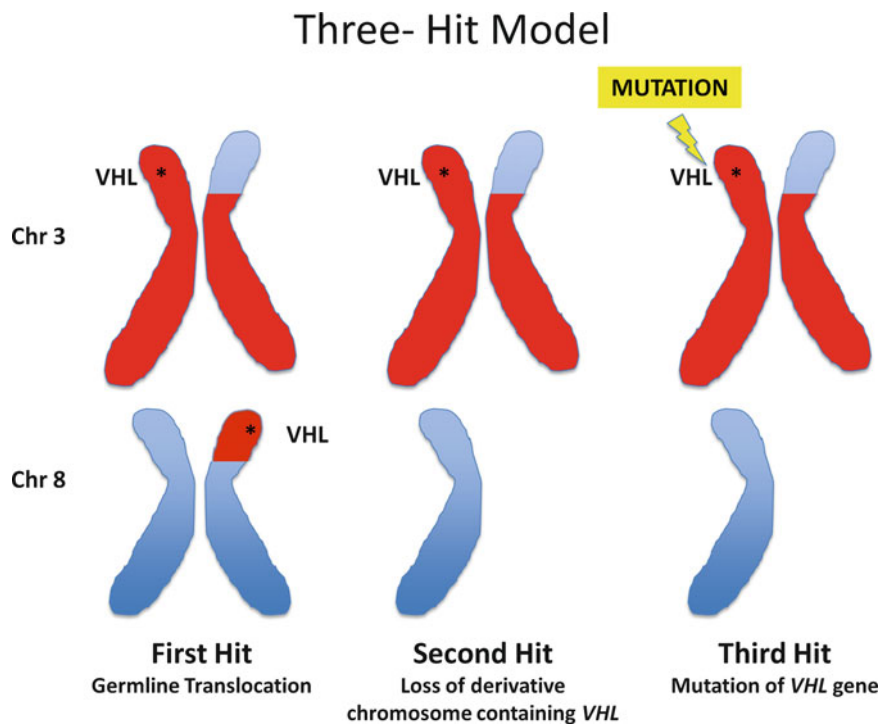

Fig. 3.5 Mechanism of the three-hit model for chromosome 3 translocation RCC

Management of Hereditary Cancer Syndromes

The principles of therapy in patients with hereditary cancer are to prevent cancer dissemination, maximize kidney function, limit the number of renal interventions, and minimize surgical morbidity. The following approaches have been developed in this patient population.

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 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 [81]. While over half of patients frequently had disease recurrence, almost all patients demonstrated excellent cancer-specific survival [81]. 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 [82]. 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 [35].

Individuals with FRO and BMF-O are predisposed to the development of multiple bilateral, multifocal oncocytomas. In an individual with a prior oncocytoma, the pathologic concordance of metachronous lesions may be between 70 % and

100 % [60, 83]. In someone with known or suspected FRO or BMF-O, close surveillance may be warranted to avoid unnecessary surgery. In individuals with rapidly growing lesions, it may be beneficial to perform a renal biopsy to exclude other histologic types that may need intervention. For tumors that are found to be oncocytoma, we recommend close observation with intervention if tumors become symptomatic.

Surveillance is not recommended for individuals with HLRCC as small lesions have shown the propensity for locoregional and distant spread [46]. 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 [75, 84]. More clinical experience is needed to evaluate the aggressiveness of kidney cancer associated with Cowden's or MITF prior to recommending a surveillance strategy.

Surgery

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 [85–87]. 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 [88, 89].

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, performing tumor removal in a coordinated, step-wide fashion, from easiest to most challenging tumor minimizes ischemic time if clamping becomes necessary. 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.

Performing a wide margin on multiple lesions would lead to significant loss of adjacent parenchyma. Tumor enucleation has emerged as the preferred method of resection in most hereditary cancer syndromes [90]. This approach has had much success in patients with VHL, BHD, and HPRC [91]. For HLRCC and SDH renal tumors, our approach has been a wide surgical excision as we have observed an infiltrating pattern outside the pseudocapsule. The role of enucleative surgery in the remaining hereditary cancer syndromes is unclear; however, as this approach has proven safe with sporadic tumors, it likely is safe in these syndromes [90].

Systemic Therapy

Due to the multifocal nature of hereditary kidney cancer, many patients face the potential morbidity of repetitive kidney cancer surgery. With each renal intervention due to scarring, the complexity and the rate of complications increase. Understanding the specific gene alterations associated with the various hereditary syndromes led to insights into therapeutic strategies aimed at exploiting the disease biology [92]. A systemic therapy approach may be useful in patients with localized disease and is the subject of various trials at the NCI. For patients with VHL, an approach using ZD6474/vandetanib (a dual VEGFR/EGFR tyrosine kinase inhibitor) is ongoing at the NCI. Patients with measurable renal lesions that would like to delay or avoid surgery are offered enrollment (NCT00566995). Similarly, a targeted strategy aimed at the biology of HPRC has been attempted. A multi-site trial assessed XL880/foretinib, a dual C-Met/VEGFR-2 tyrosine kinase inhibitor, in patients with papillary RCC (NCT00726323). Patients with HPRC with localized, solid tumors were enrolled at the NCI. A trial involving patients with localized BHD kidney cancer is planned similar to the studies with the other hereditary syndromes and will target the highly active AKT pathway [34].

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

Fang-Ming Deng, Jonathan Melamed, and Ming Zhou

Introduction

Many histological parameters obtained from routine pathological examination of renal tumor provide invaluable prognostic values. In the current WHO classification, the major histologic variants of RCC, namely, clear cell, papillary, chromophobe, and collecting duct renal cell carcinoma, account for 90–95 % of renal carcinoma. The classification also includes some less commonly encountered types 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 to predict individual tumor behavior and stratify patients into more sophisticated risk groups, ultimately rendering individualized management and treatment options.

According to the World Health Organization (WHO), more than 270,000 new cases and 116,500 deaths from kidney cancer occurred worldwide in 2008 [1]. 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 2004 classification of renal tumors [2]. 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 [3–5].

Pathological Classification of RCC

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

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Table 4.1 2004 World Health Organization classification of renal cell carcinoma [2]

Renal cell carcinoma
Clear cell renal cell carcinoma
Multilocular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinomas
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Renal cell carcinoma, unclassified

The current 2004 WHO Classification of RCC [2] follows on earlier Heidelberg [6] and Rochester classifications, [7] which in turn represent expansions of the Mainz Classification [8]. The current classification emphasizes the heterogeneity of RCC and defines distinct types of RCC based on unique morphologic and genetic characteristics. This represents a major change from the earlier classifications of RCC where tumors were considered as a single relatively uniform group and, in a pioneering fashion, incorporates 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, which are multilocular cystic clear cell carcinoma, collecting duct carcinoma, renal medullary carcinoma, Xp11 translocation carcinoma, carcinoma associated with neuroblastoma, and mucinous tubular and spindle cell carcinoma. 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 clearly different from other histological subtypes. These ten 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 ten tumors, and it is likely that additional ones will be identified in the future. As the molecular mechanisms of renal tumors are increasingly elucidated, molecular classification will supplement and may eventually replace the morphological classification.

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 [9]. Most CCRCCs arise sporadically; however, 2–4 % of the 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 [10, 11]. 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 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, alveolar, or acinar structures separated by thin-walled blood vessels. Tumor cells have clear cytoplasm (Fig. 4.1b) due

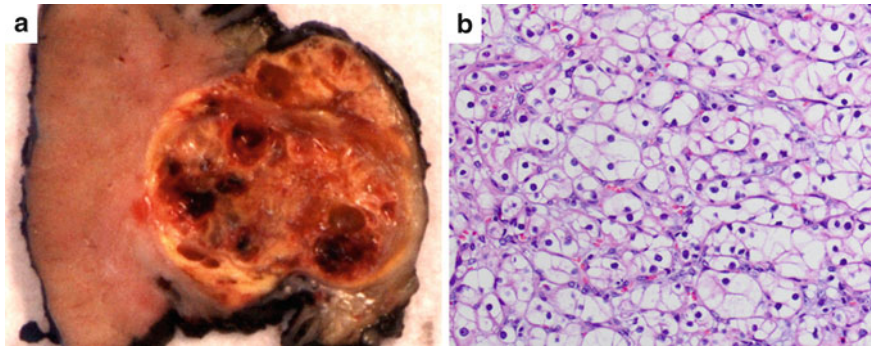

Fig. 4.1 Clear cell renal cell carcinoma. (**a**) Grossly the tumor is a well-circumscribed solid mass with characteristic *bright golden yellow color*. (**b**) Clear cell RCC is composed of compact nests of tumor cells with clear cytoplasm separated by delicate arborizing vasculature

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 sarcomatoid histology may be found. Sarcomatoid differentiation occurs in about 5 % cases and is regarded as high-grade tumor with ominous prognosis.

Molecular Genetics

Seventy to ninety percent of CCRCCs harbor chromosome 3p alterations which comprise deletion, mutation, or promoter methylation of several important genes, including *von Hippel-Lindau* (*VHL*) gene on chromosome 3p25-26, *RASSF1A* on 3p21, and *FHIT* on 3p14.2. Duplication of 5q22 is the second most common cytogenetic finding and may be associated with a better prognosis. Other cytogenetic alterations involve loss of chromosomes 6q, 8p12, 9p21, 9q22, 10q, 17p, and 14q [4, 12, 13].

Somatic mutations in *VHL* gene have been found in 18–82 % of sporadic CCRCC cases. Loss of heterozygosity at the *VHL* locus has been reported in up to 98 % of cases [14–16]. 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 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. 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 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 to tumorigenesis 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 which are no longer controlled by normal physiological mechanisms and therefore contribute to the tumorigenesis and many of the clinical manifestations of CCRCC. The elucidation of these mechanisms has allowed development of several candidate targeted therapies that specifically act within these pathways. These agents that target the critical components of these pathways are under investigation in clinical trials for patients with advanced-stage CCRCC and target VEGF using neutralizing antibody bevacizumab; VEGFR and PDGFR using small-molecule inhibitors of tyrosine kinase, such as sorafenib and sunitinib; EGFR using erlotinib; and mTOR using temsirolimus [18, 19].

Prognosis

In CCRCC, about 50 % are stage I and II, 45 % are stage III, and less than 5 % 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 10–15 % 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 % [9]. The vast majority of tumors occur sporadically, but some develop in members of families with hereditary papillary renal carcinoma (HPRCC) [20] or rarely in hereditary leiomyomatosis and renal cell cancer (HLRCC) [21].

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 the 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 divided into two morphological variants based on the histology [22]. Accounting for about two third 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).

Molecular Genetics

Trisomy or tetrasomy 7, trisomy 17, and loss of Y chromosome (in men) are the most common cytogenetic changes in PRCC [23]. Type 1 and 2 PRCCs have distinct genetic features. For example, gain of 7p and 17p is more common in type 1 tumors [24]. Deletion of 9p is present in approximately 20 % of PRCC, and loss of heterozygosity at 9p13, limited to type 2 tumors in recent studies, has been linked to shorter survival [25].

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 predictive potential. Nevertheless, recognition of the diversity, especially the genetic

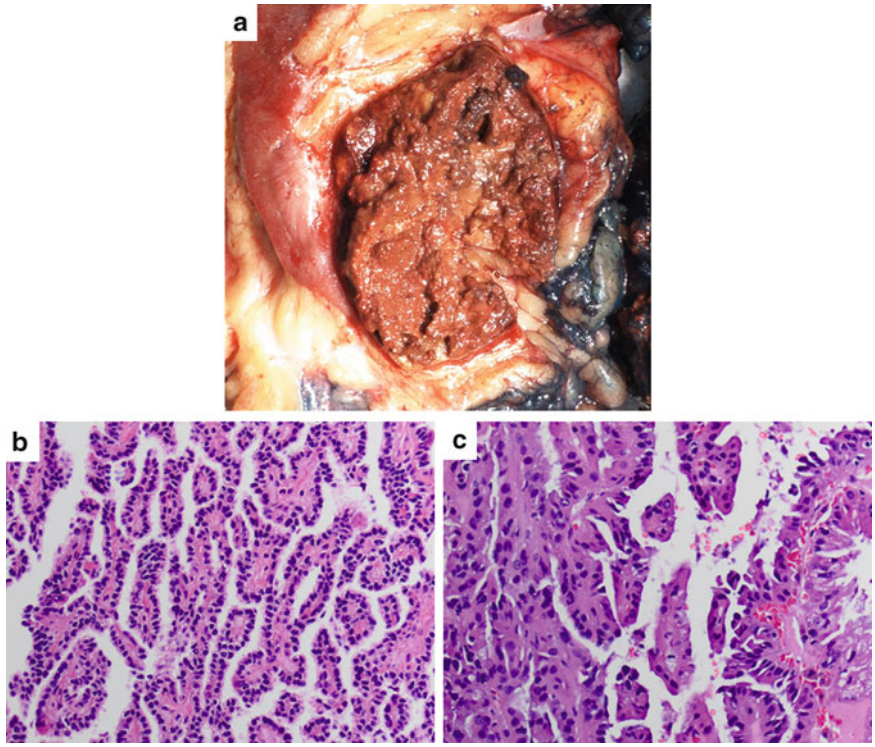

Fig. 4.2 Papillary renal cell carcinoma. (**a**) Grossly the tumor has a thick fibrous capsule with variegated dull color and is extensively necrotic. (**b**) Type 1 PRCC is composed of papillae covered by a single layer of tumor cells with scant cytoplasm and low-grade nuclei. (**c**) Type 2 tumor cells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

differences, within RCC with papillary architecture [15] 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 [26]. 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 [9]. Most cases arise sporadically, while some familial cases are associated with Birt-Hogg-Dube syndrome [27, 28].

Pathology

ChRCC is typically a solitary, well-circumscribed, and non-encapsulated mass with homogenous light-brown solid cut surface. Hemorrhage and/or necrosis is 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 [29]. However, there is no substantial difference in the clinical characteristics between the two variants.

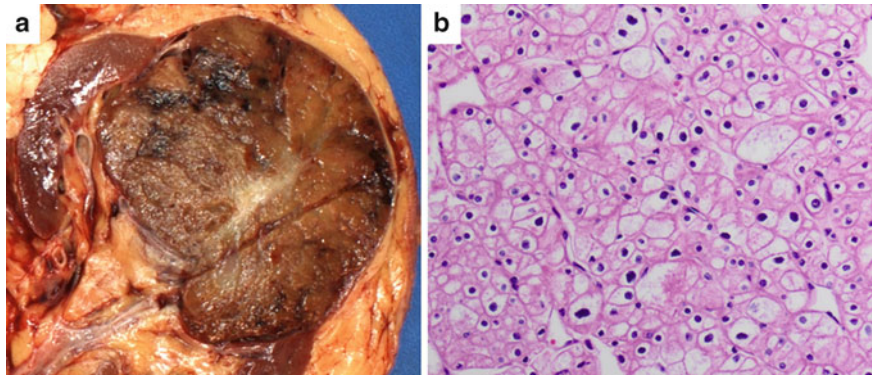

Fig. 4.3 Chromophobe renal cell carcinoma. (**a**) Grossly it is a circumscribed, non-encapsulated mass with a homogenous light-brown cut surface. (**b**) Large and polygonal tumor cells have finely reticulated cytoplasm, prominent cell border, and irregular nuclei with perinuclear clearing

Molecular Genetics

ChRCC harbors extensive chromosomal loss, most commonly involving chromosomes Y, 1, 2, 6, 10, 13, 17, and 21 [30]. 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 [31]. However, *BHD* mutations are rarely found in sporadic ChRCC. It has been suggested that ChRCC may evolve from oncocytoma after acquiring additional cytogenetic abnormality [32].

Prognosis

The prognosis of these tumors is generally accepted as favorable except in the cases with sarcomatoid transformation which is associated with aggressive biological behavior and metastasis. The subset with an adverse outcome varies in series (in part related to case selection) with death of disease ranging from none to 15 %.

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 therefore not included in the 2004 WHO classification. Several of these entities are reviewed in 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. It is important to understand that this is a diagnostic category rather than a true biological entity. These tumors represent a heterogeneous group of malignancies with poorly defined clinical, morphological, or genetic features and therefore cannot be classified using the current criteria. Most 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

Table 4.2 Clinical, pathological, and genetic features of uncommon RCC subtypes included in the 2004 WHO classification [2]

RCC subtype	Clinical features	Pathology		Genetics	Prognosis	Reference
		Grossly	Microscopically			
Multilocular cystic RCC	Variant of CCRCC 5 % of CCRCC Mean age 51 years (range 20–76) Male/female = 2–3:1	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	3p deletion as observed in CCRCC	Favorable No local or distant metastasis after complete surgical removal	[33, 34]
Carcinoma of the collecting ducts of Bellini (Fig. 4.5a)	<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 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 of patients died of disease within 2 years of diagnosis	[35–38]
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 tumor cells with reticular, microcystic, or solid patterns Desmoplastic stroma; may have abundant neutrophils	Not well defined	Highly aggressive 95 % presenting with metastasis; often died of disease within 6 months of diagnosis	[39, 40]
Xp11.2 translocation carcinoma (Fig. 4.5b)	Mainly affecting children and young adults; accounts for 40 % of RCCs in this age group; occurs post-chemotherapy in some cases Male/female = 1:1; affects adult patients with a striking female predominance	Usually circumscribed; not distinct from other RCCs	Most distinctive features: papillary structures lined with clear cells, psammomatous calcification, and hyalinized fibrovascular cores	Chromosomal translocation involving *TFE3* gene on Xp11.2 resulting in overexpression of the TFE3 protein; has several translocation partner genes	Usually resent at advanced stage but indolent clinical course in children Adult tumors may pursue more aggressive course	[41–47]
Mucinous tubular spindle cell carcinoma (Fig. 4.5c)	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	Not well defined Losses on chromosomes 1, 4, 6, 8, 9, 11, 13, 14, 15, 18, 22 reported; 3p alterations and gain of chromosome 7, 17 not present	Favorable; majority of patients remain disease-free after surgical resection; rare reports of metastasis and death of tumor	[48–51]
Post- neuroblastoma renal cell carcinoma	In long-term survivors of neuroblastoma Male/female = 1 Neuroblastoma diagnosis in the first 2 years of life; mean age of RCC diagnosis 13.5 years (range 2–35)	Same as CCRCC	Limited data; many tumors are typical CCRCC; some tumors have cells with abundant granular cytoplasm and arranged in solid, nests, or in papillae	Not well defined Loss of multiple chromosomal loci observed	Similar to other common RCC subtypes	[52]

Table 4.3 Uncommon subtypes of renal cell carcinoma not included in 2004 WHO classification [5]

RCC subtype	Clinical features	Pathology		Genetics	Prognosis	Reference
		Grossly	Microscopically			
Tubulocystic carcinoma (Fig. 4.5d)	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; the lining cells usually exhibit high-grade nuclei and eosinophilic cytoplasm	Gain in chromosome 7 and 17 in some cases; may be related to PRCC	Not fully established; majority of cases have indolent clinical course; recurrence or metastasis in a few cases	[53–55]
Clear cell tubulopapillary carcinoma	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 negative for CD10	Limited data; do not exhibit the genetic changes characteristic of CCRCC or PRCC	Low-grade and low-stage tumor Mostly biological indolent tumors	[56]
Thyroid-like follicular carcinoma	Very rare; mean age 45 years	Wide size range; tan colored	Prominent Pseudocapsule; micro- and macro-follicles lined with low-grade cells; colloid-like material present in >50 % of follicles	Limited data	Not well defined; available cases are free of disease after surgical resection	[57]
Acquired cystic kidney disease (ACKD)-associated RCC	2–7 % incidence in ACKD patients; occur in relatively young patients Male/female = 7:1	Frequently multicentric and bilateral; generally well circumscribed	About 40 % are classic CCRCC, PRCC, or ChRCC; 60 % so-called ACKD-associated RCC with various architectures; 80 % of tumor cells show abundant intratumoral calcium oxalate crystals	Limited data; gains in chromosomes 1, 2, 6, and 10	Less aggressive than sporadic RCC	[58]

(HLRCC), and Birt-Hogg-Dube (BHD) syndrome [10]. 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 [59].

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 [17]. 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 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 [10].

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 [20]. 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 [60]. 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 [61].

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)

HLRCC is an autosomal dominant disease and predisposes patients to cutaneous leiomyomas, uterine leiomyomas in women, and PRCC of type 2 histology. The renal tumors are often solitary, unilateral, and aggressive and lethal. Only 20–35 % of patients develop RCC. Germline mutations are identified in the fumarate hydratase (FH) gene on chromosome 1 (1q42.3-43) [62], an essential regulator of the Krebs cycle. Inactivation of *FH* impairs the Krebs cycle, thereby activating anaerobic metabolism and upregulation of HIF and hypoxia-inducible genes.

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 [28]. Renal neoplasms are often multifocal and bilateral, the most common being hybrid oncocytic tumors (50 %) with features of both ChRCC and oncocytoma [63]. 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.

Common Benign Renal Tumors

Papillary Adenoma

By WHO definition, papillary adenoma constitutes epithelial neoplasms <5 mm in size with papillary and/or tubular architecture lined with tumor cells with low-grade nuclei.

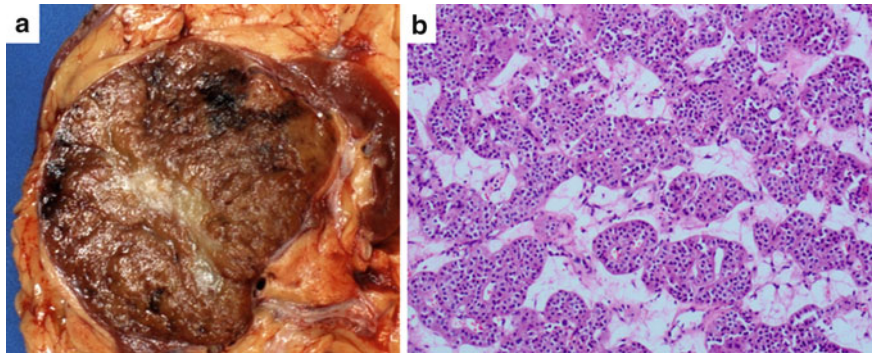

Fig. 4.4 Renal oncocytoma. (**a**) Grossly it is a solitary, well-circumscribed, non-encapsulated mass with homogeneous dark-brown cut surface. (**b**) It consists of bright eosinophilic cells nested in a loose stroma. The tumor cells are uniform, round to polygonal with granular eosinophilic cytoplasm and regular round nuclei

Clinical Features

Adenoma is the most common renal cell neoplasm, frequently 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 on long-term dialysis.

Pathology

Papillary adenomas appear as small (<5 mm), well-circumscribed, yellow or white nodules in the renal cortex. They have papillary, tubular, or tubulopapillary architecture similar to papillary RCC [64]. The tumor cells have uniform small nuclei and inconspicuous nucleoli equivalent to Fuhrman 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 [65].

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 1.7:1. 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. 4.4a). A central stellate scar can be seen in one third 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. 4.4b). 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 [66]. 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

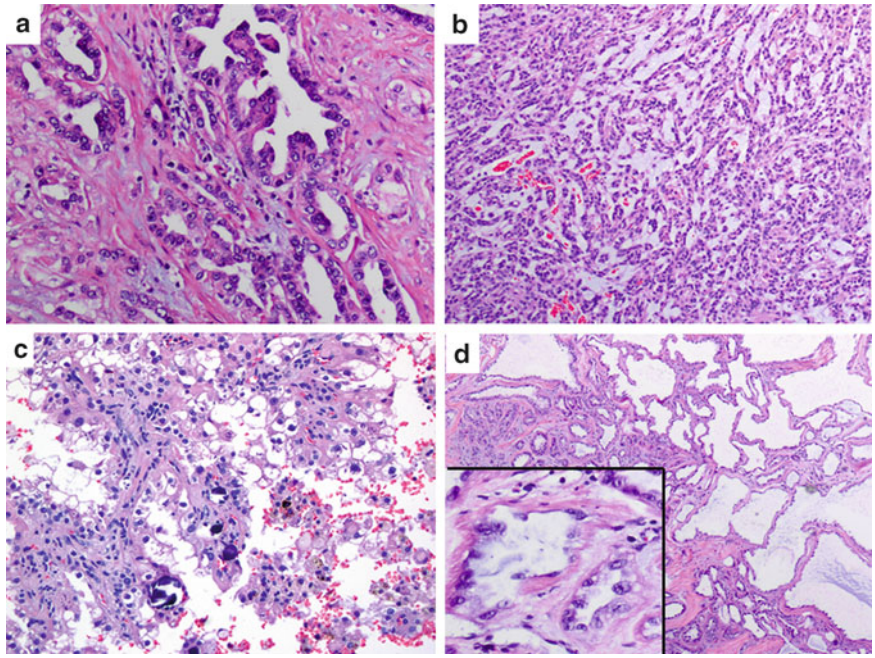

Fig. 4.5 (**a**) Collecting duct carcinoma consists of high-grade tumor cells forming complex tubules or tubulopapillary structures embedded in a remarkably desmoplastic stroma. (**b**) Mucinous tubular and spindle cell carcinoma is composed of elongated cords and collapsed tubules with slit-like spaces 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)

rearrangements have been reported, such as t(1;12)(p36;q13), loss of chromosome 14, and gain of chromosome 12 [67]. 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 [68]. However, monosomy of chromosomes 2, 10, 13, 17, and 21 occurred exclusively in ChRCC [69].

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 vs. 40–45 years without TS). The male to female ratio is 4:1. AMLs, particular 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. 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, one fourth to one third 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.

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. Loss of heterozygosity for the TSC2 region, TSC2 inactivation by mutation, is likely a necessary genetic event in the pathogenesis of most sporadic AMLs [70–72].

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. Recent studies found that risk of malignancy increases with the size of mass lesions. In an analysis of over 2,700 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 % [73]. More recently, 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 [74].

The 2010_ENREF_6 (Table 4.4) [75] TNM staging differs from the earlier 2002 version in reexamining size thresholds in T stage, specifically by dividing T2 based on a size cutoff of less than or greater than 10 cm, reclassifying renal vein invasion as T3a instead of T3b, and classifying adrenal involvement as T4 when contiguous invasion and M1when not contiguous. It also has simplified N classification into N0 and N1. The newly adopted 2010 TNM classification has also been validated as a robust predictor of cancer-specific survival and shown to provide modest improvement in predictive ability compared with the 2002 version.

Fuhrman Nuclear Grading

Currently, the four-tiered Fuhrman scheme, first described in 1982, remains the most commonly used grading system for RCC [76]. Fuhrman grade, based on the nuclear size and shape, chromatin, and nucleolar prominence, is categorized into G1-4 (Table 4.5). Most studies have confirmed that Fuhrman nuclear grade is an independent prognostic predictor for CCRCC [77]. Simplified two-tiered (G1–2 vs. G3–4) or three-tiered (G1–2 vs. G3 vs. G4) Fuhrman systems have been proposed to improve interobserver agreement and still preserve its prognostic significance [78]. Grade 1 and 2 may be grouped together as low grade since the two are not prognostically different in multivariate analysis. However, studies have shown that grade 3 and grade 4 tumors should not be grouped together as grade 3 tumors have

Table 4.4 Pathology stage of primary renal cell carcinoma (AJCC 2010) [75]

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 and renal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
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'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)	
M0	No distinct metastasis
M1	Distant metastases

Table 4.5 Fuhrman nuclear grading system [76]

Grade	Nuclear size (μm)	Nuclear shape	Chromatin	Nucleoli
1	<10	Round	Dense	Inconspicuous
2	15	Round	Finely granular	Small, not visible at 10× magnification
3	20	Round/oval	Coarsely granular	Prominent, visible at 10× magnification
4	>20	Pleomorphic, multilobated	Open, hyperchromatic	Macronucleoli

better 5-year cancer-specific survival than grade 4 tumors (45–65 % in grade 3 cancers vs. 25–40 % in grade 4 cancers). A recent study showed that the three-tiered Fuhrman grading system is an appropriate option for the prognostication of CCRCC in both univariate analysis and multivariate model setting [79]. The use of a simplified Fuhrman nuclear grading system in clinical practice requires further clarification and preferably a consensus between pathologists and urologists.

The prognostic value of Fuhrman grading for non-clear cell RCC, however, remains controversial. For papillary RCC, it is significantly associated with survival in univariate analysis, but this significance is lost in multivariate models. One recent study demonstrated that only nucleolar prominence is significantly associated with survival in both univariate and multivariate analyses [80]. Another study showed that Fuhrman grade, not the nucleolar grade, is an independent prognostic factor and should be used as the standard grading system for PRCC [81]. Only a few studies addressed the prognostic significance of Fuhrman grading system for ChRCC using univariate analysis. A recent study found that Fuhrman grading does not correlate with survival, therefore is not appropriate for ChRCC [82]. A new grading system was recently proposed for ChRCC based on the assessment of geographic nuclear crowding and anaplasia.

This grading scheme was shown to be an independent predictor of clinical outcomes for ChRCC [83].

Sarcomatoid and Rhabdoid Differentiation

Sarcomatoid differentiation is present in about 5 % of RCCs and can be observed in any RCC subtype [84]. Therefore, sarcomatoid RCC is not considered a distinct subtype of RCC by 2004 WHO classification; 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 analyses [85]. Any RCC with sarcomatoid differentiation is assigned a Fuhrman grade 4.

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 those resembling leiomyosarcoma, fibrosarcoma, angiosarcoma, rhabdomyosarcoma, and other sarcomas. The coexisting 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 5–90 % of the tumor area. It is a marker of high risk for metastasis and poor prognosis even when the rhabdoid component is limited [86].

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 univariate and multivariate analyses. Studies from Mayo Clinic clearly showed that histological necrosis is associated with twice the cancer-specific death rate compared to those without necrosis [9]. 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 [87]. Two outcome prediction models, SSIGN (stage, size, grade, and necrosis) from Mayo Clinic and the postoperative outcome nomogram from Memorial Sloan Kettering Cancer Center, both incorporate tumor necrosis in their models [88, 89]. A few recent studies also report that the proportional extent of necrosis correlates with a worse outcome and cancer-specific death in clear cell RCC [90, 91]. 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. As an important prognostic factor in other malignancies including liver, testis, bladder, and upper tract urothelial carcinoma, its prognostic role in RCC is however controversial. 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 [92, 93]. Further studies are needed to better define its prognostic significance.

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 biologic 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 [94].

The biologic 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 [95], 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 [96].

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 [97]. 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 subtype, 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 types is well accepted and substantiated on clinical, biologic, and molecular differences [94].

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 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 and Christoph Wald

Renal Imaging

The most recent data for adult renal cancer has identified almost 65,000 new cases annually within the United States [1]. The annual incidence of the predominant type, renal cell carcinoma (RCC), is associated with multifactorial etiologies [2, 3] and continues to rise at least in part due to an increase in overall imaging utilization in the USA which has been observed in the inpatient as well as outpatient setting [4, 5]. 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 [6] most likely associated with a lead time bias, permitting earlier and possibly definitive treatment.

Renal cancer is detected either during evaluation of genitourinary tract-related symptoms such as flank pain and hematuria or during workup of unrelated medical issues for a variety of abdominopelvic conditions or for instance during colon cancer screening with CT colonography. It should be noted that many computed tomography (CT) examinations of the chest also 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 surveillance [7].

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 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 treatment of renal cancer, such as focused ultrasound ablation [8] and image-guided percutaneous ablation [9, 10]. These techniques and the functional radionuclide analyses will be reviewed separately.

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 altered density (suggesting a mass), with irregular margins, or calcifications, that is intrinsic to the kidneys or resulting in local mass effect (Fig. 5.1).

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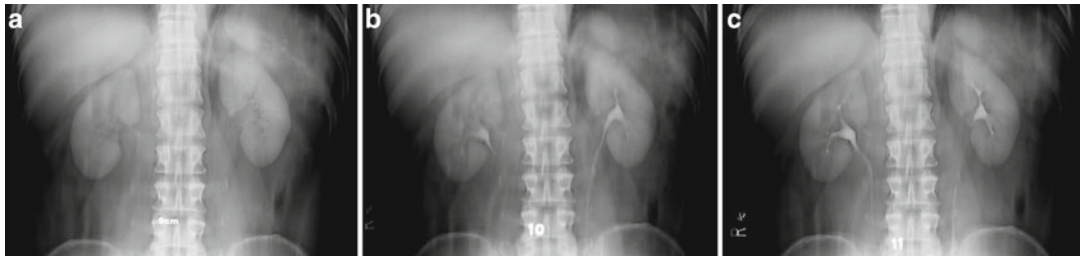

Fig. 5.1 Sequential frontal abdominal radiographs from an intravenous pyelogram (IVP), performed for hematuria, with no apparent abnormalities. Blurring of adjacent intra-abdominal structures while keeping the collecting system in focus is deliberately achieved with controlled tube-table translation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

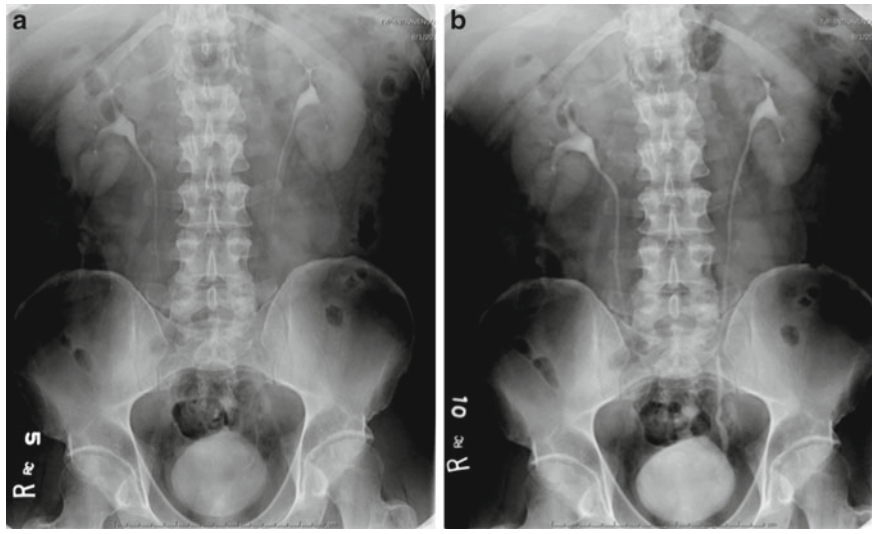

Fig. 5.2 KUB images in late excretory phase, to further delineate the ureters and bladder. Prone imaging may be helpful to show ureters to advantage. Post micturition images are subsequently acquired

However, soft tissue contrast resolution of plain radiography and fluoroscopy is 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 [11]. 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 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.

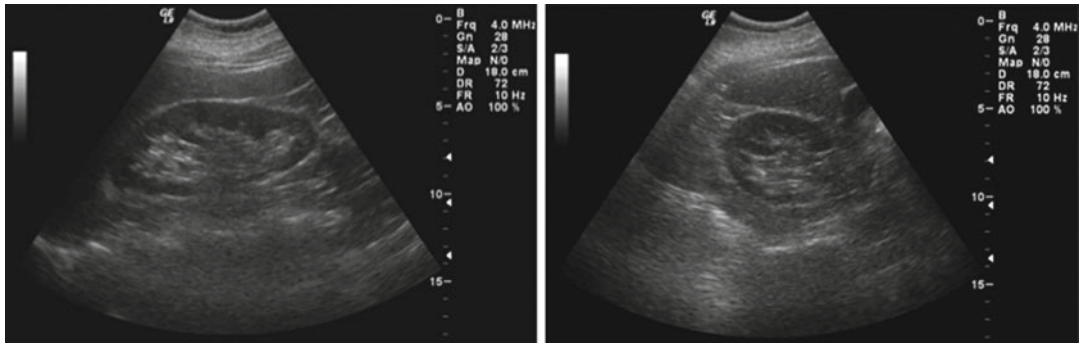

Fig. 5.3 Normal ultrasound images of the kidney, in sagittal and transverse planes. Grayscale ultrasound images were acquired with a 4.0-MHz curvilinear probe and demonstrate typical central echogenic structures of the renal sinus and overlying hypoechoic cortex

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 unattenuated ultrasound waves should be observed beyond the lesion, from which the simple nature of the fluid within the lesion is inferred (Fig. 5.4).

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 [12] (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 [13]. 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 carcinoma and non-clear cell renal

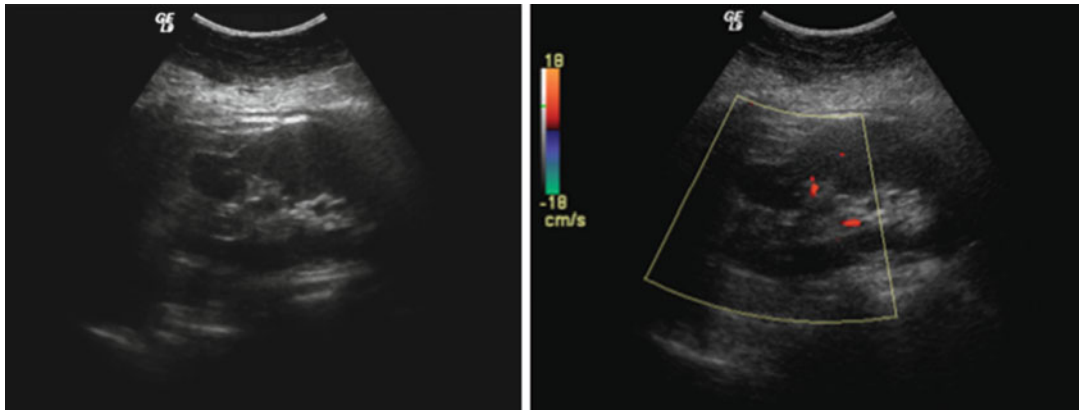

Fig. 5.4 Well-circumscribed, partially exophytic, anechoic, and thin-walled cortical cyst evident on grayscale ultrasound image on the *left*. Color Doppler evaluation (inside *yellow-framed region* of interest) confirms absence of abnormal blood flow in the cyst; findings are typical for simple renal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

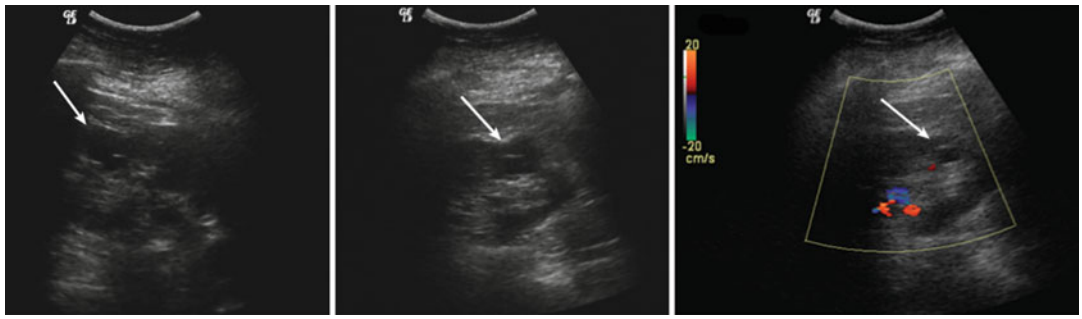

Fig. 5.5 Grayscale ultrasound images demonstrate a predominantly hypoechoic renal cortical lesion, containing a well-defined linear echogenic septation. There is no evidence of vascular flow within the septation and no associated soft tissue mass or mural nodule. Findings are consistent with a minimally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

tumors, based on grayscale heterogeneity, lesion washout, grade of contrast enhancement, and quantitative measure of peak intensity [14]. It should be noted that US contrast agents are currently not FDA approved and therefore not routinely available in the United States.

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 % [15]. The majority of such small renal masses are statistically likely to be benign [16]. Furthermore, analysis of a large prospectively collected population-based registry identified that small renal cell cancer less than 3 cm is likely to be organ-confined disease with a limited malignant potential around 5 % [17].

Although ultrasound may identify a variety of specific morphologic characteristics to aid 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 [18]. The intraoperative use of ultrasound to assist with guidance of nephron-sparing partial nephrectomy has become standard of care at Lahey Clinic and many other institutions (Fig. 5.7).

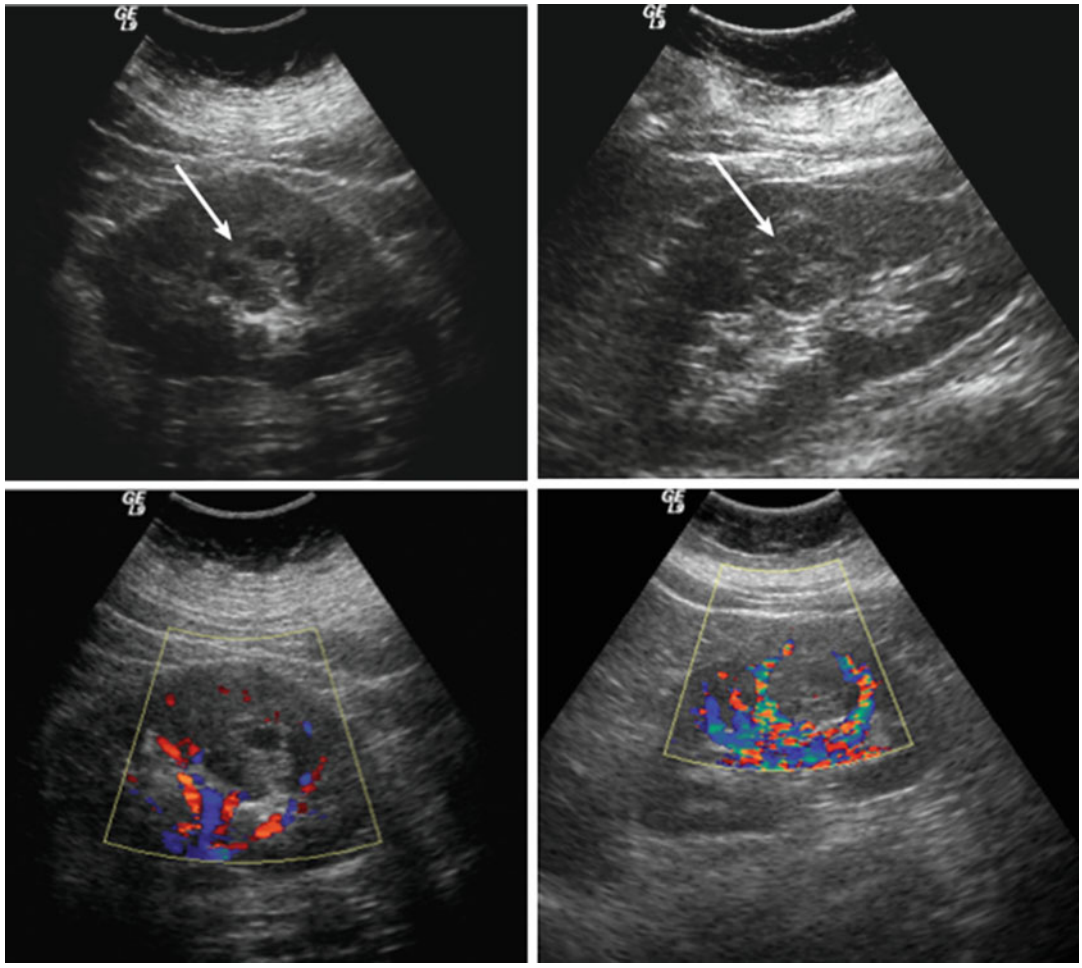

Fig. 5.6 Well-circumscribed mass of heterogeneous echogenicity is centered in the renal cortex. Trace vascular flow is seen on color Doppler images. Findings are consistent with a complex renal mass; multiphasic cross-sectional imaging would typically be recommended for further evaluation

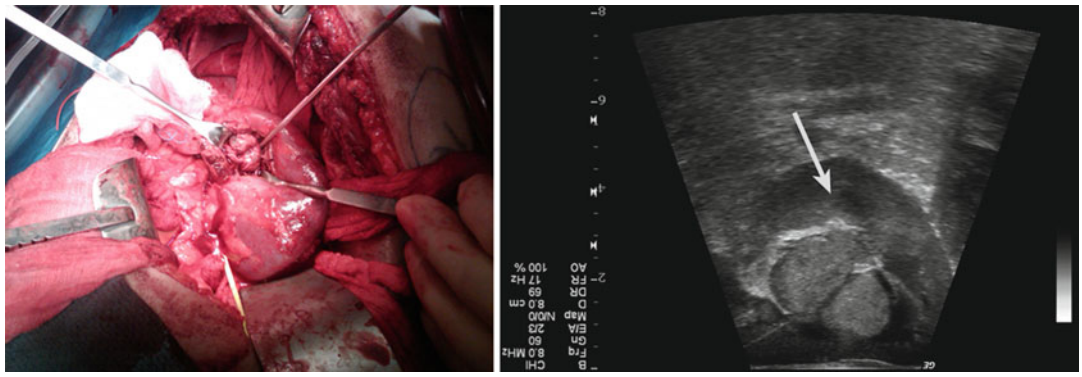

Fig. 5.7 Intraoperative photograph on the *left*, demonstrating open, partial nephrectomy for renal mass within the upper pole of the kidney. Intraoperative real-time ultrasound image on the *right* is used routinely to identify tumor and evaluate extent of local invasion during nephron-sparing surgery

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.

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 [19, 20]. Furthermore, it is estimated that more than half of patients over 50 years of age will have at least one renal mass [19]. 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 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. Guidelines are therefore necessary to strengthen confidence in identification of features concerning for a malignant versus benign process [21].

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 s post injection). An arterial phase (between 20 and 30 s) 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 [22] (Figs. 5.9–5.11).

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

Staging for renal cell cancer was first introduced in 1958 [23] and revised in 1963 [24]. 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 tissues are thereby 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

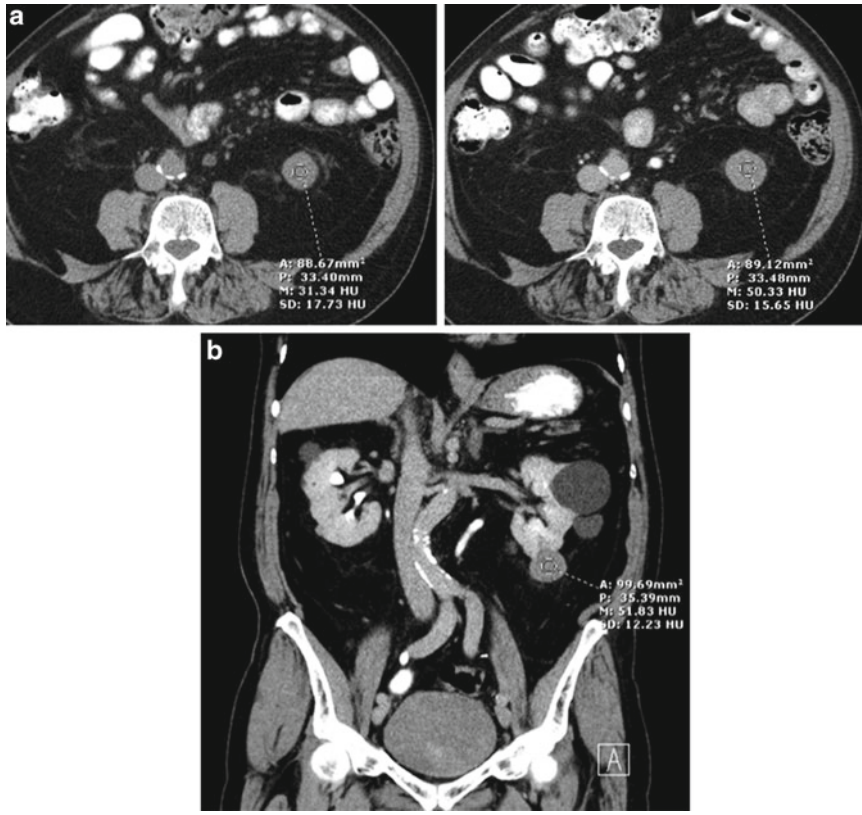

Fig. 5.8 (**a**) Precontrast and nephrogenic phase axial CT images of the left renal lower pole demonstrate moderately enhancing lesion, quantified in Hounsfield units (*HU*), evaluated by manually placing a region of interest (*ROI*) on the target. Mean HU increased from 31 to 50, suspicious for neoplasm. (**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

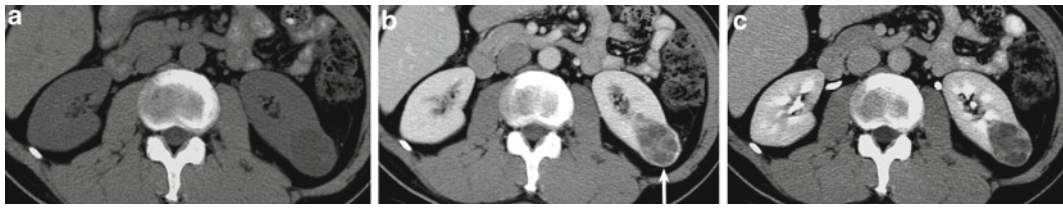

Fig. 5.9 Multiphasic CT study demonstrates precontrast (**a**), arterial phase (**b**), and nephrogenic phase (**c**) axial images of a well-circumscribed, exophytic renal cortical mass in the posterior left kidney. Septations seen on precontrast imaging demonstrate enhancement, a suspicious feature.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

at least 15 Hounsfield units (HU) measured within a representative region of interest (ROI) represents significant enhancement on a CT scan [25]. Enhancement of less than 10 HU strongly suggests a benign process, well-established criteria [26].

On precontrast imaging, and also on ultrasound, a simple cystic renal lesion that 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

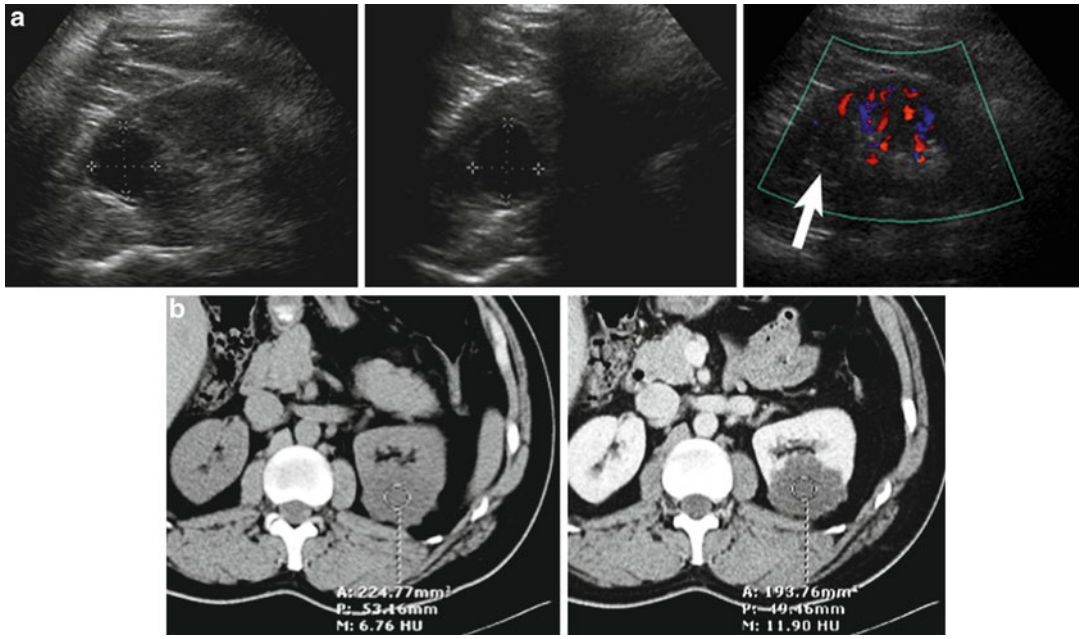

Fig. 5.10 (**a**) Grayscale ultrasound images in sagittal and transverse planes, of the left kidney, demonstrate a well-circumscribed, hypoechoic cortical lesion, no apparent vascularity. (**b**) Precontrast and late arterial phase axial CT images demonstrate a lobulated, hypodense lesion in the left 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

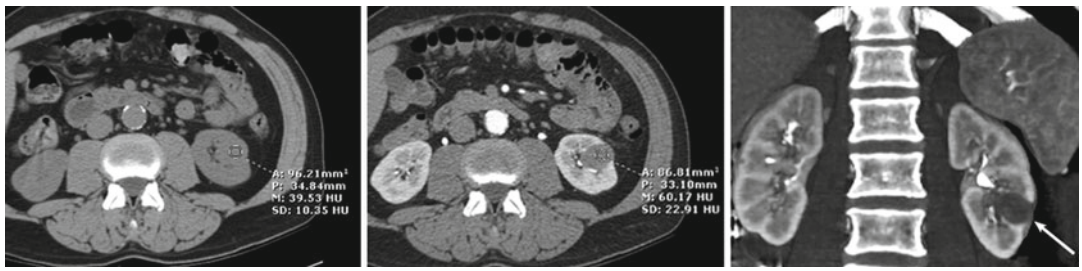

Fig. 5.11 Precontrast (*left*), nephrogenic phase (*middle*), and coronal reformat (*right*) demonstrate a hypodense, enhancing cortical lesion, abutting the collecting system. Significant differential enhancement of 21 HU is noted; pathology confirmed renal cell carcinoma, papillary type

lesions are well characterized by the Bosniak classification system that has evolved particularly in the categorization of complex lesions, in large part due to outcomes since its initial introduction in 1986 [27, 28] (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 postcontrast imaging, differentiating this from non-clear cell-type renal cell cancer, with a sensitivity of 74 % and specificity of 100 % [29]. Homogeneous enhancement and lower tumor to parenchyma enhancement ratio are noted in non-papillary-type renal cell carcinoma, particularly in smaller tumors less than 3 cm [30].

Additional features include a peripheral enhancement pattern and decreased vascularity that has been noted in chromophobe tumors,

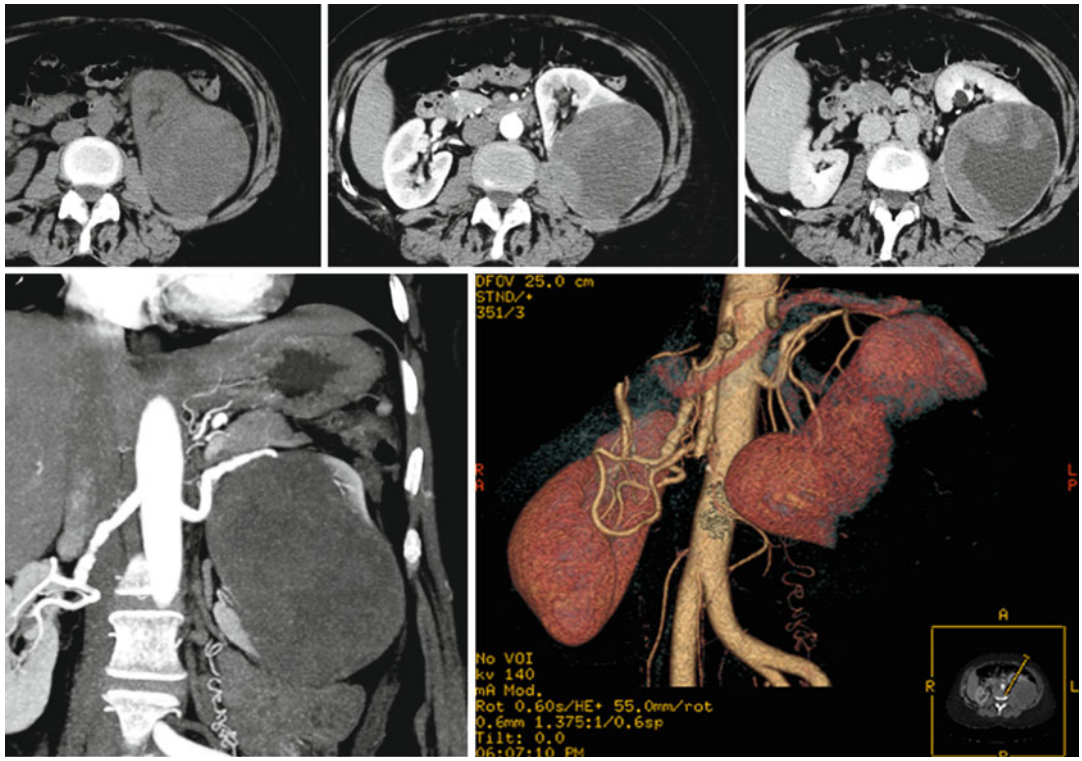

Fig. 5.12 Multiphasic axial CT images in precontrast (*upper left*), arterial (*upper middle*), and nephrogenic phases (*upper right*), demonstrate a large, heterogeneous mass arising from the left kidney, centrally cystic and peripherally nodular in appearance. Coronal reformat (*lower left*) and volume-rendered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

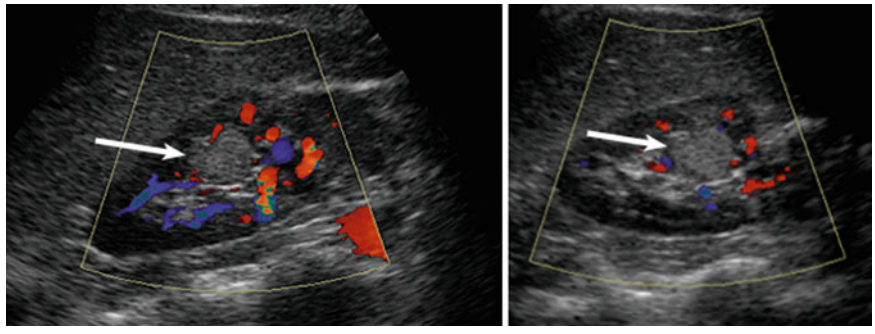

Fig. 5.13 Precontrast (*left*) and arterial phase (*middle*) CT images demonstrate a heterogeneous, right lower pole cortical tumor with avid enhancement of 61 HU. The tumor and vascular supply are well demonstrated on the volume-rendered subtracted image (*right*), useful for operative planning

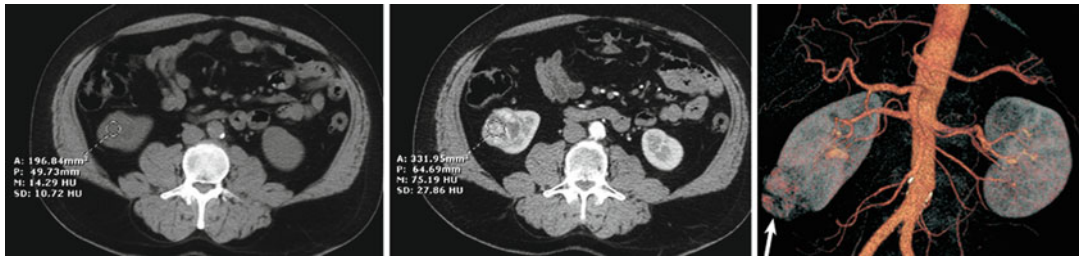

Fig. 5.14 Sagittal and transverse ultrasound images of the *right* kidney, with superimposed Doppler, demonstrate a well-circumscribed, heterogeneous slightly hyperechoic lesion. There is no significant vascularity

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 pathologic classification system rather an imaging and clinical management system [48]

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 and 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

[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

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).

Increasing awareness of radiation dose associated with CT is reflected in the principles of ALARA enshrined in the American College of Radiology Appropriateness Criteria ensuring that minimum standards are established at all accredited imaging centers. Advances in dose modulation on contemporary CT scanners and individualization of the kilovoltage to patient body habitus 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, new model-based iterative reconstruction (MBIR) algorithms are being established, in contrast to the existing adaptive statistical iterative reconstruction (ASIR) algorithm, that will permit even lower radiation doses without sacrificing image quality. The utilization of CT in the US has dramatically risen in recent years [31]. It remains a mainstay of imaging in both the elective and emergent setting, generating images of high quality that guide diagnosis, therapy, and surveillance (Table 5.2).

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 and 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

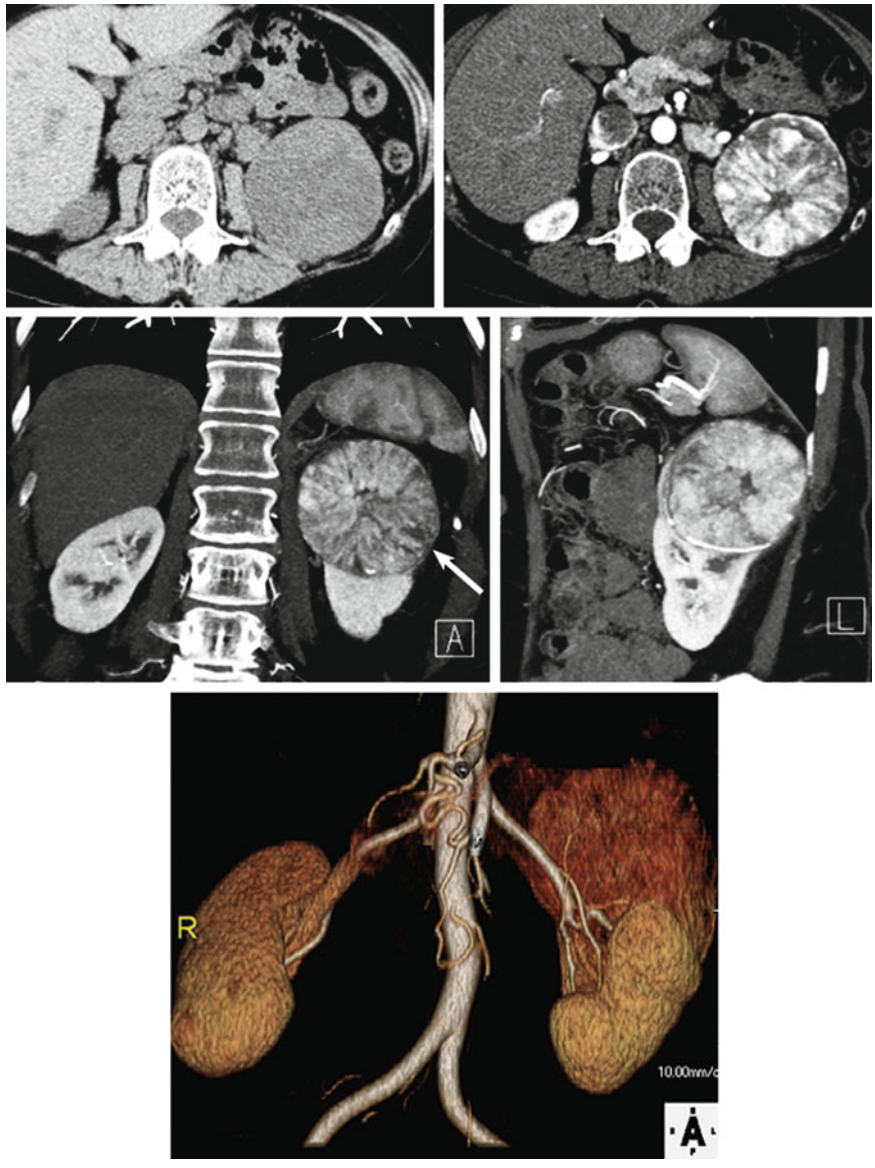

Fig. 5.15 Multiphasic axial CT images, including precontrast (*upper left*), arterial phase (*upper right*), coronal, and sagittal reformatted images (*middle row*) demonstrate a large, heterogeneously enhancing mass in the upper pole of the left kidney. There is a "spokewheel" pattern noted on axial 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

nephrectomy [32]. 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 [33]. 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 [34]. As such, surveillance for metastatic disease is suggested at 6-month intervals for the first 3 years, followed by annual surveillance. Recurrent renal cell carcinoma is typically seen as hypervascular lesions within the lung, liver, bone, and brain and is more commonly multifocal [35]. Surveillance strategies following surgery are considered in more detail in another chapter (Fig. 5.16).

Table 5.2 The TNM staging system of the American Joint Committee on Cancer (AJCC). The staging system permits stratification of treatment options and assessment of prognostic and survival characteristics [49]

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 not >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 fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota fascia
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)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases in regional lymph node(s)
M0	No distant metastasis
M1	Distant metastasis

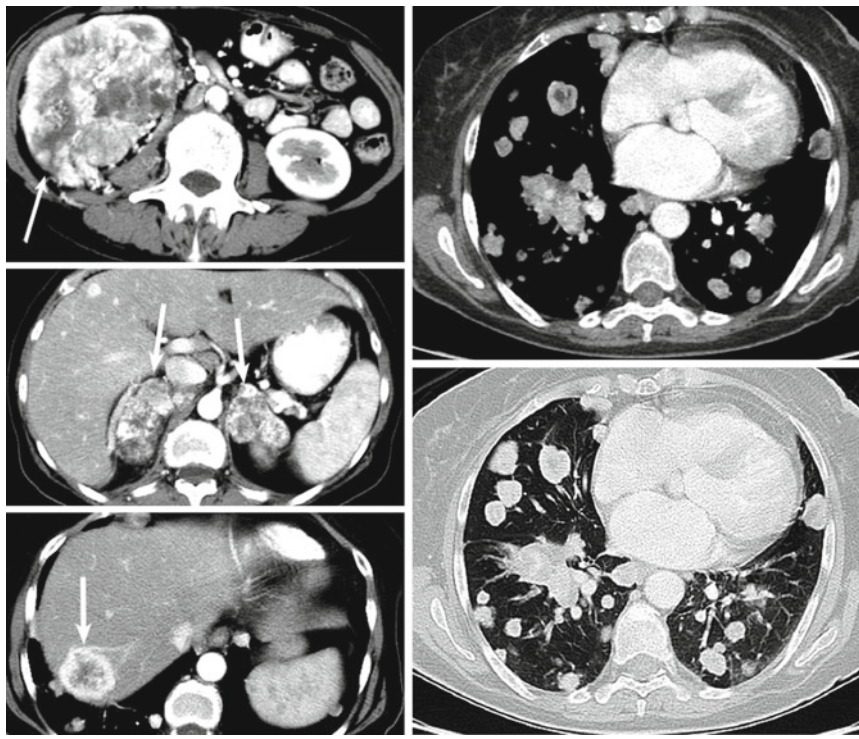

Fig. 5.16 Multiple contrast-enhanced axial CT images demonstrate evidence of numerous metastatic lesions from a renal cell carcinoma primary. The large, heterogeneous enhancing mass in the right kidney (*upper left*) was the primary tumor. Metastases to both adrenal glands are evident (*middle left*)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

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 [36]. 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 3 cm^3 in volume [37]. Between 12 and 24 months after thermal ablation, the ablation cavity reduces to less than half the original volume. The ablation cavity is typically higher in density than surrounding normal parenchyma, like 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 [38] (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.

Magnetic Resonance Imaging (MRI)

MRI offers an increasingly attractive alternative to ultrasonography and CT in the detection, characterization, and staging of renal masses. The intrinsic properties of MRI allows 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 of blood products or fluid. Typical sequences used in renal imaging include T1, T2, in- and opposed-phase imaging, and postcontrast T1 sequences employing breath-hold technique. MRI signal characteristics of simple renal cysts are homogeneously T2 bright, with thin walls, while proteinaceous or hemorrhagic cysts will appear heterogeneous to low signal intensity. Septa 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 [39, 40]. 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 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.

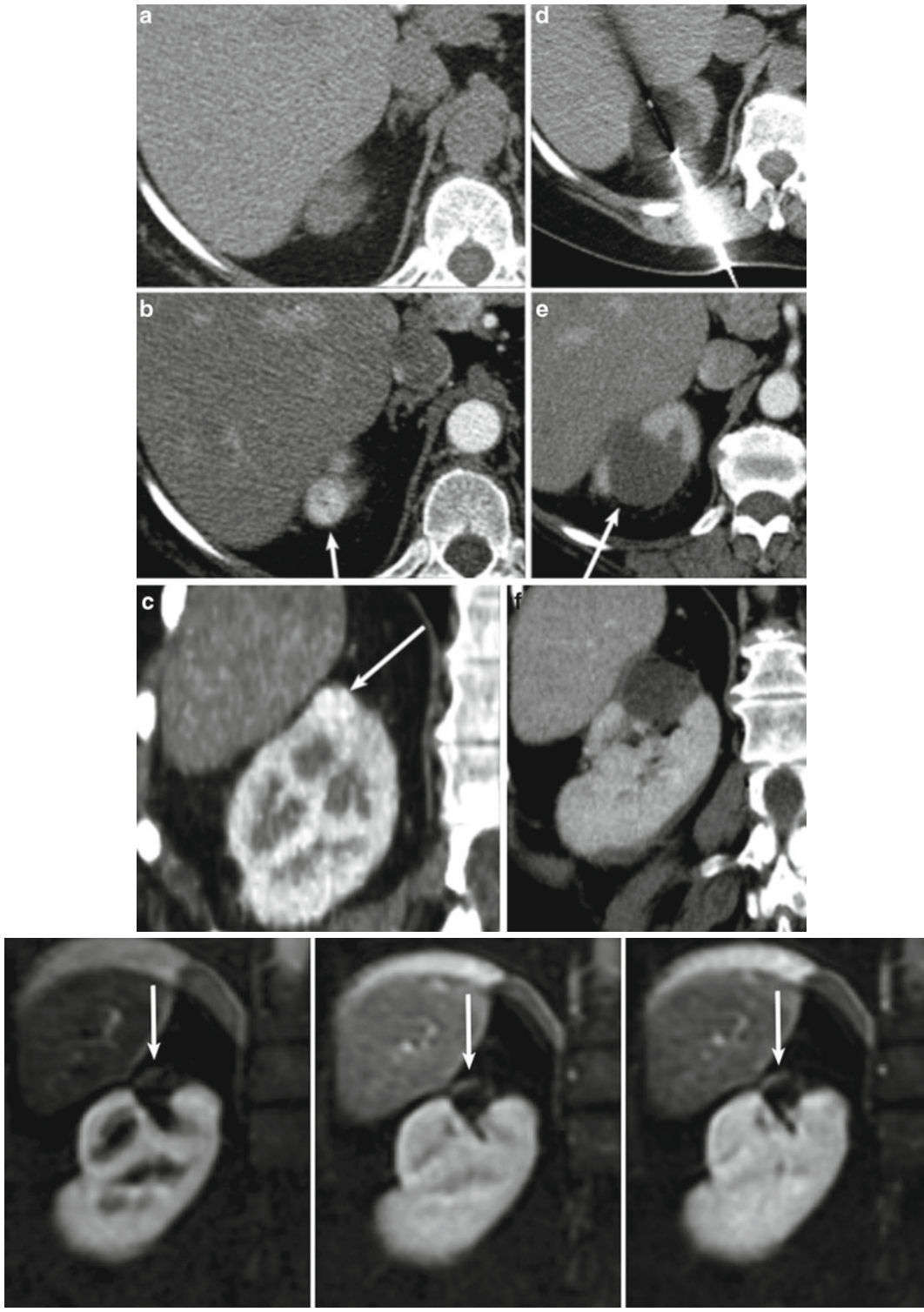

Fig. 5.17 (**a**) Axial precontrast (*A*) and postcontrast (*B*) CT images demonstrate a hypervascular upper pole lesion, better seen on coronal reformat (*C*). This was proven renal cell cancer by biopsy and treated with cryoablation (*D*). Post ablation contrast-enhanced CT images in axial (*E*) and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

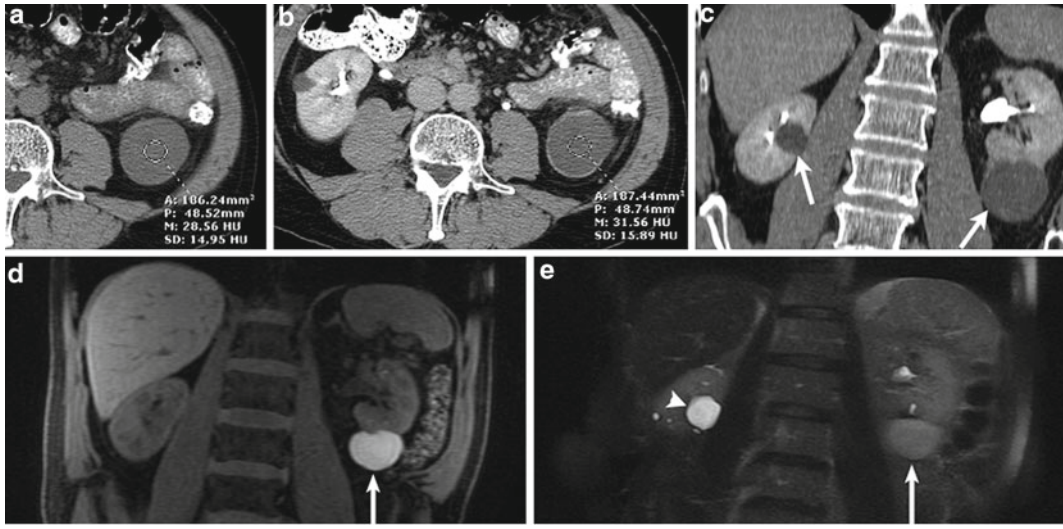

Fig. 5.18 Prominent exophytic left lower pole hypodense lesion seen on precontrast CT (**a**). Lesion is measured at 28 HU, more than would be expected for simple fluid. There is no significant enhancement on nephrogenic phase axial (**b**) or coronal (**c**) images. T1-weighted, fat-suppressed coronal 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

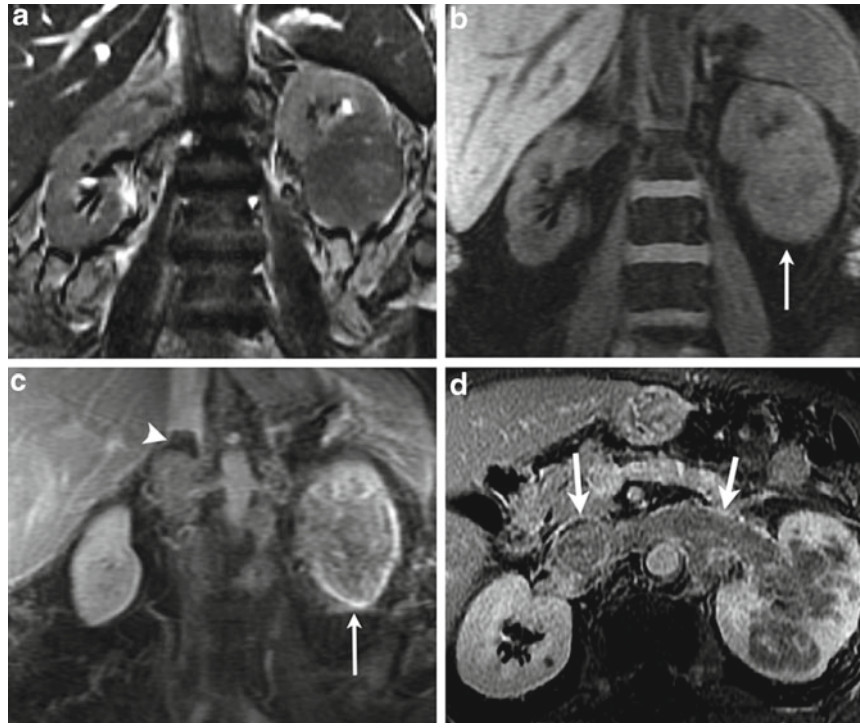

Fig. 5.19 Coronal T2-weighted sequence (**a**) demonstrates hypointense lesion in the left lower pole. This appears to be heterogeneously enhancing on T1-weighted, fat-suppressed precontrast (**b**) and postcontrast (**c**) coronal images. Note is made of a filling defect within the suprarenal IVC (*arrowhead*),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

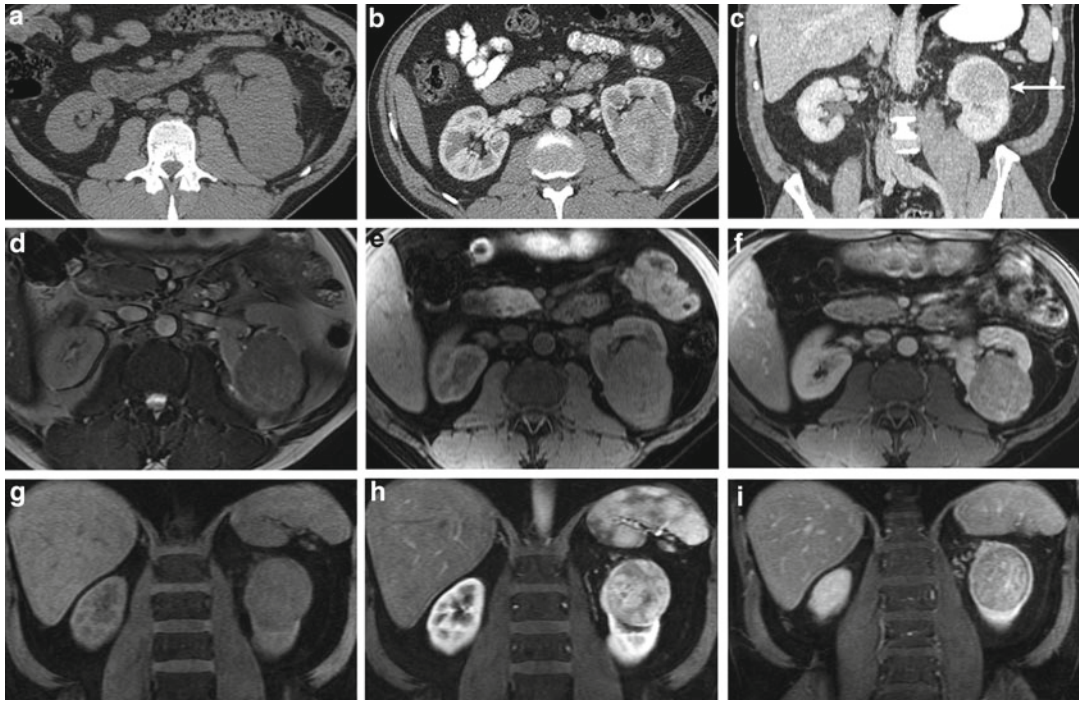

Fig. 5.20 Multiphasic CT images, including axial precontrast (**a**), nephrogenic phase (**b**), and coronal postcontrast (**c**), demonstrating a lobular, hypointense mass with heterogeneous enhancement. Axial T2-weighted (**d**), T1-weighted precontrast (**e**) and postcontrast (**f**) images confirm the left interpolar mass with heterogeneous enhancement. Coronal precontrast T1-weighted (**g**), early (**h**) and late 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

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 are 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 [41], 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 [42] (Figs. 5.21–5.24).

Renal oncocytoma is the second most common benign renal neoplasm, after angiomyolipoma, and is found in up to 7 % of solid renal masses. Morphologically, these typically appear 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

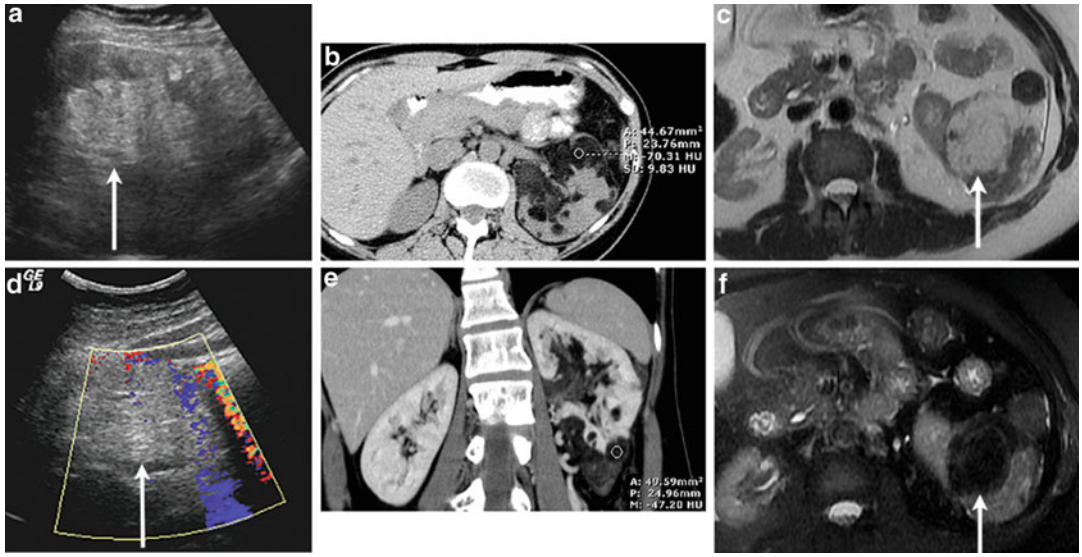

Fig. 5.21 Grayscale (**a**) and Doppler (**d**) images demonstrate an echogenic renal mass without vascular flow. Axial (**b**) and coronal (**e**) CT images demonstrate multiple fat-density lesions (between −40 and −70 HU) within the left kidney. T1-weighted axial MR image (**c**) demonstrates T1 hyperintense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

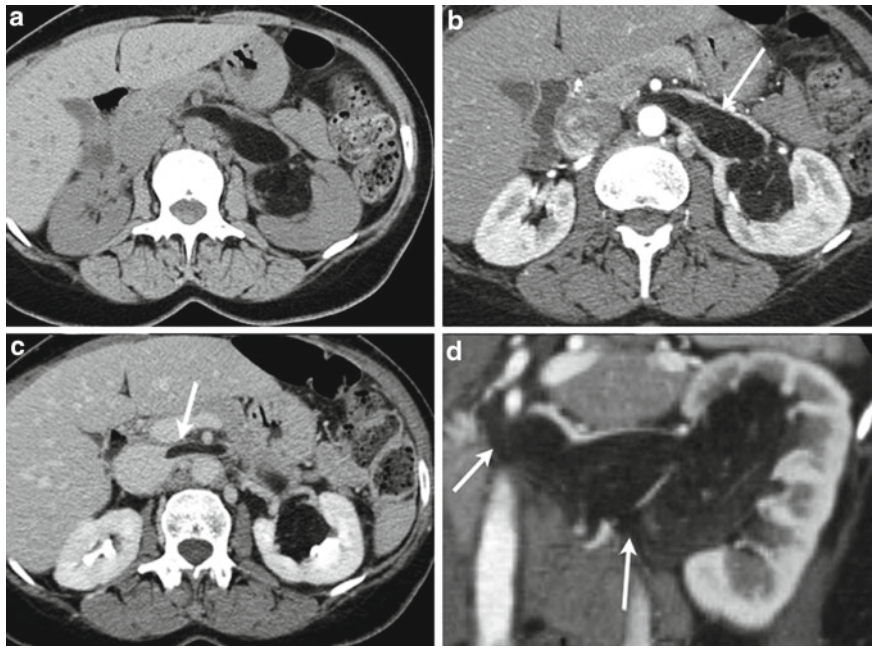

Fig. 5.22 Multiphasic axial CT images, precontrast (**a**), arterial phase (**b**), and nephrogenic phase (**c**), demonstrate a homogeneous, non-enhancing, fat-density mass within the left kidney with extension to the IVC, consistent with a large renal AML

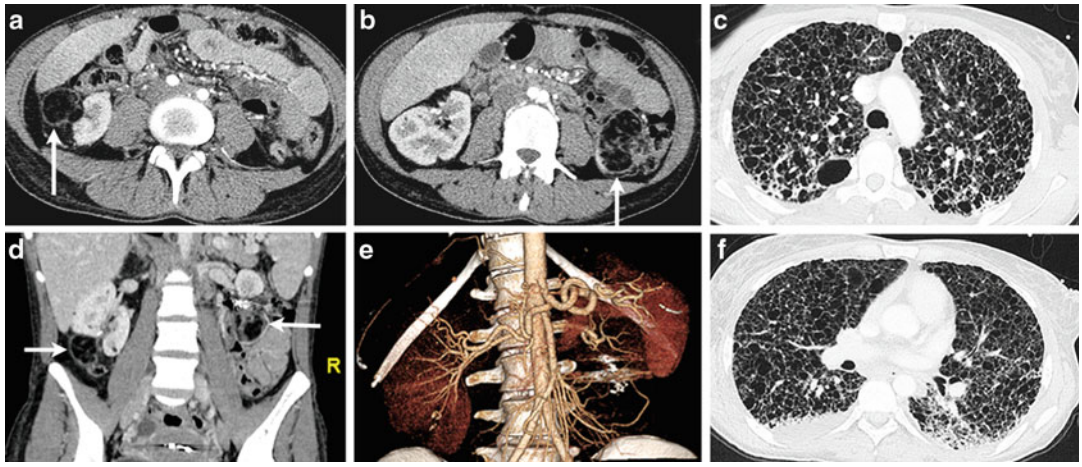

Fig. 5.23 Axial (**a**, **b**) and coronal (**d**) postcontrast images demonstrate multiple fat-density lesions within both kidneys. Corresponding lucent masses are seen on the volume-rendered image (**e**). Evaluation of the lung parenchyma (**c**, **f**) demonstrates innumerable thin-walled cysts and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

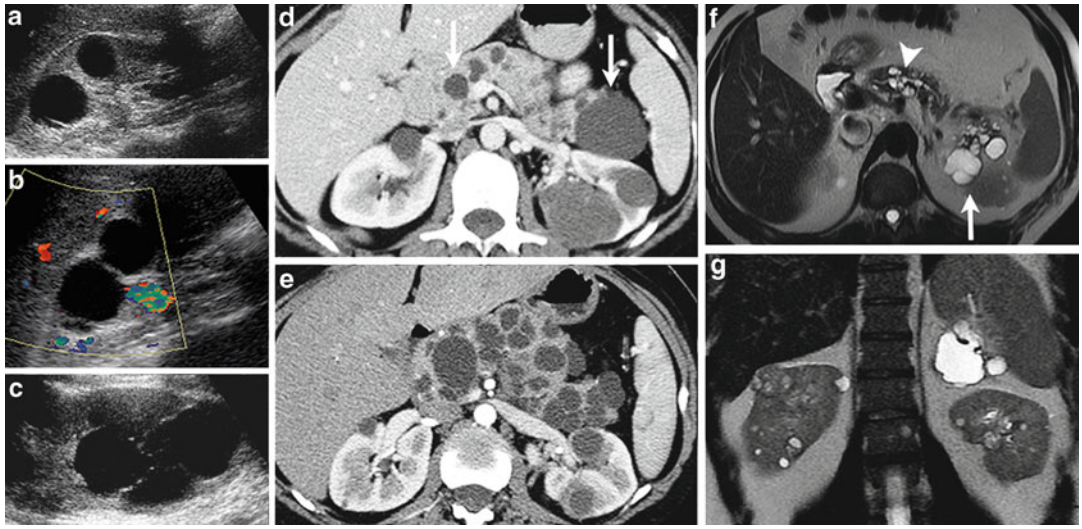

Fig. 5.24 Multiple well-circumscribed, anechoic, avascular cysts are seen within both kidneys on grayscale and Doppler ultrasound (**a**–**c**). Axial CT images in arterial phase demonstrate multiple non-enhancing, thin-walled renal and pancreatic cysts of varying sizes. These findings are also seen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

less likely to contain cysts, subacute hemorrhage, hemosiderin, and microscopic fat. There is often a stellate, central scar that enhances 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 [43].

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 coefficient (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 [44]. 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.

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 [44].

In a different study, analysis of a variety of renal masses prior to surgical resection with subsequent pathologic, histologic 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 [45].

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

Future Directions

Functional or molecular imaging represents the next big frontier of imaging, targeting a physiologic pathway or mechanism. As a bridge to that point, antibody-mediated molecular imaging has been shown to provide the potential to characterize biologic events at a cellular level. 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 [46]. 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, and ^{89}zirconium.

An example of immunoPET is G-250, an ^{124}iodine-labeled chimeric antibody (girentuximab) that reacts against carbonic anhydrase-IX (CAIX), known to be overexpressed in clear cell-type RCC, the predominant subtype of renal cell cancer, and not expressed in benign renal tumors [47]. In a recent, unpublished multicenter phase III trial that enrolled greater than 220 patients, G-250 was capable of differentiating clear cell RCC from non-clear cell RCC, with a sensitivity and specificity of 86 % and 87 %, respectively (personal communication with John Libertino, M.D., August 2012).

Nanobodies and affibodies are small in size, demonstrate high affinity for targeting agents, and are utilized in HER-2 receptor positive breast cancers. However, the renal excretion of nanobodies and their nonspecific activity in the urinary tract preclude their utility as renal imaging agents.

Although largely in the research domain at the current time, 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, which may pinpoint additional foci of disease ensuring clear surgical margins.

Also within the research field but approaching on the imaging horizon are quantum dots (QD), or semiconductor nanocrystals, essentially light-emitting colloidal nanocrystals, with a broad excitation spectrum and narrow range of emission wavelengths. QD's 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.

Consideration may also be given to a class of drug delivery agents, antibody-targeted nanoparticles, that may be utilized both for imaging purposes and delivery of chemotherapeutic agent directly to the primary tumor and foci of metastatic disease. Appropriate imaging remains integral to the accurate diagnosis of renal cancer and will continue to develop in quantum steps, driven relentlessly by perpetual technological advancements.

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Molecular Imaging for Renal Cell Carcinoma

6

Jian Q. Yu and Yamin Dou

Introduction

Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems defined by the Society of Nuclear Medicine. Molecular imaging includes nuclear medicine and expands the tracer principle to include the use of molecules that report on biological function using light or other detectable signals. In the following, we will mainly discuss applications of positron emission tomography (PET) imaging for renal cell carcinoma (RCC).

PET is an imaging technique used by obtaining a three-dimensional display of functional processes in the body. The state-of-the-art PET/CT scanner combines physiological/pathological distribution of the tracer from PET with anatomical information from CT. Most clinical services in the United States use dedicated, integrated/hybrid PET/CT technology. Currently, 18F-labeled fluorodeoxyglucose (FDG) is the only PET tracer approved for routine clinical use. The principle of the FDG-PET imaging is that tumor cells utilize more glucose for metabolism than normal cells and produce higher signals than the normal tissues or the background. One of the major strengths for FDG-PET is to detect metastatic disease. However, inflammation and infection are the major confounding factors for FDG-PET in oncologic images.

Renal cell carcinoma (RCC) accounts for about 3 % of all adult cancers and 85–90 % of all primary renal tumors. The incidence of RCC is rising, 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. To date, the role of FDG-PET in the initial detection and diagnosis of RCC is limited. 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.

Targeted therapies have become standard for metastatic RCC (mRCC). The most successful molecular target therapies are VEGF receptor tyrosine kinase inhibitor (TKI) such as sunitinib and sorafenib. Those drugs are aimed at specific

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biological molecules or processes to modify response or signal transduction. These drugs are cytostatic and inhibit growth rather than induce tumor regression. Conventional imaging techniques such as CT and MRI are structure and 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.

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 (PET/CT) for RCC 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 there are different types of cancers of the kidney with different histological patterns and different 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 renal mass is usually made with ultrasound, CT, or MRI. Most cases (up to 70 %) are discovered incidentally during procedures for other indications [1, 4].

CT is currently the imaging modality of choice to stage and detect metastases in patients with RCC. It provides important information about size, tumor extension, vascular invasion, and regional metastasis. This information is essential for prognostic evaluation and surgical planning.

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 rates for primary RCC. Ramdave et al. [5] studied 17 patients with known or suspected primary tumors and found true positive in 15, true negative in one, and false negative in one. The accuracy of FDG-PET and CT was similar (94 %). Similar results were also reported by Goldberg et al. [6]. However, two other studies with larger samples 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 specificity of 100 % for primary RCC 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 RCC is limited by low sensitivity. However, the superior specificity of the PET may have a complementary role as a problem solving tool 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) ranged from 2.5 to 18.4, with average SUVmax 6.8 [10]. Second, the kidney 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 anatomical correlation of the old generation PET scanner, 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 the PET camera when compared to 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 scanner with improved

Fig. 6.1 *Clear cell renal carcinoma*. FDG-PET/CT appearance of 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

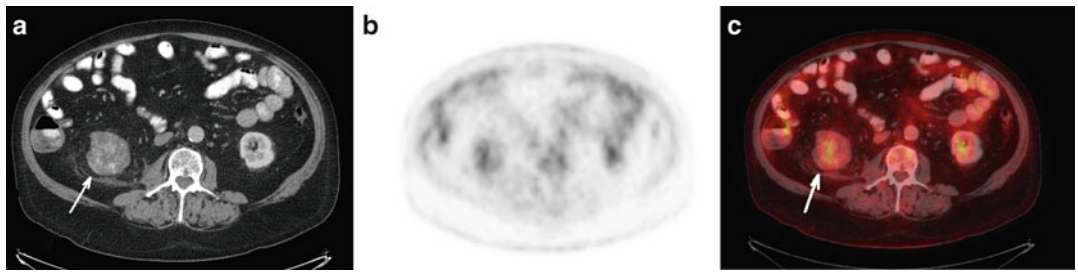

Fig. 6.2 *Oncocytoma*. FDG-PET/CT appearance of renal oncocytoma. (**a**) CT with IV contrast shows a well-defined 5-cm mass with mild heterogeneous enhancement. (**b**) FDG-PET shows mild increased uptake, SUVmax 2.9. (**c**) Fused PET/CT image

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 RCCs 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 anatomical 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 RCCs demonstrate increased FDG uptake to a certain degree (Fig. 6.1). SUVmax (maximum standardized uptake value) has reported ranging from 2.5 to 18.4 with 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-contrast imaging. 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 as in our case in Fig. 6.3.

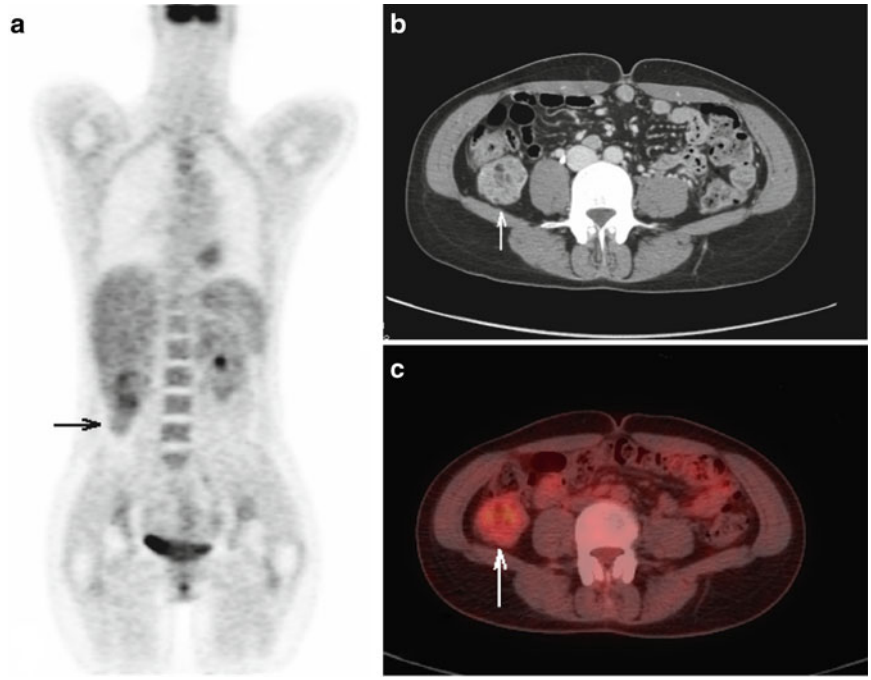

Fig. 6.3 *Angiomyolipoma of the kidney*. FDG-PET/CT appearance of a benign renal neoplasm, angiomyolipoma. (**a**) FDG-PET shows focal mild uptake in right lower kidney (*arrow*), equal to or less than background renal parenchymal activity. SUVmax, 1.9. (**b**) A well-marginated tumor with fatty attenuation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

Locoregional Metastasis

Metastasis to regional lymph nodes is found in 10–20 % of patients with RCC [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 [17]. Lymphadenopathy remains a major challenge to cross-sectional imaging of patients with RCC. Current cross-sectional imaging criteria for suspicious lymph nodes include a short-axis diameter of 1 cm or more and loss of kidney shape with a lymph node hilum that includes fat. 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 [18].

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 1/2 patients; in contrast, CT correctly identified both. Kocher et al. [19] 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.

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 [20]. It seems that FDG-PET is not

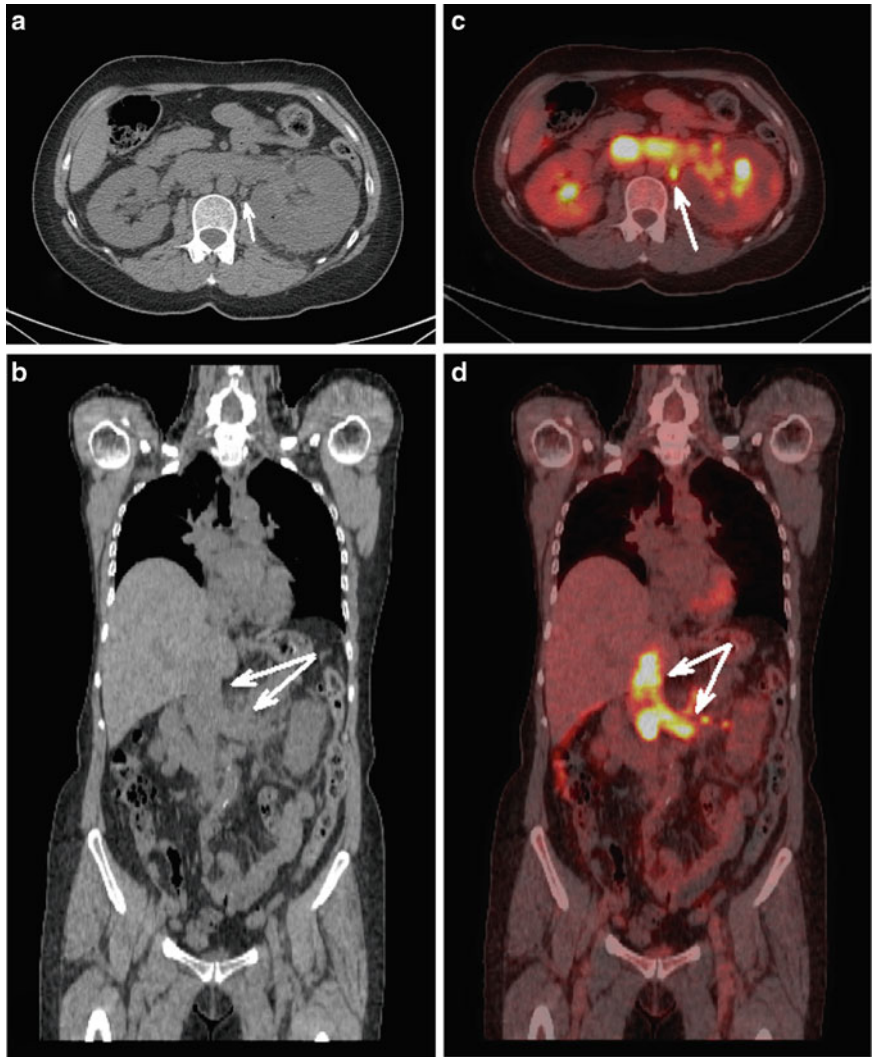

Fig. 6.4 *Papillary renal cell carcinoma with local small nodal metastasis and tumor invading renal vein and IVC*. (**a**) Staging FDG-PET/CT demonstrates a large *left* renal mass and a 10-mm *left* para-aortic node (*arrow*) on non-contrast CT. (**b**) There is a markedly dilated *left* renal vein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

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. A case with tumor thrombosis is shown in Fig. 6.4.

The incidence of local recurrence ranges from 1.8 % to 27 % after nephrectomy [21]. 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, the patient is more likely to develop renal failure after nephrectomy which makes 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,

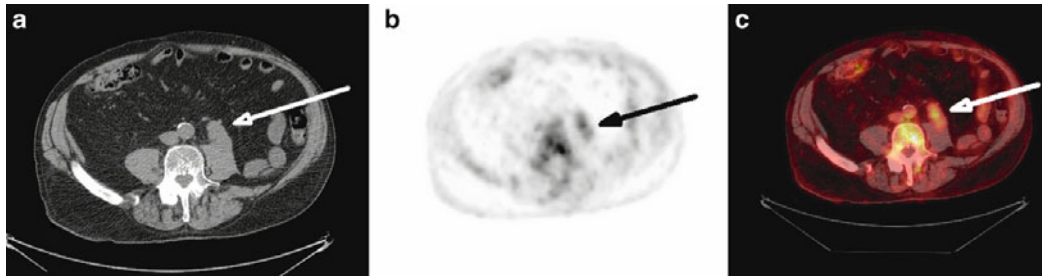

Fig. 6.5 *Chromophobic renal cell cancer with local recurrence*. (**a**) Re-staging FDG-PET/CT demonstrates a *left* retroperitoneal soft-tissue mass on non-contrast CT, question of postsurgical change vs local recurrence. (**b**) FDG-PET demonstrates focally increased uptake, SUVmax 2.5, consistent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

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 whole body (routine skull base to mid thigh) nature of the scan. It has shown promising results with RCC, with sensitivity range from low 60–100 % and the specificity close to 100 % for the majority of cases [7, 18, 22–26]. 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 [22]. In another study [27], FDG-PET detected 77/112 of the metastatic lesions. Of those, 32 lesions had not been detected by any other anatomical 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. [28] reported a study of 20 patients with 25 lesions biopsied. FDG-PET accurately identified 21/25 metastases and demonstrated a sensitivity of 87 % and specificity of 100 %. Park et al. [18] 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 a better accuracy compared with 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 [29–31]. Liver metastasis is associated with poor prognosis [32]. 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 [33]. There are limited studies which describe the appearance of liver metastasis on FDG-PET [34–38]. On a non-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 specificity of 100 % for liver metastases. In contrast, CT has a sensitivity of 76.9 % and specificity of 94.1 %. FDG-PET detected 2/13 metastases that were negative on CT. In the study by Park et al. [20], FDG-PET/CT has a sensitivity of 100 % for liver metastasis.

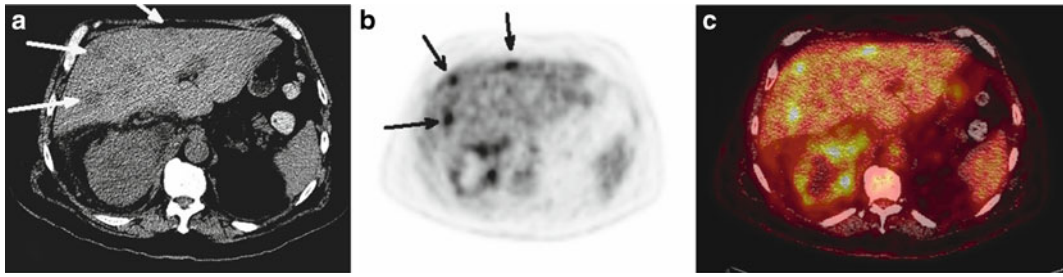

Fig. 6.6 *Clear cell renal cancer with liver metastases*. Staging FDG-PET/CT in a 72-year-old male with a large *right* renal mass. (**a**) CT shows a large *right* renal mass and subtle livers lesions (*arrows*). (**b**) FDG-PET shows intense heterogeneous uptake in the *right* renal mass (*arrow head*) and clearly multiple foci of liver uptake (*arrows*). (**c**) Fused FDG-PET/CT

Lung Metastasis

Lung is the most common site of mRCC and accounts for 50–60 % of metastasis [29–31]. Patients with lung-only metastases have a better survival rate than patients with other sites of metastases [32]. 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 [33]. CT with contrast is the current study of choice to evaluate lung metastases with high sensitivity. However, there is a limitation of CT due to its low specificity for pulmonary nodules. CT is unreliable 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 higher the likelihood of malignancy [39]. Fortes et al. [40] 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 to 5 mm, the sensitivity of FDGPET 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. [22] 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, 1.3–2.7 cm) compared with 0.8 cm (95 % CI, 0.5–1.2 cm) in patients with false-negative FDG-PET. In another study [8], FDG-PET demonstrated a sensitivity of 75.0 % and specificity of 97.1 % in detecting metastases to lung compared to 91.1 % and 73.1 %, respectively, for chest CT.

A dual-modality hybrid PET/CT scanner takes advantage of the high sensitivity from CT and the greater specificity of FDG-PET and results in 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 distant metastasis in RCC [41]. Bone metastases classically appear as large expansile lytic lesions on plain radiography, most commonly in the axial

Fig. 6.7 *Clear cell renal cancer with lung metastasis*. Staging FDG-PET/CT in a 60-year-old male with *right* kidney clear cell carcinoma. (**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

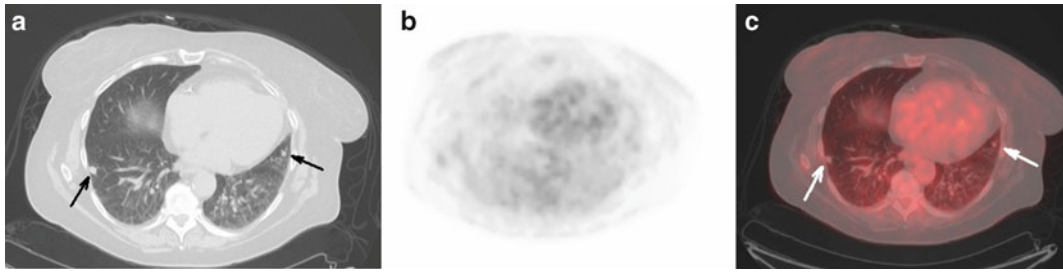

Fig. 6.8 *Metabolic negative lung metastases from clear cell renal cancer*. FDG-PET/CT in a 63-year-old female with clear cell renal cancer and biopsy-proven pulmonary metastases. (**a**) Multiple lung nodules, largest measuring 10 mm (*arrows*) on CT. (**b**) No significant FDG uptake corresponding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

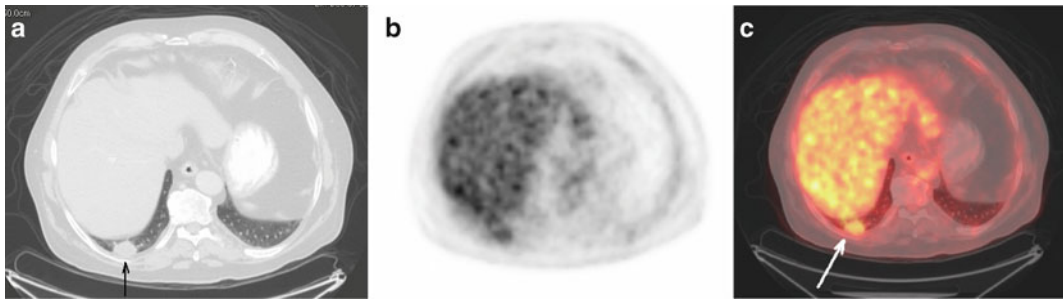

Fig. 6.9 *False-positive lung metastasis from clear cell renal carcinoma*. Staging FDG-PET/CT in a 54-year-old male with clear cell renal carcinoma. (**a**) CT component shows several lung nodules, largest measuring 2.7 × 1.7 cm (*arrow*). (**b**) FDG-PET demonstrates increased uptake corresponding to the largest nodule, SUVmax 2.7. (**c**) Fused image. Biopsy of this nodule shows inflammation and necrotic tissue

skeleton [33]. 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 due to 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 [28, 42].

FDG-PET has been reported to be very accurate to stage bone metastasis in breast and lung cancer [43, 44]. 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 easy to see on CT scan (Fig. 6.11).

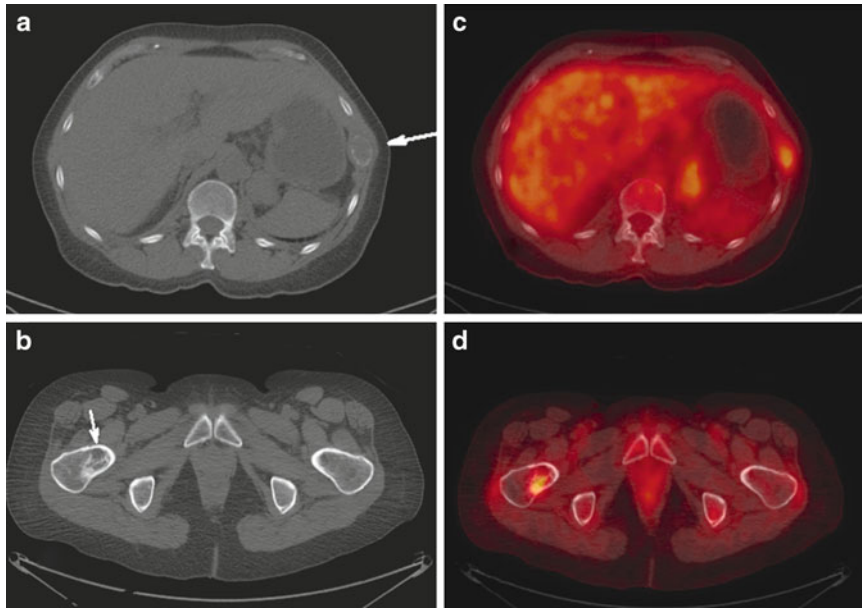

Fig. 6.10 *Multiple bone metastases from clear cell renal carcinoma*. FDG-PET/CT in 71-year-old male with history of clear cell renal carcinoma. (**a**) and (**b**) Re-staging scan demonstrates destructive and lytic bone lesions on CT component (*arrows*). (**c**) and (**d**) PET/CT fused images demonstrate moderate increased uptake corresponding to these bone lesions

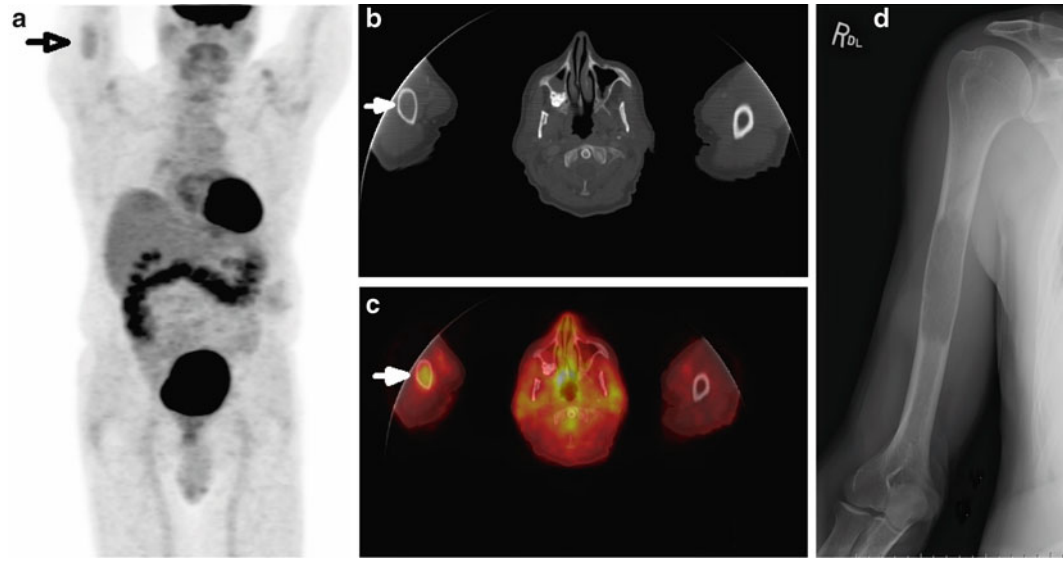

Fig. 6.11 *Solitary bone metastasis from clear cell renal carcinoma*. (**a**) Re-staging FDG-PET/CT in a 63-year-old male with clear cell renal carcinoma. PET demonstrates a focal moderate uptake in *right* humerus. (**b**) On the corresponding CT, there is an easy-to-miss lesion with subtle cortex thinning.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

Wu et al. [45] showed that for detecting bone metastasis, FDG-PET had both a 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 bony metastases were 99 % and 93.2 % and indicate that FDG-PET is the most sensitive test for bony metastasis of RCC.

A recent review showed that NaF-18 PET is more accurate than 99mTc-diphosphonate SPECT for identifying both malignant and benign lesions of the skeleton [46]. Combining the NaF-18 PET with CT using a PET/CT scanner can improve the specificity and overall accuracy of detecting skeletal metastasis. NaF-18 PET may become the routine clinical practice for detecting bone metastasis. Center for Medicare and Medicaid Services is currently covering the NaF-18 PET scan under the mechanism of Cover for Evidence Development for all Medicare recipients.

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 [30]. Thus, they recommend follow-up imaging should be performed intensively within 2 years after surgery. Most guidelines use anatomical and conventional imaging to monitor relapse and recurrence. FDG-PET has been shown to identify relapse and/or recurrence more readily than conventional imaging with higher sensitivity and specificity [18]. 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 renal preservation for RCC patients. Nakatani and coworkers [47] reviewed 28 scans in 23 patients who had undergone FDG-PET scans after surgery for RCC. They correlated the PET findings with other imaging, histology, or by clinical follow-up at least 6 months. They reported overall sensitivity, specificity, and diagnostic accuracy of 81 %, 71 %, and 79 %, respectively. 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. [48]. 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. [49] 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) on FDG-PET/CT is an independent prognostic factor in lung, head and neck, and esophageal cancer [50–52]. Other studies showed that SUVmax (maximum standardized uptake value) of FDG predicts prognosis in various cancers [53–55]. The role of FDG uptake such as SUVmax or MTB as a prognostic factor has not been fully established in RCC. One study showed that RCC patients with SUVmax equal or above 8.8 demonstrated poor prognosis [56]. 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. [57] 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). These findings are important and

SUVmax should be considered as a criterion for incorporation in future prognostic models.

Monitoring Therapeutic Response

The treatment of metastatic RCC is rapidly evolving. Emerging therapies include TKIs such as sorafenib and sunitinib, inhibitors of mammalian target of rapamycin (mTOR) such as temsirolimus and everolimus, and other biological agents such as bevacizumab. Currently, TKIs are the agents of choice for patients with relapsed or metastatic RCC. These agents block cell signaling through various mechanisms and demonstrate better outcomes in patients with advanced clear cell RCC compared with standard therapies [58]. Most of these new agents can induce stabilization of RCC. Decrease in primary tumor diameter >30 % while on targeted therapy is rare [59]. Since these therapies induce tumor necrosis with little tumor shrinkage, an unchanged residual mass does not necessary imply poor therapeutic responses. This makes anatomical imaging less suitable for monitoring treatment response for mRCC. In addition, differentiation between vital tumor and fibrosis or necrosis is difficult using anatomical 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 [60, 61]. New data is now available on monitoring the therapeutic response of mRCC using FDG-PET and FDG-PET/CT [62–64]. A recent study [57] demonstrated that in patients with metastatic RCC, a high baseline 18F-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 response is possible with molecular imaging since the signal change in the cellular level will take quite some time to translate into size change (Fig. 6.12). Interestingly, in a

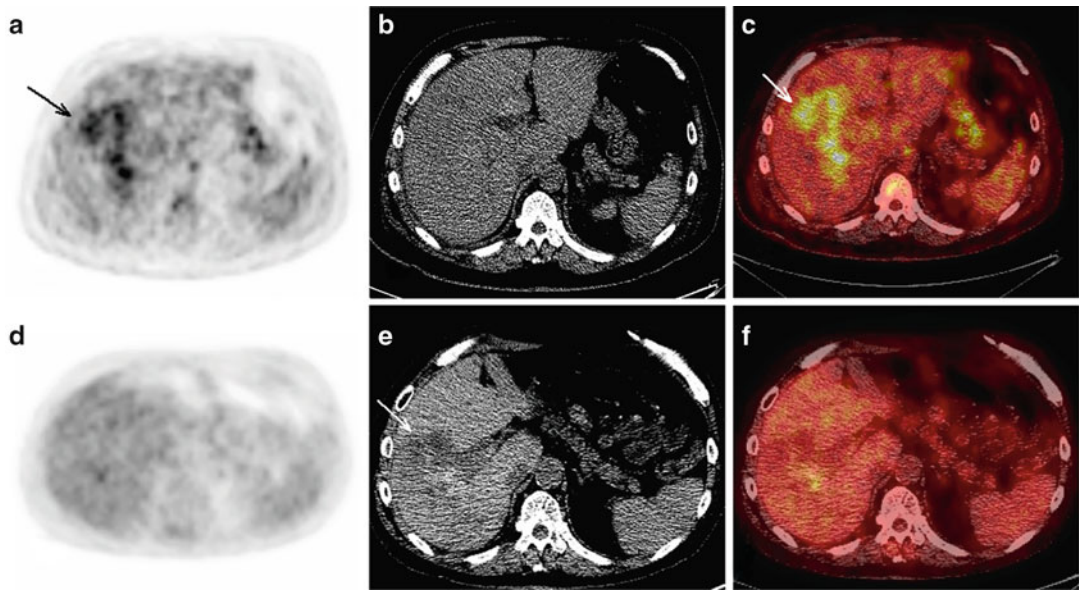

Fig. 6.12 *Good response to therapy*. FDG-PET/CT in a 61-year-old male with bilateral renal cell cancer and liver metastasis. *Top row*: (**a**) pre-therapy staging scan shows large focus of abnormal uptake in the *right* hepatic lobe (*arrow*). SUVmax 6.5. (**b**) Subtle hypodense lesion noted on non-contrast CT. (**c**) Fused PET/CT. *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 (*arrow*). (**f**) Fused PET/CT image. Patient's disease is still under control with sorafenib 4 years after initial diagnosis

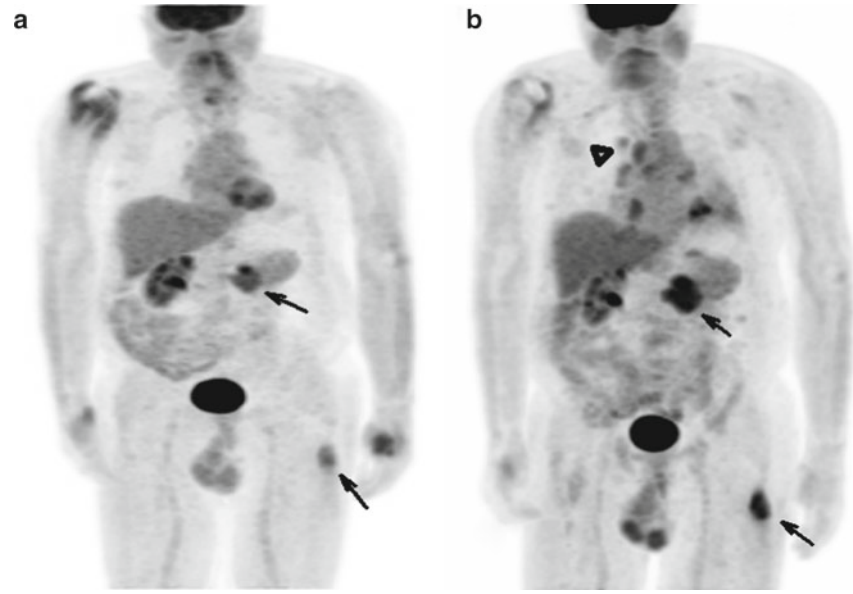

Fig. 6.13 *Progression of metastatic disease*. FDG-PET/CT scans in a 70-year-old male with metastatic clear cell renal ca. (**a**) Pre-therapy FDG-PET/CT scan shows disease in paraspinal soft tissue and *left* thigh (*arrows*). There is postsurgical/radiation uptake in *right* humeral metastasis. (**b**) Post-therapy with sunitinib FDG-PET/CT scan shows interval increased in size and intensity of FDG uptake in paraspinal mass and *left* thigh soft-tissue mass (*arrows*). There are multiple new pulmonary and mediastinal metastases (*arrow head*), indicating progression of the disease

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 nonresponders early in the treatment phase (Fig. 6.13). This can guide a personalized treatment plan and avoid unnecessary therapy; the benefits to patients, the medical community, and the economy could be enormous.

Influence on Management

It is very important to know whether FDG-PET has an impact on patient management in terms of clinical decision making. Studies have shown that FDG-PET altered management of patients with mRCC. In one study [5], FDG-PET was carried out in 25 patients with known or suspected primary RCC and/or metastasis and the results compared with those of conventional imaging techniques. All patients would normally go to surgery with conventional imaging, PET scan altered treatment plan for six (35 %); three could be treated with partial nephrectomy rather than radical surgery, and three avoided surgery owing to confirmation of benign pathology or detection of unsuspected metastasis leading to systemic therapy. Similar results were reported by others [7, 8, 28, 42].

In order to fully evaluate the impact of FDG-PET, the Center for Medicare and Medicaid Services (CMS) in the United States provided payment for PET scan to answer this question under National Oncologic PET Registry (NOPR). The design and analysis plan will not be discussed here, but the reference is provided [65, 66]. The results of the NOPR were published in several high-impact journals through peer review process [67–69]. The first paper was published in the Journal of Clinical Oncology in May 2008 with over 22,000 studies analyzed [67]. Hillner and colleagues concluded: 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 [67]. In this article, there are 1,600 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, 35.9–37.2) 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 [69]: including 895 cases for RCC initial staging, 41.1 % change in management; 979 cases for RCC restaging, 34.4 % change in management; and 1,003 cases for monitoring response, 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 choice of treatment for RCC. Carbonic anhydrase IX (CA IX), a membrane protein overexpressed in clear cell RCC, was found in 94 % of clear cell carcinomas, and decreased CAIX levels are independently associated with poor survival in advanced RCC [70]. G250, a monoclonal antibody to carbonic anhydrase IX (CAIX), has extreme high affinity binding to clear cell RCC with tumor uptake approaching 0.5 % of injected dose per gram of tumor tissue [71]. G250 was originally labeled with I131 [72]. Later, positron emitters such as Zr89 [73, 74] and 124I have been labeled to G250 [75, 76]. 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 [75] demonstrated that 124I-cG250 PET can accurately distinguish clear cell RCC histology from other renal lesions with a sensitivity of 94 % and a specificity of 100 %, indicating the potential clinical utility of this tracer in the noninvasive molecular evaluation and subtyping of RCC. A renal tumor with a positive 124I-cG250 scan is almost 100 % clear cell type (Fig. 6.14), while a negative scan is suggestive of non-clear cell type 90 % of the time (Figs. 6.15 and 6.16). False-negative scans have been seen in tumors with extended necrosis and small size (less than 1 cm). In addition, a metastatic lesion can also be seen on the scan with high confidence (Fig. 6.17).

Based on this phase 1 result, a comprehensive and multicenter comparative study for presurgical detection of clear cell RCC using 124I-radiolabeled cG250 antibody was performed and completed in late 2009; FDA approval pending. 124I-cG250 will improve the decision

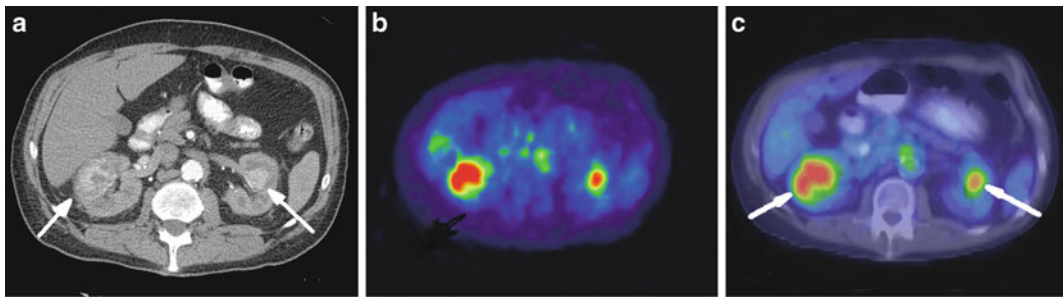

Fig. 6.14 *Bilateral clear cell renal carcinoma*. 124I-G250 PET/CT in a 65-year-old male with bilateral renal masses. (**a**) Triphasic CT shows 5-cm enhancing lesion in *right* kidney and 2-cm enhancing lesion in *left* kidney (*arrows*). (**b**) 124I-G250 PET shows intense uptake in both renal lesions, indicating clear cell renal carcinoma. (**c**) Fused PET/CT image

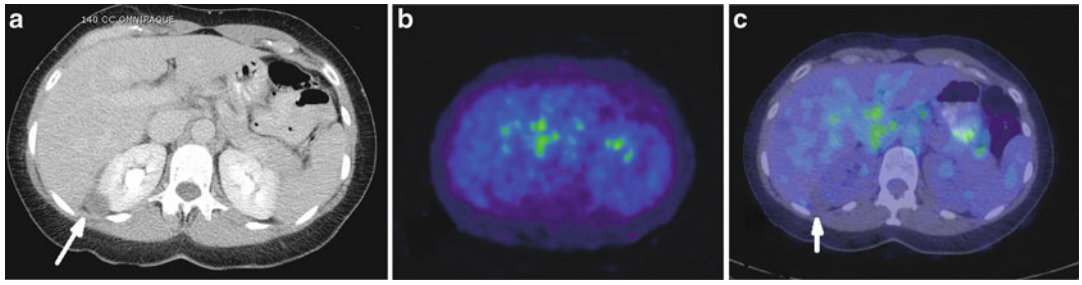

Fig. 6.15 *Papillary renal cell carcinoma*. 124I-G250 PET/CT scan in a 49-year-old female with *right* kidney mass. (**a**) Triphasic CT scan demonstrates a mild enhancing lesion in *right* lower pole (*arrow*), HU 41. (**b**) No significant 124I-G250 uptake corresponding to this renal mass, suggesting non-clear cell renal tumor. (**c**) Fused 124I-G250 PET/CT image

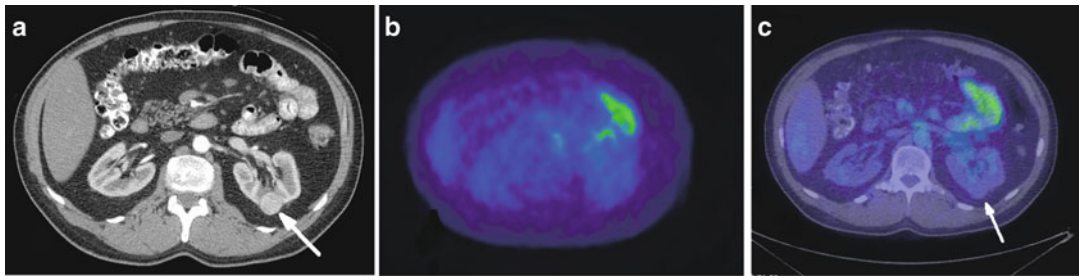

Fig. 6.16 *Left renal oncocytoma*. 124I-G250 PET/CT scan in a 59-year-old male with a *left* renal mass. (**a**) Triphasic CT shows a 2-cm enhancing lesion (*arrow*), HU120. (**b**) 124I-G250 PET shows no significant corresponding uptake in the lesion, ruling out clear cell carcinoma. (**c**) Fused 124I-G250 PET/CT

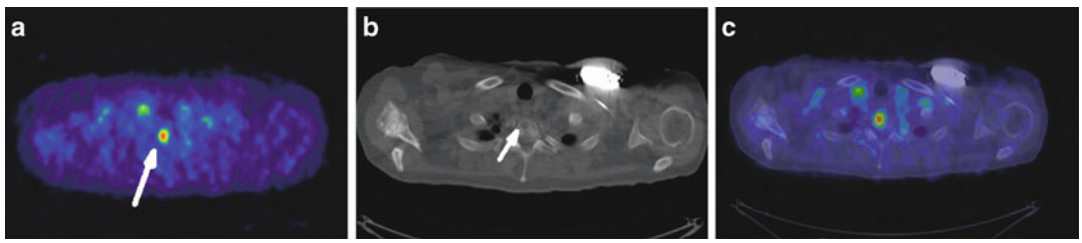

Fig. 6.17 *Bone metastasis from clear cell renal cancer detected by 124I-G250*. 124I-G250 PET/CT scan in a 65-year-old male with bilateral clear cell renal carcinoma. (**a**) PET shows a focal abnormal uptake (*arrow*). (**b**) There is a small corresponding lytic bone lesion in T1 vertebral body on CT (*arrow*). (**c**) Fused image

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, and the detection of metastasis may alter the 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 aspects of 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, has emerged as an important 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 [77]. Data regarding the clinical use of 18F-FLT in RCC is limited.

Hypoxia is another process commonly studied with novel PET tracers and imaging. There are over 30 trials involving hypoxia tracers currently in progress. The tracers include 18F-FMISO, F18-FAZA, 18F-EF3 and EF5, Cu-labeled ATSM, 124I-IAZGP, 18F-HX4, and 18F-VM4. The 18F-FMISO appears to be the most commonly used tracer for hypoxia. In a study, 18F-FMISO PET was performed in 17 patients with presumed RCC and showed only minimal increased uptake in RCC as compared to normal renal tissue [78]. The mean SUV for RCC was 1.3, while that in the normal contralateral kidney was 1.1. A more recent study [79] with 53 patients evaluated relationship between initial metastasis hypoxia, change after 1 month's sunitinib, and therapeutic response by FMISO-PET scans. They conclude that sunitinib reduced hypoxia in initially hypoxic metastases but did not induce significant hypoxia in nonhypoxic lesions. If this result could be validated, there will be implications for patient selection for drug therapy and improving response.

Angiogenesis is the physiologic process involving the growth of new blood vessels. Many tumors have high angiogenic capability, and there are several cancer therapy drugs to target this property as a mean to control/combat cancer. The most commonly studied angiogenesis PET tracer is Arg-Gly-Asp (RGD) peptide. This compound has been labeled as 18F-RGD [80–83], 64Cu-DOTA-RGD [84–86], and 68Ga-DOTA-RGD [87]. Clinical utility of these tracers in RCC is unclear.

Apoptosis is the process of programmed cell death, and many cancer cells lose this ability. Caspases are responsible for the execution of the cell death program and are potentially suitable targets for the specific imaging of apoptosis in vivo. The main compounds used in the research are annexin V [88] and derivatives.

18F-labeled choline has been used for other tumors [89–92] such as lung and prostate. Middendorp and coworkers [93] published their initial experience with 18F-fluoroethylcholine PET/CT in staging and monitoring therapy response of advanced renal cell carcinoma. This is a small sample study with only two patients. 18F-fluoroethylcholine PET/CT detected 56 % of mRCC lesions on the baseline scan. Response evaluation by 18F-fluoroethylcholine PET/CT after tyrosine kinase inhibitor treatment was correct in both patients. 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 [94] as well. One other study showed low uptake [95]. 11C-acetate has been used for early prediction of sunitinib response in metastatic RCC with some success [94]. This agent is limited due to its short half-life (20 min). Recent availability of 18-F-labeled acetate makes the delivery and commercialization of the tracer possible.

Conclusions

FDG-PET offers little advantage over conventional imaging in diagnosis of primary RCC. FDG-PET is complementary to anatomical imaging in detecting locoregional and distant RCC metastasis. State-of-the-art hybrid PET/CT provides both anatomical information and molecular function of the disease processes and is more accurate than stand-alone CT or PET. FDG-PET/CT has the advantage of detecting small nodal metastasis and locoregional recurrent disease after nephrectomy. FDG-PET/CT is the most accurate study for bone metastasis from RCC. Monitoring therapeutic response of metastatic RCC is very important especially in the era of targeted therapies. These targeted therapeutic agents inhibit tumor growth rather than kill the

tumor cells, and thus conventional imaging modalities that rely on size criteria are limited. FDG-PET/CT has proven its usefulness in monitoring targeted therapies for metastatic RCC. The information provided by molecular imaging such as maximum standardized uptake value (SUVmax) has shown to be an independent prognostic factor for RCC, and SUVmax should be considered as a criterion for incorporation in future prognostic models. There are limitations for FDG-PET as a diagnostic tool for RCC, but new tracers such as 124I-cG250 have demonstrated encouraging results. Several tracers that have been in research for many years, such as FLT and FMISO, might have certain value for RCC. PET tracers focusing on disease processes such as hypoxia, angiogenesis, and apoptosis might be of value in RCC as well. If a specific tracer for each disease process could be found, we might improve patient care significantly and provide true individualized therapy for patients.

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History of Renal Surgery for Cancer

7

Kamal Nagpal and Karim Hamawy

History of Renal Surgery

The late nineteenth century was when the first documented nephrectomy took place. In 1861, Wolcott mistakenly removed a kidney when operating for liver cysts. It weighed 2 ½ pounds and was described by Stoddard who assisted Wolcott. Subsequently, Speigelberg in 1867 performed a nephrectomy while excising an echinococcus cyst. This was an inauspicious beginning as both patients died, and this procedure was not readily accepted. Theodor Kocher carried out a transperitoneal nephrectomy for carcinoma in 1876 in two patients, both of whom died of peritonitis following surgery. The first successful planned nephrectomy was completed by Simon in 1869 for a persistent urinary fistula and hydronephrosis [1] in the University of Heidelberg (Fig. 7.1). This patient survived and two important factors were discovered: firstly, that a patient could survive elective removal of a kidney and, secondly, could live with only one kidney. Finally in 1870, Gilmore successfully performed the first elective nephrectomy in the United States for the treatment of pyelonephritis and persistent urinary tract infection.

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The diagnosis of renal cell cancer was readily made during the early 1900s. The kidneys were visualized using intravenous pyelography and retrograde pyelogram. A filling defect combined with a palpable mass would give ample assurance of the tumor's existence. The extent and degree of fixation could be assessed. Arteriography [2] as well as retroperitoneal coccygeal air insufflation [3] were techniques used to further characterize kidney tumors. Parke Smith et al. [4] used arteriography not just to define the arterial structure but also to differentiate benign from malignant lesions.

The end of the nineteenth century also introduced advances in surgical technique that allowed improvement in the survival of patients undergoing nephrectomy. Joseph Lister, in London, introduced antiseptic techniques. Hand washing and disinfection of instruments as well as steam sterilization resulted in a significant reduction in perioperative complications and mortality from nephrectomy. These discoveries helped gain a greater acceptance of kidney surgery. During this time, more than 300 radical nephrectomies were performed both in America and Europe.

Era of Radical Nephrectomy: Gold Standard

Once the diagnosis was made, the surgical approach for malignant disease was a total (or radical) nephrectomy. The retroperitoneal approach was favored by most urologists in this

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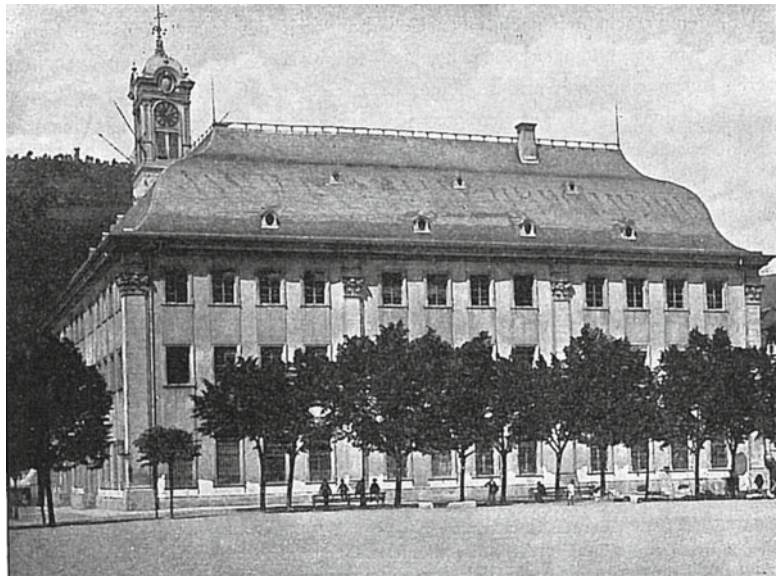

Fig. 7.1 University of Heidelberg (Courtesy: http://en.wikipedia.org)

era; however, Emil Kocher removed a kidney via the transperitoneal approach in 1878 [5]. Dr. Atle Berg modified his technique, utilizing the lateral incision and mobilization of the colon to improve visualization of the renal pedicle. Finally, during the late 1940s, Chute et al. [6] performed a thoracoabdominal approach. This technique gave excellent exposure of the tumor and renal pedicle as well as neighboring structures that may be involved. Radical nephrectomy for kidney cancer was subsequently adopted by numerous surgeons both in the USA as well as Europe. Vernon Dick and others from the Lahey Clinic described a series of 280 cases of renal cell carcinoma over 20 years. The technique described by Foley et al. [7] was recommended as it removes all perirenal fat as well as sampling of local lymph nodes. Three-year survival rates of 88 % and 80 % were described by Robson and Somerset and provided encouraging results for renal cell cancer [8]. Solitary metastases were also successfully removed from various organs, including the lungs, brain, and bones with reasonable success. It has also been demonstrated that regression of metastatic disease may follow excision of the primary tumor [9]. As time went on, a larger number of nephrectomy series were published. Several hundred cases, many of them for malignant disease, were evaluated both in the United States and in Europe. Radical nephrectomy became the gold standard for tumors of the kidney.

With greater acceptance of this surgical technique came the ability to examine these tumors histologically. In the mid-1800s, Robson [8] evaluated solid renal tumors and concluded that renal cell carcinoma arose from renal tubular epithelium. Other pathologists suggested that these tumors were derived from adrenal rests within the kidney. This idea persisted throughout the early 1900s. The term hypernephroid tumor was used extensively and was first used to describe the origin of renal tumors above the kidney. However, there were many who objected this concept. Hugh H. Young in his book [10] "Practice of Urology" reinforces the idea that the term hypernephroma should be abandoned as it assumes that the tumor arises from adrenal tissue.

The classification of kidney tumors also allowed for better stratification of this disease and more improved selection of those who could undergo renal-sparing surgery. Glenn [11] provided a simple pathologic outline of renal tumors. Benign disease, including oncocytomas and cystic disease, was categorized as well as malignant and embryonic lesions. Prior to this, Deming and Harvard [12] had proposed a more complex and compre-

hensive system based on all known cellular subtypes. This system has 11 categories with multiple subtypes that cover most renal lesions. It, however, was felt to be a difficult way of looking at kidney pathology. Ideally, classification based on simple clinical and radiographic criteria would become more appealing to the surgeon. In 1994, Barbaric approached this concern by suggesting that renal masses be categorized into three large groups. The pathologic features were benign, malignant, or inflammatory. This afforded the surgeon with more information in order to suggest the best treatment option for the particular pathologic diagnosis. More recently, renal cell carcinoma has been examined looking at different subtypes using genetic markers and tumor biology.

The Rise of Nephron-Sparing Surgery (Partial Nephrectomy)

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

Although there was interest in renal-sparing surgery at the time, the complications were much too significant to adopt this technique. Many patients died because of sepsis, uremia, and shock from attempted partial nephrectomy. Massive hemorrhage, urinary fistula formation, and poor patient selection all contributed to the preferential use of radical nephrectomy for both benign and malignant disease.

In the early stages of kidney surgery, partial nephrectomy was a procedure used only in certain circumstances. This procedure was first performed by Czerny in 1887 for an angiosarcoma [13] (Fig. 7.2). As mentioned above, the early experience with partial nephrectomy was abandoned quickly due to the injudicious use of this technique and the high rate of complications. With improvement in preoperative evaluation of patients as well as the postoperative management, more conservative operations for benign disease gained acceptance [14]. It was however the pioneering ideas of Vermooten [15] in the 1950s that led to the modern era of partial nephrectomy for

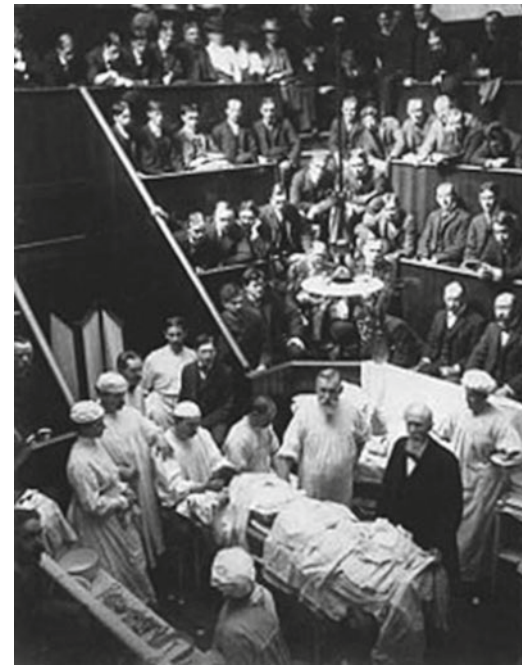

Fig. 7.2 Vincenz Czerny as a surgeon (Courtesy: http://en.wikipedia.org/wiki/Vincenz_Czerny)

renal neoplasms. His observations were based on the pathological studies showing that clear cell carcinomas were locally advancing and grew by expansion. Few lesions under 3 cms were found to be metastatic, and some tumors could safely be excised with a 1 cm margin, with little fear of local recurrence. Collectively, 321 procedures were done safely by these surgeons; however, partial nephrectomy was still reserved for patients with a functional contralateral kidney [16].

It was unfortunate that few urologists believed Dr. Vermooten's ideas and observations. As mentioned, the majority felt that radical nephrectomy was the procedure of choice for renal cancers, especially in cases with two functional kidneys. Partial nephrectomy was reserved for cases of solitary kidneys, marginal renal function, or tumors in both kidneys. Zinman and Dowd [17] collected a series of partial nephrectomy between 1950 and 1967. They described the feasibility of this technique but reinforced the use of radical nephrectomy with excision of adipose tissue and lymphatics in all cases with a normal contralateral kidney. Semb [18] performed the removal of

a carcinoma in a solitary kidney. However, most surgeons of that era rarely, if ever, published on partial nephrectomy, and radical nephrectomy would remain the gold standard for the next several decades.

It was during the later part of the twentieth century that multiple centers worldwide began to publish their experience with partial nephrectomy. Renal hypothermia allowed longer and more complicated reconstruction of the kidney. Bench surgery gained acceptance in some centers, but many prominent surgeons realized that most cases could be done in situ. The 1980s would see some groups who favored partial nephrectomy for certain patients with a normal, contralateral kidney. Criteria were developed that allowed for the accurate prediction of survival in this patient population. The major concern among the urological community was recurrence after partial nephrectomy which was amplified by Mukamel et al. [19] when they reported evidence of occult multifocal renal tumors in 30 % of nephrectomy specimens, which might recur if only the primary tumor was removed. However, in 1993, Licht and Novick [20] reported only two recurrences and 95 % survival in a series of 241 cases collected from literature (1967–1991). Their follow-up was only 3 years. Herr [21] and Fergany et al. [22] later showed a rare local recurrence and almost 100 % survival on patients undergoing partial nephrectomy especially in those tumors less than 4 cm. Dr. Herr states that this survival can be explained by the fact that a majority of these tumors were less than 4 cm and had benign characteristics or favorable pathology [23].

As surgical techniques improved, so did imaging of the patient, both preoperatively as well as intraoperatively. 3D imaging using CT scan and MRI is standard and imperative for surgical planning of partial nephrectomy. Intraoperative imaging, using ultrasound, is helpful and at times mandatory for these cases. Although there was a time that many groups remained skeptical about the merits of partial nephrectomy in patients with a contralateral normal kidney, the results demonstrated equivalent long-term oncological outcomes to radical nephrectomy in specific patient populations. For most patients with a surgical, small, clinical T1 tumor who are surgical candidates, partial nephrectomy is now the accepted gold standard.

Twenty-First Century and the Future

The advent of minimally invasive technique allowed urologists to perform nephrectomy with less blood loss, lower narcotic requirements, shorter hospitalization, and faster return to normal activity. Ralph Clayman [24] from Washington University in St. Louis was the first urologist to remove a kidney through an 11 mm incision. Hand-assisted radical nephrectomy or HALN was introduced by Stephen Nakada in 1997 [25]. This technique allowed minimally invasive surgery to provide similar steps performed in classic open surgery. Debates ensued regarding these various techniques. There are avid proponents on all sides, and it is important to understand the reasons for offering a certain technique to our patients. Limitations in experience should not overshadow the patient's best interest.

Lastly, we have begun to understand the necessity of renal preservation. Huang et al. [26] published the first series describing the importance of maintaining renal parenchyma. He notes that chronic kidney disease may be present in 30 % of patients with small renal lesions. More importantly, patients who undergo radical nephrectomy have a twofold increase in developing chronic renal insufficiency as compared to patients who underwent partial nephrectomy. Dr. Libertino [27] has described more than 800 cases of nonclamping partial nephrectomy, one of the largest experiences in the world. In his series, GFR is significantly reduced in patients who have undergone clamping during partial nephrectomy. Inderber Gill has also examined this phenomenon. He clearly states that every minute of ischemia counts during laparoscopic and robotic partial nephrectomy [28]. The increasing understanding of tumor biology and advances in radiological imaging and surgical technology have led to expanding the indications of partial nephrectomy. Minimally invasive laparoscopic and percutaneous energy ablation procedures promise to

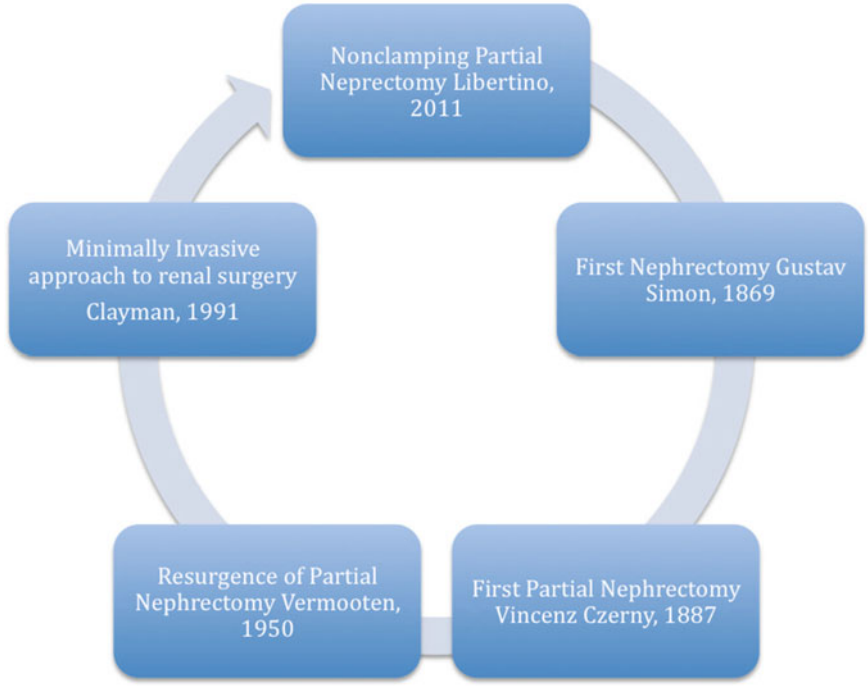

Fig. 7.3 History of renal surgery for cancers

control renal tumors with far less morbidity and better quality of life than open surgery. Robotic approaches as well as single-port surgery and the use of natural orifice transluminal endoscopic surgery all offer the field a variety of techniques to improve surgical outcomes.

As one can see, renal surgery has evolved significantly over the past 150 years (Fig. 7.3); however, there is much to do and learn in this area of urology. Advancement in tumor detection and biology will more adequately stage our patients, hoping to maximize renal function and longevity. Surgical techniques will continue to improve, and the role of partial nephrectomy will gather greater momentum in the treatment of renal disease. There are still many surgeons who would sacrifice a patient's functional renal parenchyma because they are unfamiliar with the techniques of partial nephrectomy. We need to reinforce the Hippocratic oath, know our limits, and do no harm to the patient. As educators, it is our responsibility to teach those who follow in our footsteps about the latest developments in the management of renal tumors.

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

Anthony T. Corcoran, Marc C. Smaldone, Robert G. Uzzo, and David Y.T. Chen

Introduction

Renal cell carcinoma (RCC) is the most common primary malignancy of the kidney, and it is the most lethal of all urologic malignancies. Close to 60,000 men and women were diagnosed with RCC in 2011, and the mortality rate of RCC has been and continues to be close to 25 % [1, 2]. Due to the increased use of cross-sectional abdominal imaging over the past several decades, a stage migration towards low-grade low-stage RCC has been observed in large population-based cohorts [3, 4]. In the decade from 1993 to 2004, the proportion of new RCC cases diagnosed at stage I increased from approximately 43–57 % [5], and the incidence of tumors less than 3.0 cm in diameter at presentation increased from 32.5 to 43.4 % [6] (Fig. 8.1). Today, the vast majority of small renal masses (SRMs) are discovered incidentally [7], are asymptomatic, and have a variable malignant potential. Approximately 15 % of SRMs are benign tumors [8], and only an estimated 20–30 % of RCC cases are determined by pathologic assessment to have features suggestive for potentially aggressive biology and behavior [9, 10]. Concurrent with the increasing incidence in SRMs, a concurrent "age migration" of RCC has been observed, with SRMs more frequently identified in patients of increasing median age, with a peak rise in incidence in persons between 70 and 90 years of age [11]. Paradoxically, although the rates of renal surgery and other interventions have risen as well, the mortality from RCC has not improved over the last decades, suggesting that the absolute number of lethal lesions has not diminished [4]. 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 overdiagnosis and overtreatment.

The concept of overdiagnosis and overtreatment 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 [12]. While stage I RCCs are suggested to be one of the most "curable" urologic malignancies, whereas surgical treatment for stage I RCC demonstrates 5-year cancer-specific survival rates in excess of 95 % [13], some have begun to question if the driving force behind these favorable outcomes is simply 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 a SRMs in elderly and/or infirmed patients [14].

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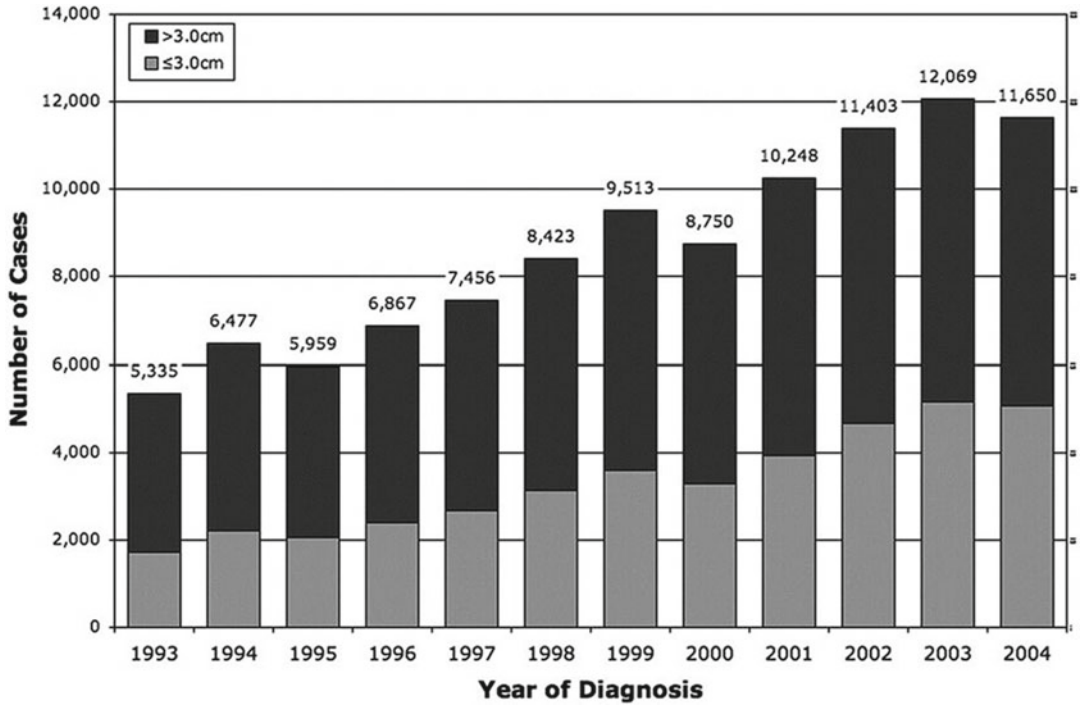

Fig. 8.1 Number of stage I renal cell carcinoma cases by diagnosis year (1993–2004) stratified by tumor size (<3 cm or ≥3 cm) (Reproduced with permission from "Cooperberg et al. Decreasing size at diagnosis of stage 1 renal cell carcinoma: analysis from the national cancer database, 1993 to 2004. J Urol. 2008; 179(6):2132"; American Urological Association by Elsevier, Inc.)

One clear example of this idea is reflected in the evolution of the management of prostate cancer. Over the past 25 years, the development and aggressive utilization of PSA-based prostate cancer screening in the United States has also resulted in a significant stage migration [15]. The great majority of prostate cancer diagnoses care currently made in asymptomatic men who are identified to have organ-confined malignancies. Though this stage of prostate cancer can be highly successfully treated with standard therapy, 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, and most men with prostate cancer will likely die of other causes and not from their disease [16]. From this observation was born the management approach of "watchful waiting," especially for men of advanced age having prostate cancer and substantial concurrent comorbidity, and there is the expectation that definitive treatment of prostate cancer in that scenario provides marginal benefit. Recognizing that low-volume, low-grade prostate cancer might behave in an indolent manner for decades, the concept of expectant management with serial reassessment and possible delayed intervention (active surveillance (AS) with curative intent) has also been further extended and applied to younger or healthier men. This approach has the intent of proceeding with curative treatment only in the event of a change in the predicted prostate cancer behavior or in its perceived risk. This practice of AS defers immediate intervention to avoid the potential morbidities of treatment until evidence of increased clinical risk is identified, at which time curative treatment can still be applied and its impact is then justified [17]. Limited long-term data supports the AS management approach for selected men with prostate cancer [18], and similarly, AS has been applied in select patients with SRMs and significant competing risks. Although limited by small cohorts and retrospective methodology, the current data supporting AS

for management of the incidental SRMs represents 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

Predominantly from the experience of centers applying delayed intervention in select patients with SRMs both on and off formal AS protocols, much has been learned about their natural history. Knowledge of the expected course and behavior of SRMs under observation yields insight into identifying which lesions might be safely observed and which might benefit from routine immediate and definitive intervention. This ideal classification would importantly result in avoidance of overtreatment of lesions with little to no malignant potential. Overall, the data regarding the natural history of untreated SRMs are limited, since historically reflexive surgical excision and treatment of SRMs has been routinely performed soon after diagnosis. The majority of existing evidence is 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].

Benign Versus Malignant SRMs

Recently, the contemporary published literature examining the rates of benign versus malignant lesions in patients with SRMs undergoing immediate treatment was reviewed [8]. The available data included 26 studies published in the past decade and incorporated 27,272 patients from 8 countries. The frequency of benign findings in SRMs 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 recent separate review assessing outcome of SRMs under surveillance, similar results were seen [37] 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.

Growth Characteristics of Untreated SRMs

There are several studies using pooled analytic methods to consolidate institutional data and characterize growth trends in SRMs. A recent pooled analysis of nine single institution retrospective series identified 234 masses followed for a mean duration of 34 months [38]. 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). A second, more recent, comprehensive systematic literature review identified 18 studies including 880 patients with 936 SRMs managed by AS that demonstrated consistent findings (Table 8.2) [37].

Table 8.1 Meta-analysis of the natural history of observed masses (Adapted from Chawla et al. [38])

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 (mos)	# 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%*

Table 8.2 Pooled analysis of small renal masses managed with active surveillance (Adapted from Smaldone et al. [37])

Study	Year	Median age, yrs (range)	No. of patient/ no of SRMs	Initial mean tumor diameter, cm (range)	Mean linear growth rate, cm/year (range)	Mean follow-up, mos (range)	# 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 %*

Mean linear growth rate, cm/year (range)

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 [37]. 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/year) and volume of 16.5 cm^3 (7.3 cm^3/year). The development of metastatic disease was low in this cohort 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.

Radiographic Characteristics of SRMs

While SRMs are identified typically as incidental findings on body axial imaging, additional detail regarding their nature or estimated behavior is limited. Few radiographic characteristics inform on the risk of SRMs, and generally this information is inadequate to affect the way such lesions are managed. Despite considerable effort towards this goal, we continue to utilize tumor growth, a relatively crude method to predict disease progression, as the most reproducible imaging characteristic on cross-sectional imaging. In recent large series, increase in maximal linear tumor has been shown to correlate with increasing risk of malignant pathology [37, 39, 40], high-grade disease [37, 40, 41], clear cell histology [39, 42], and presence of synchronous metastases [43–45]. In retrospective studies from the Mayo Clinic and Memorial Sloan Kettering Cancer Center encompassing 5,445 patients with surgically treated clinically localized renal masses, increasing tumor diameter has been demonstrated to be associated with increasing rates of malignant pathology as well as high-grade nuclear features [39, 40]. A smaller 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 %, $p=0.05$) [10]. This correlation has been confirmed using population data investigating the relationship between the primary tumor size at presentation and histopathological features. From the Surveillance, Epidemiology, and End Results (SEER) dataset, for each 1 cm increase in size, the probability of finding a high-grade tumor in 19,932 patients with localized disease increased by 13 % (OR 1.13, $p<0.001$) [42]. While almost 85 % of localized RCCs <4 cm were low grade, the authors found that 70 % of contained lesions >7 cm were also low-grade lesions; therefore, it is important to note that renal tumors can grow quite large without acquiring the ability to metastasize.

With the knowledge that growth rate can provide insight into malignant potential, the ability to identify features on the initial axial imaging study that predicted future rapid growth would be clinically useful. Unfortunately, despite the ability to measure growth rates accurately, cheaply, and quickly, no discernible CT imaging features have proven sensitive enough to predict a tumor's future growth rate. Dodelzon et al. recently examined the relationship between growth rate and MR imaging characteristics in patients on active surveillance [46]. 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 the data that suggest only a small proportion of renal masses have the ability to display aggressive biology and metastasize early, distinguishing 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 [45]. 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 ($p<0.001$) [45]. 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 of synchronous metastatic disease was clearly related to initial tumor size and occurred infrequently with small tumors [47]. Despite the data presented, no clear cutoff exists above which one would imminently fear 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 [48]. This concept is supported from experience with nonfamilial 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 [43, 44].

Role of Percutaneous Biopsy and Other Diagnostic Modalities

Traditionally, when renal masses are found on cross-sectional imaging, the diagnosis of malignancy is suspected based on the presence of mass enhancement with intravenous contrast [13]. Contemporary management, including patient counseling and treatment planning, is often delivered in the absence of definitive pathologic information and based solely on the imaging findings, despite the expectation that approximately 15 % of these presumed RCC lesions are actually benign and less than 30 % display aggressive malignant potential [8, 40]. In contrast to other urologic malignancies, where specific pathologic information from biopsy is applied to predict risk and tumor behavior and subsequently to guide management and treatment, the ability to similarly evaluate a SRMs preoperatively and tailor treatment strategies based on these results remains elusive [49]. While efforts have been made to use preoperative clinical and radiographic variables to predict malignant potential [50, 51], to date, the clinical utility of noninvasive diagnostic information and predictive models remains limited [52]. Despite the potential suggested benefits of percutaneous renal mass biopsy, this diagnostic procedure has yet to be accepted as a standard component of the evaluation and management of patients with SRMs. A majority of urologists appear to use percutaneous biopsy in selected cases; however, only a small minority do so routinely.

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 SRMs. 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 SRMs diagnosis or provide actionable clinical information which alters the need for intervention. 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. Modern noninvasive imaging and image-guided biopsy techniques of renal masses have improved and can provide an accurate diagnosis in a majority of cases [53]. 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 [54]. 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 [54]. Since the application of larger 18-gauge core needles for tissue procurement and with improvements in immunohistological techniques, percutaneous renal biopsy mass has demonstrated improved accuracy in differentiating benign from malignant histology (>90 %) and is safely performed with minimal procedure-related complications [55]. From modern biopsy series, the positive predictive value is reported to be over 95 % in cases where a malignancy is detected [54]. In addition, the negative predictive value has been reported to be over 80 % in contemporary series with false-negative rates less than 5 % [55, 56]. In a recent contemporary series of 152 biopsies using the 18-gauge core biopsy technique, Maturen et al. reported highly accurate sensitivity (97.7 %), specificity (100 %), positive predictive value (100 %), and negative predictive values (100 %) for malignancy [57].

Despite these demonstrated improvements in yield, 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 [58]. 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 nondiagnostic result in 67 cases (19 %) [59]. Solid appearance on imaging and tumor size were associated with a diagnostic result on multivariate analysis. If the first biopsy was nondiagnostic, then when a repeat biopsy was performed, a diagnosis was subsequently reached in 83 % of cases.

Despite the increasing evidence showing the high accuracy of renal mass biopsy in determining a tumor's histologic subtype, little data exists on the ability of the biopsy to accurately predict a tumor's grade [54]. Since increasing tumor grade has been shown to be correlated with cancer-specific survival [60], pretreatment 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 [61]. 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 [62].

Despite the renewed interest and consideration of pretreatment percutaneous renal mass biopsy in the management of the SRMs, its indication and role remains controversial [52]. In a recent survey of practice patterns conducted in the United Kingdom, only 34 % of urologists reported always using biopsy in the treatment algorithm of indeterminate SRMs, with the remaining respondents reporting either selectively (23 %) or never using biopsy (43 %) to inform their management decisions [63]. 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 [64, 65]. Although limited by selection bias, these findings have led some to change their practice and recommend an image-guided biopsy of SRMs always be performed before treatment to confirm malignancy, to classify histologic subtype, and to establish tumor grade [66]. While the benefit and use of biopsy has increased and gained traction, it is likely that 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 [67].

Complications of Biopsy

Potential complications of biopsy are tumor seeding along the needle tract, bleeding, arteriovenous fistula, infection, pneumothorax, and ultimately death. In a large review of more than 16,000 abdominal fine needle biopsies, mortality following renal biopsy was an extremely rare and unlikely event, with an overall mortality rate of 0.031 % [68]. Overall, few major complications have been reported in recent series, and the risk of minor complications (<5 %) or tumor seeding (<0.01 %) with contemporary coaxial biopsy techniques is also low [53]. 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 [69–76]. 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 noncutting 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 [77]. Demonstrating the accuracy of biopsy complex cystic lesions, Richter et al. used a combination of FNA and core biopsy on 227 Bosniak II/III lesions to successfully histologically characterize 89 % [78]. 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 % [79]. 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 [53].

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 interventions. 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 treatment strategy to tumor biology [49]. 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) [80, 81], p53 (marker of apoptosis) [82, 83], HER-2 (epidermal growth factor) [84], vascular endothelial growth factor (VEGF) [85], bcl-2 (apoptotic inhibitor) [86], cyclin-D1 (cell cycle regulatory molecule) [87], vimentin (epithelial cell adhesion molecule) [88], C-reactive inflammatory protein [89], and carbonic anhydrase IX (cell surface transmembrane enzyme upregulated by hypoxia inducible factor in low oxygen environments) [90], among others [91]. Unfortunately only preliminary data currently exist, and we are not yet able to use this information to determine which patients with SRMs require immediate intervention and which can be safely observed [49].

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 ($r = 0.71$; $P = 0.01$) [92]. Unfortunately, the role of biomarkers in the selection and management of patients under AS remains clinically limited [49]. 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, 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 subcellular level noninvasively, 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 [93]. Unfortunately the initial enthusiasm for the utilization of ^{18}F-FDG PET to diagnose, stage, or restage 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 %) [94]. 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 [95–97]. 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) with its associated antibody G250. Expressed on the cell surface of almost all RCC 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 [98]. 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 noninvasive 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 [99]. Preliminary 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.

Predictive Models and Assessment of SRMs Malignant Potential

Recently, several methods of objectively measuring renal mass anatomy have been developed and described, and they are slowly being utilized in regular clinical practice [100–102]. There is increasing evidence to suggest that 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 [103]. 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 [101]. 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) [103]. 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 [51].

Active Surveillance

The Rationale for AS

Between 1983 and 2002, RCC tumors identified between 2 and 4 cm in size have increased in incidence from 1.0 to 3.3 per 100,000 [4]. Resected tumor size dropped from a maximum diameter of 7.8–5.3 cm between 1989 and 1998 [104]. The incidental diagnosis of RCC increased from 7 % to 13 % in the early 1970s to 48–66 % of kidney cancer cases currently [66]; incidental tumors are most commonly found in patients older than 65 years [66], 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 [105]. 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.

As described in this and previous sections of this chapter, an appropriate algorithm for management of the SRMs would include a pretreatment renal mass biopsy to confirm the diagnosis

and to consider AS and expectant management in appropriately selected persons. The evidence to supporting this protocol includes the following:

1. Not all renal masses are RCC. Review of the literature indicates that 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 nonaggressive 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 versus 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 SRMs 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 recently published 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 [37].

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 posttreatment nomograms have been developed to predict risk of cancer-specific death or disease recurrence which is beyond the scope of this review [106]. 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 [107].

Subsequent efforts to determine renal grade preoperatively were also unsuccessful with limited predictive accuracy [108]. In contrast, a number of clinical tools have recently been developed to determine tumor malignant potential and risk of death based on pretreatment characteristics with acceptable predictive accuracies facilitating use 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 (Fig. 8.2) tool to predict the probabilities of harboring malignant and high-grade pathology based on anatomic variables which was described in

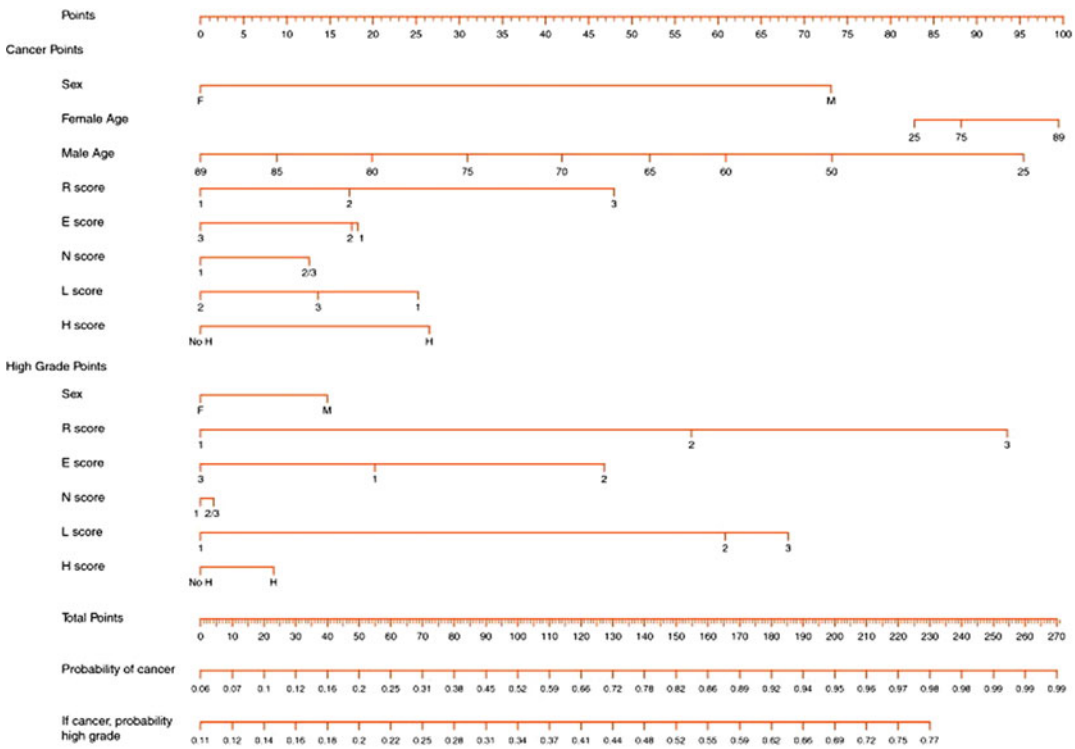

Fig. 8.2 Nomogram evaluating risks of an enhancing renal mass being malignant and high grade. Total point values are independently calculated for the cancer and the high-grade models and then applied to the corresponding probability scale at the bottom of the figure (Reproduced with permission from "Kutikov et al. Anatomic features of enhancing renal masses predict malignant and high-grade pathology: a preoperative nomogram using the RENAL Nephrometry score. Euro Urol. 2011; 60(2):246"; European Association of Urology by Elsevier, Inc.)

more detail earlier in this review [103]. 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 lesion 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 nephrometry score of 2+2+2+a+3h=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) [14]. 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

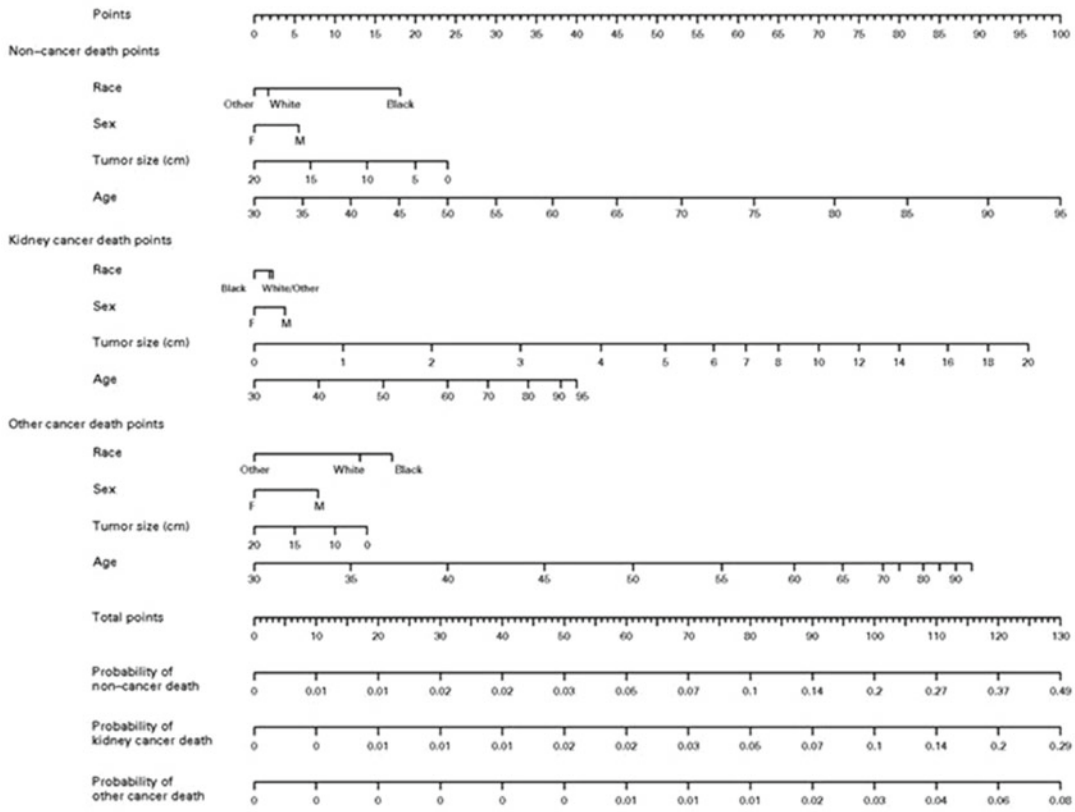

Fig. 8.3 Nomogram evaluating 5-year competing risks of death in patients with localized renal cell carcinoma. Total point values are independently calculated for each cause of death and then applied to the corresponding probability scale at the bottom of the figure (Reproduced with permission from "Kutikov et al. Evaluating overall survival and competing risks of death in patients with localized renal cell carcinoma using a comprehensive nomogram. J Clin Oncol. 2010; 28(2): 315"; American Society of Clinical Oncology by Elsevier, Inc.)

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 [109]. 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 counseling 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 SRMs 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 [110]. Furthermore, increased risks of death, cardiovascular events, and hospitalization have been demonstrated in patients with mild renal insufficiency in recent

large population-based cohort data [111]. 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 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 performed. Patients must consider and accepted the calculated risk involved due to the occasionally unpredictable behavior of RCC prior to proceeding with AS.

AS Protocols

Currently, there is no data to support any specific AS protocol (frequency and type of radiographic follow-up). Unfortunately no studies comparing the effectiveness of active surveillance/delayed intervention with traditional surgical therapies or ablative techniques have been performed. 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 and, for some, the demanding follow-up schedule. Studies must also examine the costs of surgical morbidity and mortality in such 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) [13]. The choice of imaging interval should be based on clinical risk factors specific to the renal mass and the patient's overall health status. We typically obtain imaging at 3–6-month interval following initiation of AS with the goal of establishing baseline growth kinetics (time zero to point one). 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 at the same tumor level [26]. Most importantly, in the event that their tumor exhibits a rapid growth rate, a new lesion appears, or the onset of clinical symptoms occurs, patients must be appropriately counseled objectively regarding the risks of continued AS versus immediate treatment in their individual circumstances.

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 [37, 112]. Definitive radiographic characteristics associated with rapid growth rate 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, 52], tumor size >4 cm [25, 33], development of clinical symptoms versus incidental detection [33], multifocality [113], 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) [114]. Some series have reported on the observation of larger tumors (clinical T1b and T2) in select patients with significant medical comorbidity signifying that the indications for surveillance may be expanding [115]. However, the biology of these lesions must be distinguished from the infrequent case of a localized mass 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 on final pathology and growth rate during surveillance

showed that grade 3 lesions grew faster than grade 2 lesions (0.93 vs. 0.28 cm/year; $p=0.01$); 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/year) although this trend was not statistically significant ($p=0.47$) [21]. Others have retrospectively compared patients with proven RCC ($n=10$) versus oncocytoma ($n=6$), reporting no statistical differences in tumor growth rate between groups (0.71 vs. 0.52 cm/year) [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 histologic. 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/year; $p=0.15$) in oncocytomas versus RCC [38]. 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 [116, 117]. Kawaguchi et al. observed a yearly linear growth rate of 0.2 cm, which is not too dissimilar from the growth rates of SRMs of variable histology reported in other series [117]. Only eight of the 45 oncocytomas underwent extirpation, with one of the eight lesions harboring 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/year [19–35]. Two recent publications summarizing the available data reported mean linear growth rates ranging from 0.28 [38] to 0.31 [37] cm/year. However, within these reported series of SRMs on AS, a subset of SRMs that demonstrated no interval growth on serial imaging has been identified. 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 ($p=0.38$) [118]. 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 ± 1.3 cm; $p=0.21$) 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 [37]. 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 measureable metastatic disease.

Observed SRMs Progressing to Metastases

Fortunately, progression to metastatic disease in patients with SRMs under AS has been an uncommonly observed event. Of 880 patients with SRMs under AS identified in a systematic review, only 18 (2.1 %) patients progressed to metastatic disease [37]. In the 13 patients with reported indications for AS, indications were absolute in 61.5 % and elective in 38.5 %. Distant visceral or bony disease with or without positive lymphadenopathy (eight patients; 73 %) and lymph node involvement only (three patients; 27 %) was identified in the patients with available information. Histology was predominantly clear cell (66.7 %) [23, 26, 29, 32, 36, 116] and papillary (22.2 %) [23, 31], with one lesion exhibiting mixed clear cell and papillary features (11.1 %.) [26]. Fortunately, the mean time to detection of metastasis, on average, occurred later in the course of AS (mean of 40.2; range 12–132 months).

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 (Reproduced with permission from "Smaldone et al. Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. Cancer. 2012; 118(4):1003", American Cancer Society by Wiley, Inc.)

	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
Intitial 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)	.47

AS active surveillance, *ETV* estimated tumor volume, *MTD* maximum linear tumor dimension, *SD* standard deviation

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 [37]. Lesions progressing were predominantly high grade at the time of histologic confirmation. Those that progressed were more common in elderly patients with absolute indications for surveillance with higher risk tumors. This group included some individuals who were lost to follow-up, and it is conceivable that a proportion of these patients would have undergone definitive treatment if more closely followed.

AS remains an underutilized and evolving management strategy, and the interpretation of these data involves significant limitations including the level of evidence (all ≤ level III) and lack of centralized pathologic evaluation. 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 show that metastasis tended to occur late in the course of AS (>3 years following diagnosis), almost all lesions that progressed to metastasis were >3 cm when metastases were detected and demonstrated positive growth rates, and no lesion exhibiting zero net growth while under surveillance has developed metastases while under observation* [37]. 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. Based on the best available data, lesions demonstrating zero net growth have not metastasized and appear most appropriate for prolonged AS. Only one case (2.4 cm renal mass) progressing to bony metastases (after 5 months) with no change in tumor size has been reported [116]. Although this tumor may have been systemic at its initial diagnosis, this one case reinforces the need for careful patient selection for entry onto an AS protocols.

Cost-Effectiveness of AS Versus Active Treatment

With the increasing costs of healthcare globally, 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 treatment of choice has questionable effect on disease biology, such as the treatment of low-risk early-stage cancers. Using decision analytical modeling, a means to evaluate evidence from

multiple sources and evaluate the impact of uncertainty on clinical outcomes, several recently published studies have evaluated the cost-effectiveness of various approaches for treatment of SRMs. Evaluating the costs associated with diagnosis, Heilbrun et al. performed a cost-effectiveness analysis of percutaneous biopsy and AS versus active treatment in a hypothetical cohort of 2 cm renal masses in 60-year-old healthy men [117]. 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" diagnostic 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 dominated immediate treatment as the most cost-effective diagnostic strategy at $33,840 per quality adjusted life-year gained. Using the base case of a SRMs 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 [118]. It should be noted that laparoscopic partial nephrectomy has largely been supplanted by the more expensive robotic 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 markers or imaging techniques will be important factors in the cost-effectiveness analysis of the treatment of SRMs.

Conclusions

Due to the increased utilization of cross-sectional abdominal imaging, we have witnessed a significant stage migration with the incidental detection of small clinically localized renal masses <4 cm. The gold standard for the management of enhancing renal lesions remains surgical excision. Cancer-specific mortality remains unchanged despite a concurrent increase in surgical resection rates. This implies that a proportion of these SRMs may be indolent tumors that may not require curative intervention. Despite the limited contemporary body of literature on the natural history of untreated SRMs, recent pooled data demonstrate that the vast majority demonstrate slow growth kinetics with a very low rate of progression to metastatic disease. A significant percentage (20–30 %) of SRMs exhibit zero net growth under observation. It appears that malignancy rates are equivalent in zero growth lesions when compared to lesions demonstrating positive growth; however, to date, no zero growth lesion has progressed to metastatic disease nor has any SRMs <3 cm at the time of progression. Lesions that are more likely to progress to metastases under observation tend to be larger at diagnosis with a high nuclear grade and significantly more rapid growth kinetics. In addition, metastatic progression in these patients appears to be a late event. 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 immediate definitive intervention. Lesions exhibiting zero or minimal growth appear to be safe for continued AS. As the experience with AS progress, we anticipate that improved imaging techniques, utilization of percutaneous biopsy, and biomarker discovery will allow physicians to more confidently match treatment to individual tumor biology. Until then, use of preoperative nomograms to stratify SRMs malignant potential and account for competing medical

risks will remain valuable in treatment planning. Ideally randomized prospective trials would be performed to evaluate the efficacy of AS. In the absence of level I data, AS for localized solid renal masses remains an alternative treatment strategy to definitive extirpation in select patients with limited life expectancy, competing comorbidities that preclude operative intervention, or significant risk of requiring hemodialysis following intervention. When discussing observation of the incidentally diagnosed SRMs, patients and clinicians must calculate and accept the risks of surveillance. These risks must be weighed against the risk of intervention when considering all treatment trade-off decisions.

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9 Interventional Radiology and Angioinfarction: Transcatheter Embolization of Renal Tumors

Sebastian Flacke and Shams Iqbal

Indications for Renal Artery Embolization

The key indications for renal artery embolization include:

- 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. 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 or brachial artery with the insertion of a catheter sheath. In 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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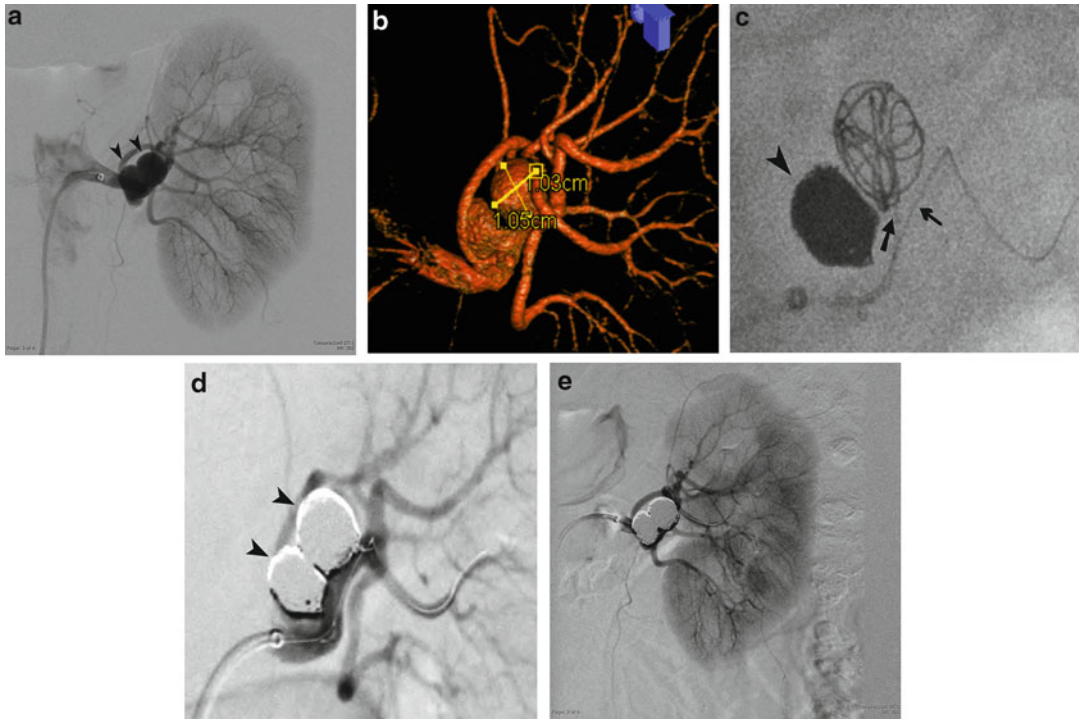

Fig. 9.1 Saccular aneurysm arising from the main renal artery in a 73-year-old patient with a planned contralateral partial nephrectomy for renal cancer. Both aneurysms were detected on cross-sectional imaging, and selective coil embolization was performed prior to surgery. Initially, a 6 French vascular 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. 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 angiogram are obtained by injected the guiding sheath. The parenchymal phase (**e**) shows patency of the entire vascular tree without embolic events

In the presence of renal artery aneurysm, detachable microcoils, which can be introduced through a 3F 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. 9.1).

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 is variable and changes over time.

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 1,200 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 arteriovenous 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. 9.2). A gentle injection may confirm stasis of blood flow, while 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),

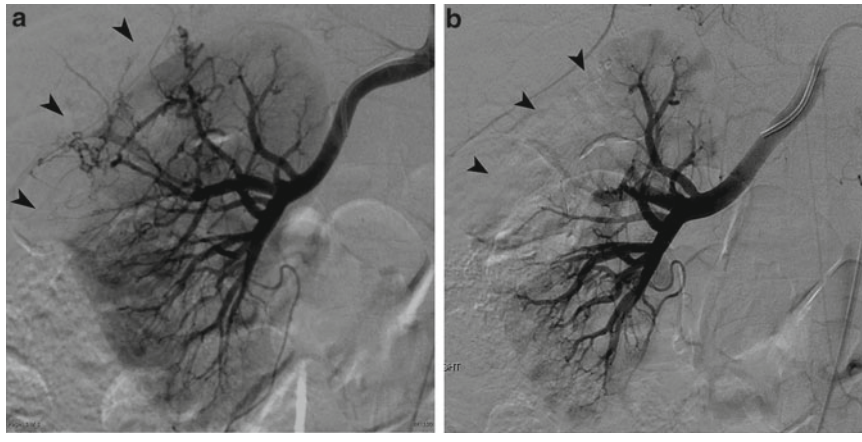

Fig. 9.2 Preventive embolization of a large angiomyolipoma in a 54-year-old female with recurrent hematuria. A selective angiogram of the left kidney shows a rounded poorly defined mass of approximately 5 cm in diameter in the left upper pole of the kidney. Superselective embolization of three segmental 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

Curaspon (CuraMedical BV, Amsterdam, the Netherlands), Gelita-Spon (Gelita Medical BV, Amsterdam, the Netherlands). The foam 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-2cyanoacrylate 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 setup. 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. 9.3). 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 min before iodine contrast is injected to document

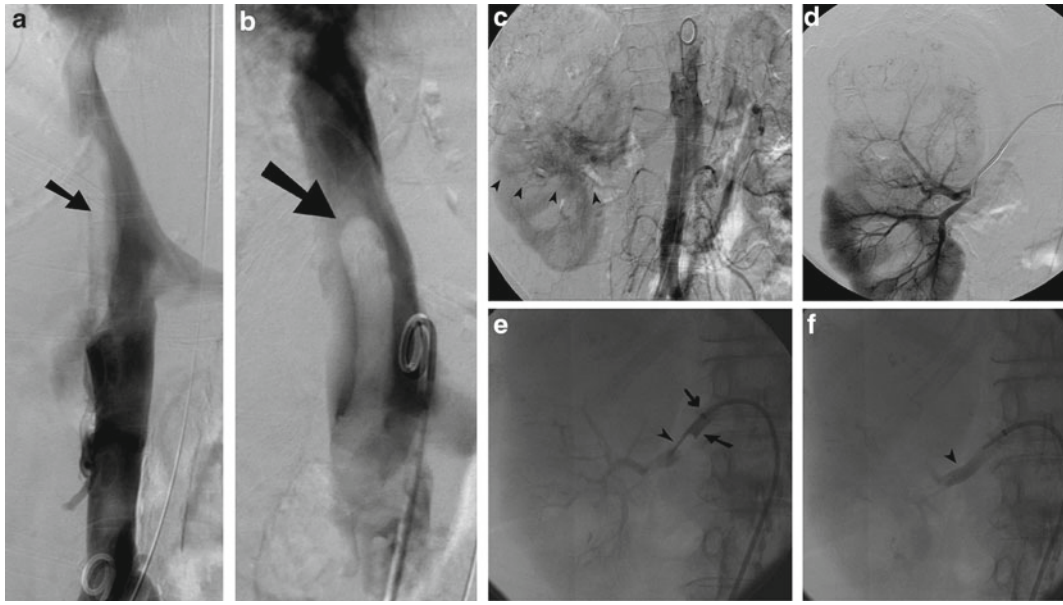

Fig. 9.3 Angioinfarction of a large left renal mass with extension into the inferior vena cava. An initial venogram of the inferior vena cava obtained after injection of a pigtail catheter placed at the level of the common iliac vein shows a filling defect in the IVC (**a**, *arrow*). A second injection with the pigtail catheter placed in the suprarenal 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 min, 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

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 complete 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 h 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. 9.4).

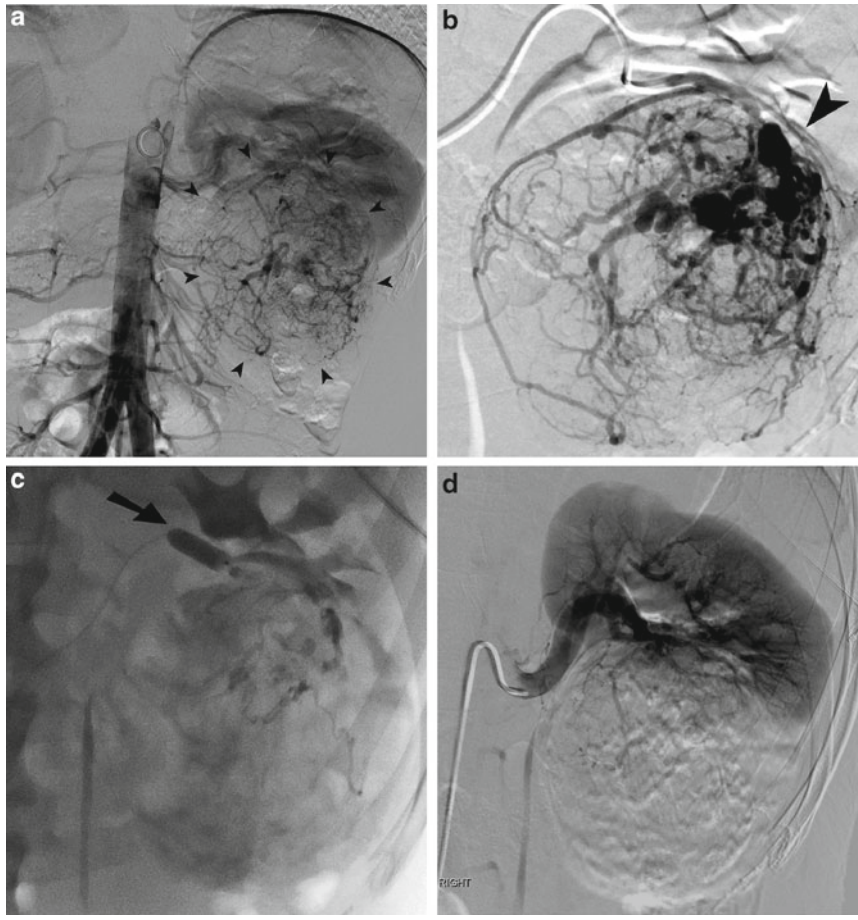

Fig. 9.4 Embolization of large angiomyolipoma in a 32-year-old female with recurrent retroperitoneal bleeding prior to intended partial nephrectomy. The initial aortogram shows a large, 7.6 cm in diameter, exophytic right lower pole renal mass (**a**, *arrowheads*) with pathological vessels. Aneurismal 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 min. A final selective angiogram shows complete devascularization of the tumor with preserved perfusion of the uninvolved upper pole

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 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 5–7 F 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. 9.5). The selective deployment of such coils in small branches up to the interlobular artery level allows for a very selective embolization sparing the remaining parenchyma (Fig. 9.6). 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. 9.7). Superselective embolization may also be considered to reduce tumor bleeding prior or during focal resection or percutaneous ablation [18, 19] (Fig. 9.8).

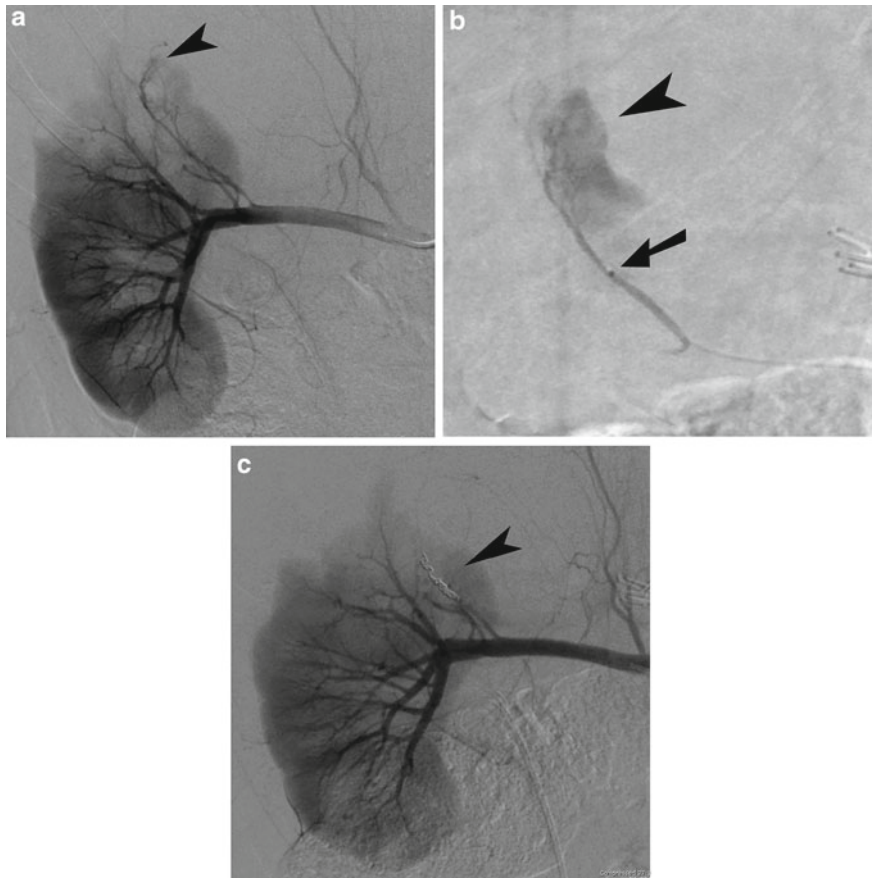

Fig. 9.5 Superselective embolization of a bleeding segmental artery after partial nephrectomy in a 67-year-old male. A selective angiogram of the left kidney shows a faint blush (**a**, *arrowhead*) next to an upper pole segmental artery after resection of a portion of the upper pole. A 2.3 French microcatheter (**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

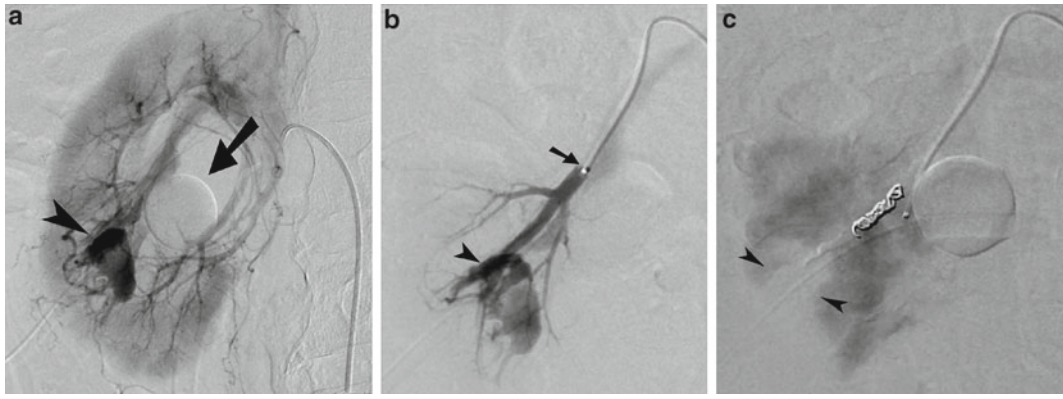

Fig. 9.6 Embolization of a false aneurysm after percutaneous nephrolithotomy. A selective angiogram of the left renal artery shows a false aneurysm (**a**, *arrowhead*) arising from the access site into the kidney. A Foley catheter (**a**, *arrow*) was placed initially to tamponade the bleeding. A 3 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*)

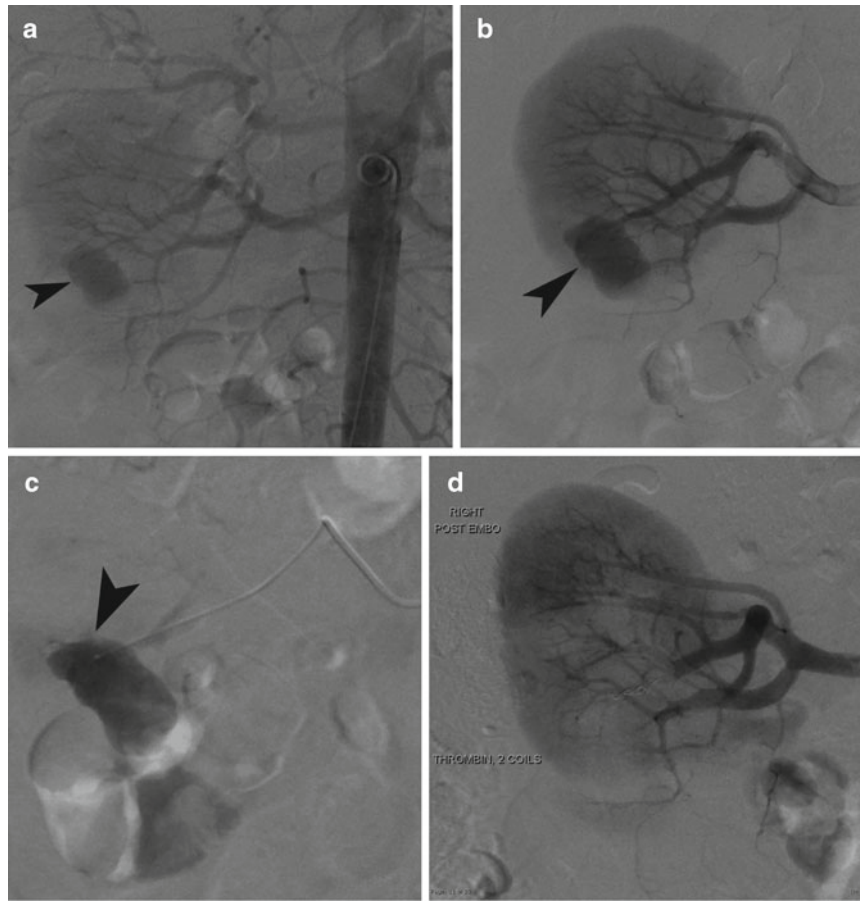

Fig. 9.7 Embolization of a false aneurysm in a 64-year-old male with massive hematuria after left lower pole partial nephrectomy. The initial aortogram shows a large contained contrast extravasation (**a**, *arrowhead*) near the resection plane of the lower pole. The total extent of the false aneurysm is better appreciated with a selective angiogram (**b**, *arrowhead*). A microcatheter was advanced into the false aneurysm (**c**, *arrowhead*), and 1,000 units of thrombin were injected before withdrawal of the microcatheter from the false aneurysm and coiling of the feeding artery with two microcoils. The final selective angiogram shows complete exclusion of the aneurysm with no parenchymal defect

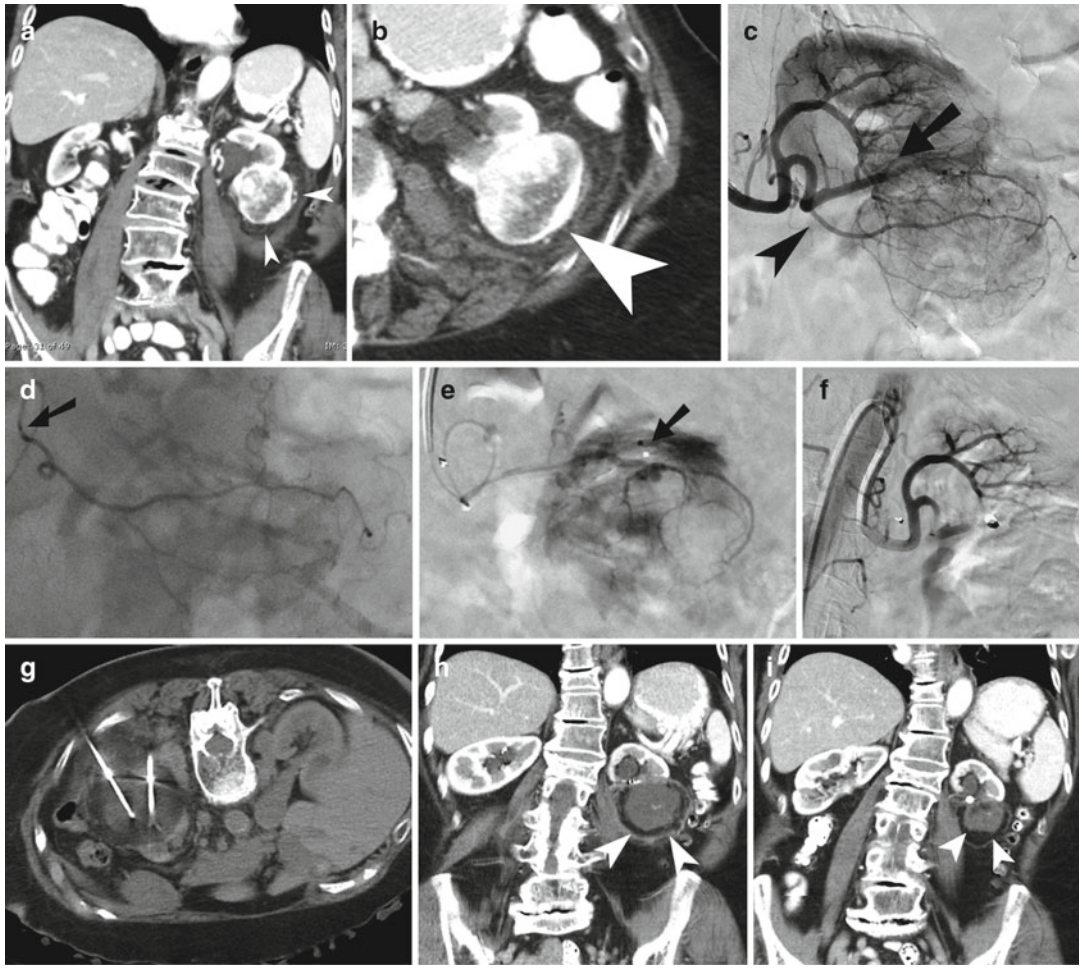

Fig. 9.8 Combined selective embolization and cryoablation of a large lower pole renal mass in a 91-year-old female with multiple comorbidities. A fast growing 5.8 cm in diameter mass of the lower pole of the right kidney (**a**, **b**, *arrowheads*) was treated on patient's request. Embolization was performed 24 h prior to cryoablation of the lesion. A selective angiogram demonstrated the blood supply to the tumor area. A capsular branch (**c**, *arrowhead*) arising from the adrenal artery and the lower pole artery (*arrow*) was 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 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 four 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

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 vena cava 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 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 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. 9.9).

Despite the fact that more than several thousand cases of embolization have been published, we still do lack clear evidence of the benefits of

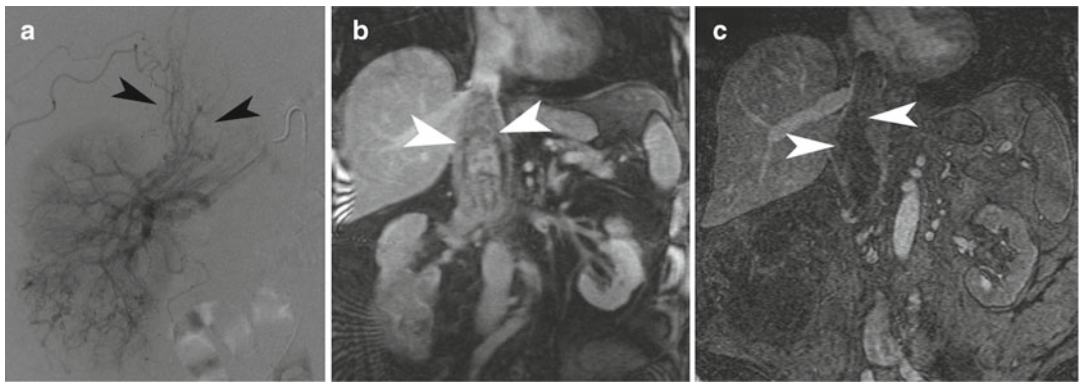

Fig. 9.9 Angiogram prior to angioinfarction of a large renal mass with inferior vena cava involvement in a 74-year-old man. The large mass has infiltrated and replaced the entire lower left kidney. Small arteries (**a**, *arrowheads*) are seen extending from the renal hilum into the large tumor thrombus within the inferior vena cava. MR images before and after the embolization are displayed in (**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 craniocaudal directions but appears less voluminous

renal angioinfarction. Randomized controlled trial should be undertaken to compare treatment of locally advanced renal carcinoma with and without embolization. To date, 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 exist regarding the value of embolization in a palliative setting [23, 30]. Palliation of unresectable renal cell carcinoma aims to stop hematuria, paraneoplastic syndromes, 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 lesions may contain a multitude of vessels with impaired vessel wall function due to a lack of elastic fibers and are thus prone to aneurysm formation (Fig. 9.4). Rupture of these aneurysms creates perirenal bleeding or massive hematuria [32]. Hemorrhagic complications occur more frequently in tumors greater than 4 cm in diameter, in the order of one out of five per year [33, 34]. This is why prophylactic embolization of renal angiomyolipomas may be considered in hypervascular lesions exceeding 4 cm in diameter. The goal of the embolization procedure is to devascularize the tumor nodule while preserving as much healthy renal parenchyma as possible. This is especially important in the presence of multiple lesion [34]. Long-term control can be achieved with superselective capillary occlusion of the hypervascular tumor nodules [35, 36]. 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 these finding could not be confirm independently.

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Unified Approaches to Surgery and Systemic Therapy for Renal Cell Carcinoma

10

Patrick A. Kenney and Christopher G. Wood

Introduction

Nearly 60,000 people in the United States were diagnosed with kidney cancer in 2010, and >13,000 died of the disease [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.

Disclosures: Pfizer (Investigator, Consultant, Speaker's Bureau); Argos (Investigator, Consultant); GlaxoSmithKline (Investigator); Bayer (Investigator); Novartis (Investigator); Wilex (Investigator)

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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.

Predictive models exist that are based solely on preoperative variables such as gender, symptoms, and imaging findings including necrosis,

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lymphadenopathy, and tumor size [5–7]. These models may help select intervention versus 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 10.1) [11–15]. 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, 16–18]. 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].

The UISS, which has been externally validated, 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 >2,400 patients [10]. The concordance indices 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 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-indices 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. 10.1) [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 (concordance index 0.84 vs. 0.78), the accuracy of the full nomogram which incorporated clinical, pathologic, 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. 10.2). 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 local cancer control in most cases. Secondly,

Table 10.1 Models that use clinical and pathologic variables to predict oncologic outcomes after surgery for localized RCC [11–14]. Adapted from [15]

Inclusion					Variables															
Author	Year	Institution	Type	Study population (n)	TNM	Histology	Nephrectomy	Years	Symptoms	Performance status	Tumor size	pT	pN	Grade	Histology	Necrosis	Vascular invasion	Outcome	Time point (y)	Concordance index
Kattan	2001	MSKCC	Nomogram	601	T1–3c, N0/x, M0	Papillary, chromophobe, ccRCC	Partial, Radical	1989–1998	✓		✓	✓ (1997)			✓			Recurrence-free survival[a]	5	0.74
Zisman	2002	UCLA	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
Leibovich	2003	Mayo	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
Sorbellini	2005	MSKCC	Nomogram	701	T1–3c, N0/x, M0	ccRCC	Partial, Radical	1989–2002	✓		✓	✓ (2002)		✓	NA	✓	✓	Recurrence-free survival[a]	5	0.82

*Local, distant, or contralateral kidney

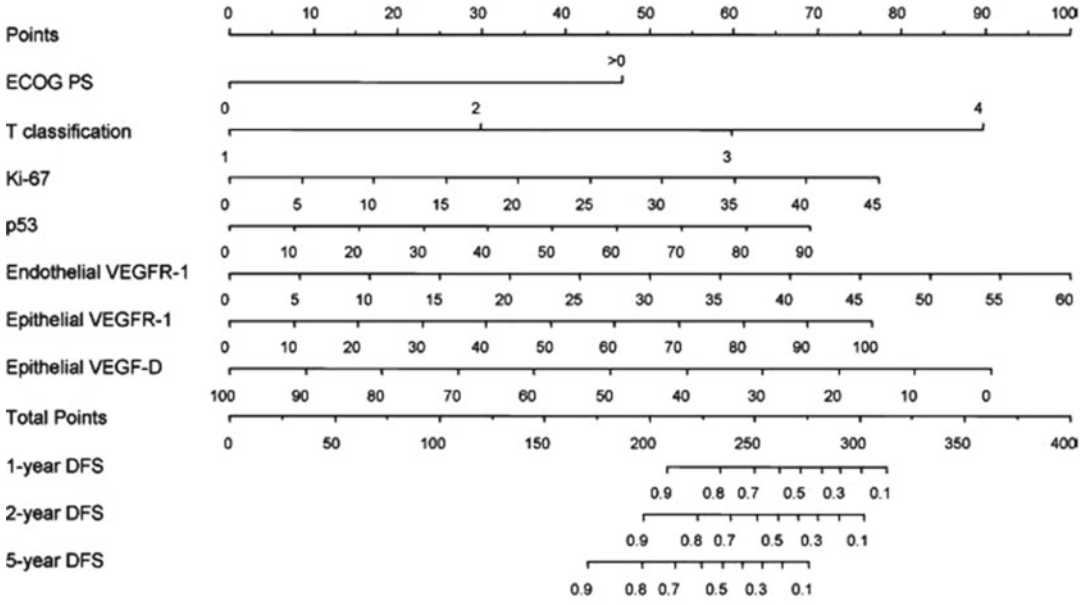

Fig. 10.1 This nomogram predicts disease-free survival using molecular data in addition to clinical and pathologic variables. The number of points assigned to each variable is determined by drawing a vertical line up to the point's axis. Total points correspond to predicted disease-free survival (Reprinted with permission from [21])

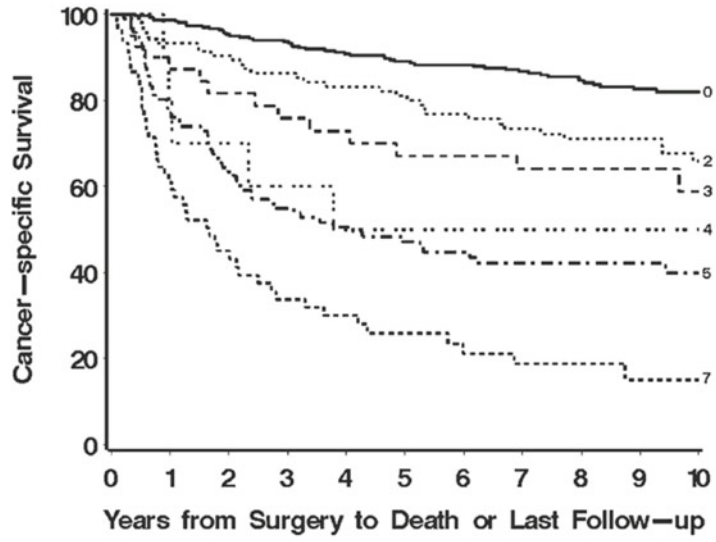

Fig. 10.2 BioScore is an algorithm that incorporates molecular markers to improve prognostication following nephrectomy for ccRCC. Total score is predictive of cancer-specific survival (Reprinted with permission from [22])

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.

Hormonal Therapy

Medroxyprogesterone acetate (MPA) can block glucocorticoid receptors that are expressed by some renal tumors [27]. 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 nonmetastatic RCC [28]. 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 %).

Immunotherapy

The primary tumor is thought to have an immunosuppressive effect [29–32]. 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 [33–35].

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 antitumor activity [36–40]. In part, the immune system's 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 [34, 41–43]. 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-∝ (Table 10.2) [44–47]. Patients who received adjuvant chemoimmunotherapy in one trial had worse 5-year overall survival when compared to control (58 vs. 76 %, p = 0.028) [47].

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) [48]. 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 only successful adjuvant trial in RCC was reported in 2004 by Jocham and colleagues [49]. 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 pT--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

Table 10.2 No randomized trial that investigated IL-2 and IFN-∝ as adjuvant therapy showed a survival benefit [44–47]. Adapted from [15]

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

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 [50]. 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 [51]. 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 [52]. 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 [50].

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 [53]. 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, 27]. 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 [54]. Thalidomide has demonstrable activity in metastatic RCC [55]. High-risk patients (high-grade T2 to 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).

Ongoing or Unreported Adjuvant Trials

Despite the demonstrated difficulty in identifying an effective adjuvant therapy, there are numerous ongoing adjuvant trials using targeted agents. Five of the trials compare agents with demonstrated activity in metastatic disease to placebo: ASSURE, S-TRAC, SORCE, and PROTECT evaluate adjuvant VEGF-targeted therapy, while EVEREST evaluates adjuvant mammalian target of rapamycin (mTOR) inhibition (Table 10.3). An additional trial evaluates a chimeric monoclonal antibody against CA IX, a strongly expressed cell surface antigen in ccRCC that is also called the G250 antigen. 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 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, 28, 44–47, 54, 56]. 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 [49]. No other adjuvant vaccine study had favorable results, including the largest adjuvant trial in RCC [48, 53]. At the present time, adjuvant therapy should only be used in high-risk patients in the setting of a research trial.

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 it may also facilitate surgery by converting unresectable disease to resectable, 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 [57]. Applying this concept to the neoadjuvant setting, one would not expect cytokines to shrink the primary tumor [58].

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 [59]. There are reports of regression of RCC metastases following RAE and nephrectomy [60, 61]. In addition, the common postinfarction 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 [62–64]. 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 %, $p=0.01$) [65]. 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

Table 10.3 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
ARISER	Girentuximab (Rencarex)	Industry	Chimeric monoclonal antibody against CA IX. Proposed to induce antibody-dependent cellular cytotoxicity via immune system including natural killer cells	NCT00087022	Randomized, double-blind, placebo-controlled, Phase III	High-grade T1b/T2, or T3/T4, or N + ccRCC	864	Weekly girentuximab x 24weeks	Disease-free survival and overall survival	Quality of life, safety and pharmacokinetics	Enrollment completed in 2008. 340 recurrences reported by January 2011. (Reference 8) Final data analysis expected in 2012
ASSURE	Sorafenib (Nexavar) or sunitinib (Sutent)	ECOG	Sorafenib: Oral small molecule inhibitor of multi-tyrosine kinases including VEGFR and Raf-kinase. Sunitinib: Oral small molecule inhibitor of multi-tyrosine kinases including VEGFR, PDGFR, and KIT	NCT00326898	Randomized, double-blind, placebo-controlled, Phase III	T1b (high grade) to T4 or N+	1,923	Up to 96-week courses of adjuvant sunitinib or sorafenib or placebo	Disease-free survival	Overall survival, quality of life	Enrollment completed. Final collection date for primary outcome anticipated in April 2016
S-TRAC	Sunitinib (Sutent)	Industry	See above	NCT00375674	Randomized, double-blind, placebo-controlled, Phase III	High-risk ccRCC as defined by UISS	720	1year of sunitinib or placebo	Disease-free survival	Overall survival, safety, patient-reported outcomes	Enrollment started July 2007. Final collection of primary outcome data expected in November 2015

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)	1,656	1year of sorafenib or 3years 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
PROTECT	Pazopanib (Votrient)	Industry	Potent inhibitor of multi-tyrosine kinases including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR, and c-kit	NCT01235962	Randomized, double-blind, placebo-controlled, Phase III	T2 (high grade) to T4 or N+	1,500	12months pazopanib or placebo	Disease-free survival	Overall survival, safety, quality of life	Enrollment started November 2010. Final data collection anticipated in October 2015 with study completion in April 2017
EVEREST	Everolimus (Afinitor)	SWOG	mTOR inhibitor	NCT01120249	Randomized, double-blind, placebo-controlled, Phase III	Intermediate high risk to very high risk	1,218	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

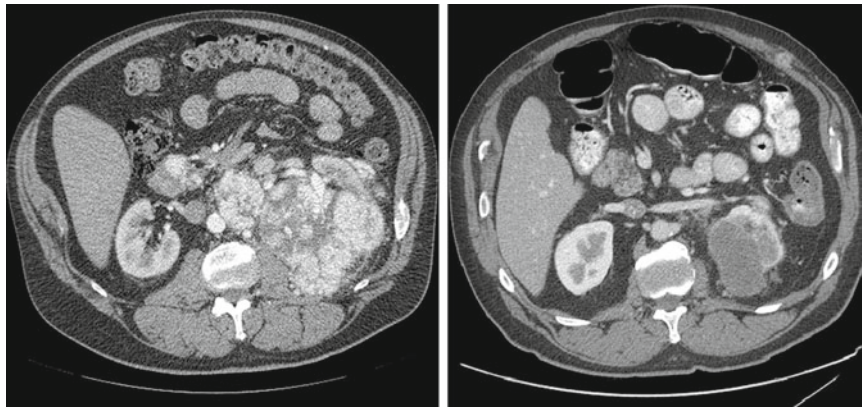

Fig. 10.3 Before therapy with sunitinib (*left*), a CT scan demonstrates a large left-sided primary tumor with associated adenopathy. There was a significant decrease in both the primary tumor and nodes following treatment with sunitinib (*right*) (Reprinted with permission from [66])

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. 10.3a–b) [67]. 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 other targeted therapies [8]. Imaging for 17 patients who were treated with sunitinib at two Dutch Centers from 2005 to 2007 were retrospectively analyzed [68]. The primary tumor was in place. Radiographic response 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 [69]. There were four partial responses, one 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 [70]. 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 10.4).

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 [71]. 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 %).

Similarly, Cowey and colleagues performed a single-arm phase II trial of neoadjuvant or

Table 10.4 In mRCC patients who were treated with systemic therapy with the primary tumor in situ, radiographic response in the primary tumor varied by drug. Adapted from [66]

Agent	Number 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)

presurgical sorafenib in 30 patients with ≥ stage II RCC [72]. 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 +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 [66]. Adequate imaging was available for 168 patients with 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 10.3). 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 [58, 73]. Attributes that contribute to unresectability may include tumor size, extensive hilar involvement, considerable lymphadenopathy, or adjacent organ invasion [70]. 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 proximity of adjacent structures (n = 4), vascular involvement (n = 2), and substantial adenopathy (n = 2) [70]. 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 [74]. 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 of 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 [73]. 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 [75, 76]. 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 [77]. 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) [78]. 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[79].

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 [58, 80]. 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 [81]. 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 [82].

Sunitinib was also used in 12 patients, five of whom had metastatic disease, prior to partial nephrectomy as reported by Silberstein et al. in 2010 [83]. 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 cm 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) [84, 85]. 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 [80]. After 2 months of sunitinib, 17/20 (85 %) of 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

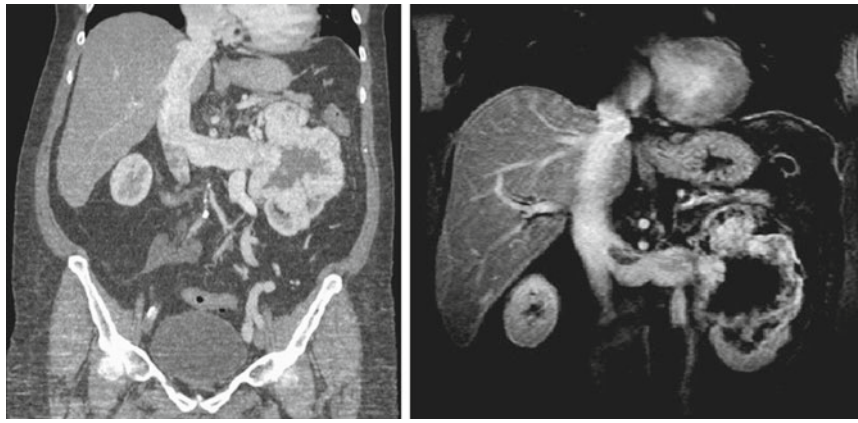

Fig. 10.4 CT scan demonstrating a left-sided RCC with an associated tumor thrombus extending into the right atrium (**a**) The thrombus substantially regressed in response to 2 cycles of sunitinib. Following therapy, it is visible as a dark filling defect at the junction of the renal vein and cava (**b**) (Reprinted with permission from [86])

thrombi. Karakiewicz and colleagues reported a patient who refused sternotomy for an 11 cm renal tumor with an atrial thrombus [86]. Following 12 weeks of neoadjuvant sunitinib, the tumor thrombus had regressed to the infrahepatic IVC (Fig. 10.4a–b). In another report, presurgical sunitinib was used to shrink a caval thrombus which permitted laparoscopic rather than open cytoreductive nephrectomy [87].

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 [88]. 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 [89]. The majority of the patients (76 %) had 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 has little impact on the primary tumor [57]. Targeted therapies can affect the primary tumor, but overall the impact with current 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 is 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. 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 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 [90]. Further, nephrectomy was a favorable, independent prognostic factor in several retrospective immunotherapy series [91–95]. 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 [95].

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 [96, 97]. In both trials, patients were randomized to cytoreductive nephrectomy followed by IFN-∝ versus 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 vs. 7.8 months, p=–0.002) [98]. 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) [98]. Without a measurable improvement in metastatic disease, the mechanism of improved survival is unclear [2, 90]. 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, 90].

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 of 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, 90, 99–103]. Good performance status, lack of central nervous system, liver or extensive bone metastases, absence of sarcomatoid or other poor

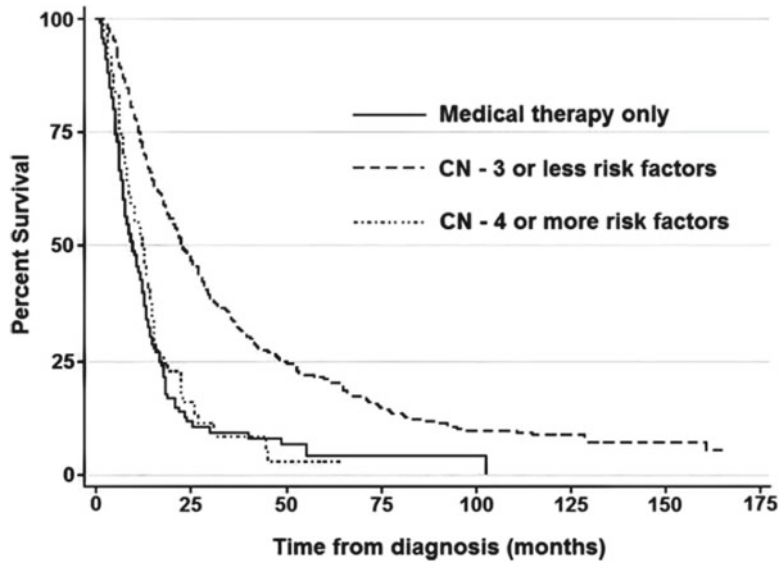

Fig. 10.5 In this Kaplan-Meier curve of overall survival after cytoreductive nephrectomy, survival of patients with 4 or more risk factors approximates that of patients treated with medical therapy alone (Reprinted with permission from [104])

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 [104]. 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 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. 10.5). 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 immunotherapy. It is not a foregone conclusion that there should continue to be a role for cytoreduction with targeted therapy.

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 [105–110]. The lower rate of nephrectomy in the temsirolimus trial is explained by the proportion of high-risk patients in that trial [105]. Although commonly employed, the uncertain benefit and potential adverse consequences of surgery have prompted 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 [111–113]. A multicenter collaboration reported a retrospective review of 645 patients who were treated with sunitinib, sorafenib, or bevacizumab [112]. 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 [114].

An ongoing phase III trial is designed to more rigorously establish whether or not cytoreductive nephrectomy is associated with improved survival when undertaken prior to sunitinib (www.clinicaltrials.gov, NCT00930033). To be eligible for The Clinical Trial to Assess the Importance of Nephrectomy (CARMENA), patients must have metastatic ccRCC, good performance status, and absence of brain metastases. The goal is to randomize 576 patients to sunitinib alone or cytoreductive nephrectomy followed by sunitinib. Enrollment, which started in 2009, is scheduled to finish in May 2013. The primary endpoint of this important study is overall survival, with secondary endpoints including objective response, progression-free survival, and postoperative morbidity.

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. Until the results of CARMENA or other prospective studies are available, cytoreductive nephrectomy in properly selected patients will remain the prevailing archetype [114–116].

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, 115]. Investigators have proposed several reasons that presurgical targeted therapy might be beneficial. First, presurgical therapy may decrease RCC-related morbidity prior to surgery [115]. Second, molecular evaluations of posttreatment 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 [68]. 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 [117]. There were two partial responses by

RECIST. The median change in primary tumor size was −10 % (range −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) [118]. 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 [71]. 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 [70, 82, 87, 117, 119–123]. Additionally, the safety and efficacy of presurgical targeted agents has been addressed in several prospective single-arm studies [71, 72, 117, 124].

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 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 [124]. A total of 17 patients (33 %) had MSKCC poor-risk disease. The rest had intermediate-risk disease. Patients received 2 or 3 cycles of sunitinib prior to nephrectomy. Median decrease in the primary was 12 %. Cytoreductive nephrectomy was undertaken in 37/53 (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, 125–127]. 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. 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 99/173 patients (57 %) 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. The median maximum change in 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, 68]. 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 is being rigorously evaluated in an important phase III EORTC trial called Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME) (www.clinicaltrials.gov, NCT01099423). The study randomizes metastatic ccRCC patients with a resectable primary to immediate cytoreductive nephrectomy followed by sunitinib or three upfront courses of sunitinib followed by cytoreductive nephrectomy. Progression-free survival is the primary endpoint with secondary endpoints including overall survival, morbidity, primary tumor response to presurgical sunitinib, and early progression. Tissue will be collected at baseline and at surgery for correlative studies, including gene expression profiling. The study started in April 2010. A total of 458 patients are expected to be enrolled. The final data collection for the primary endpoint is projected to be in October 2014. Along with CARMENA, SURTIME promises to substantially improve our understanding of the proper integration of cytoreductive nephrectomy and targeted therapy.

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 will remain a standard component of the treatment paradigm pending the results of ongoing studies [114–116]. In terms of treatment sequence, upfront cytoreductive nephrectomy will likely remain the default algorithm while we await the results of SURTIME and other studies.

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 current role for adjuvant therapy following nephrectomy for clinically localized disease. There are several studies in progress that aim to identify effective agents in the adjuvant setting, including mTOR and tyrosine kinase inhibitors as well as a monoclonal antibody against CA IX. 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 for integrating cytoreductive surgery and systemic therapy. In particular, the proper criteria for selecting patients for surgery, the benefit of cytoreduction in the targeted therapy era, and the correct order of surgery and systemic therapy are all active areas of debate and research.

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Rationale for Partial Nephrectomy

11

Nicholas Donin and William Huang

Abbreviations

AS	Active surveillance
CKD	Chronic kidney disease
ESRD	End-stage renal disease
LPN	Laparoscopic partial nephrectomy
LRN	Laparoscopic radical nephrectomy
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
RN	Radical nephrectomy
RPN	Robotic partial nephrectomy
SRMs	Small renal masses

There are certain instances, when, for the patient's well being, it is unwise to do a nephrectomy, even in the presence of a malignant growth involving the kidney. The question is, whether such a procedure is ever justifiable when the opposite kidney is normal. [1]

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Introduction

The oncologic and medical rationale for partial nephrectomy (PN) has evolved over the past two decades and is built on 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 renal cortical tumors (RCTs) while aggressively preserving renal function and minimizing the long-term risks associated with a decreased number of functioning nephrons. Historically, localized solid renal masses were treated with radical nephrectomy (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 with underlying chronic kidney disease (CKD), because of its surgical complexity, increased rate of complications, and a lack of recognition of the morbidity associated with the removal of a significant amount of functioning, nonneoplastic tissue. This paradigm began to shift in the early 1990s, driven by a host of new radiologic, pathologic, oncologic, and cardiovascular developments and discoveries. At this time, an increasing use of cross-sectional imaging meant that greater numbers of small, asymptomatic lesions were being diagnosed incidentally, resulting in an overall downward stage migration in kidney cancer. Pathologic examinations from nephrectomy specimens revealing that

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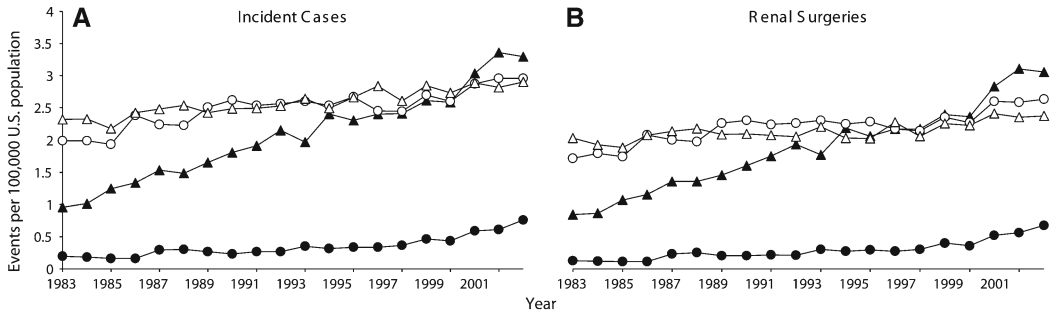
a substantial proportion of these small, asymptomatic solid renal lesions were benign meant that many patients undergoing RN for these lesions were losing significant portions of their renal function in the treatment of lesions with little metastatic potential and minimal mortality threat. Concurrent with these observations was newly available long-term follow-up data of large series of patients undergoing PN for small renal lesions that demonstrated oncologic equivalency between PN and RN. Finally, in the last two decades, physicians across multiple disciplines have developed increased awareness of the adverse impact RN has on the postoperative renal function of patients with RCTs, as well as a recognition of the increased risk of adverse cardiovascular events conferred by this diminished renal function. Given these newly appreciated risks conferred by RN, as well as the oncologic equivalency between PN and RN, PN has become increasingly recognized, in the United States and abroad, as the optimal strategy for the treatment of small RCTs, both maximizing oncologic control and minimizing morbidity. This is reflected in the 2009 American Urological Association Guideline for Management of the Clinical T1 (<7 cm) Renal Mass, in which PN is the recommended standard treatment for clinical stage T1a (<4 cm) renal masses and is one of two standard treatments for clinical T1b (>4 cm, <7 cm) renal masses. Despite the strong data in favor of PN and clear guidelines recommending its use, there is substantial evidence that PN is currently being underutilized in the treatment of RCTs in the United States and abroad. This chapter will outline the evidence and rationale for PN as the treatment of choice for cT1 RCTs.

Epidemiology of Renal Masses

Kidney cancer accounts for approximately 3 % of all adult malignant neoplasms and is the third most commonly diagnosed genitourinary malignancy. In 2012, there are predicted to be 64,770 incident cases and 13,570 deaths from kidney cancer in the United States, with an approximately 3:2 male-to-female predominance [2]. 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 that the annual rate of localized disease increased from 7.6 per 100,000 in 1999 to 12.2 per 100,000 in 2008 [3]. 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) [3–5] or small renal masses (SRMs) (see Fig. 11.1). 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 [6, 7]. The gradual increase in the number and proportion of SRMs has been met with a parallel increase



Age-adjusted (2000 US) annual kidney cancer incidence (**A**) and annual rates of renal surgery (**B**), stratified by tumor size. Rates are expressed as the number of events per 100 000 US population. ● = <2 cm, ▲ = 2–4 cm, ○ = >4–7 cm, and Δ = >7 cm. Data used to calculate incidence of kidney cancer and rates of renal surgery were obtained from nine Surveillance, Epidemiology, and End Results areas: San Francisco-Oakland, Connecticut, Metropolitan Detroit, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Utah, Metropolitan Atlanta.

Fig. 11.1 Incidence of renal masses and renal surgeries stratified by size (Adapted from Hollingsworth et al. [8])

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, often unrelated to the 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 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 diagnosed renal masses are less than 4 cm. This, however, has not been clearly demonstrated in the epidemiological data. A 2006 study by Hollingsworth et al. of 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 has not provided an overall survival benefit.

More recent epidemiologic data, however, appears to suggest that mortality from kidney cancer may be leveling off. Population-based data published in 2012 demonstrates that both 5-year survival and mortality rates for localized kidney cancer may be improving. Simard et al. demonstrated 5-year survival increases, from 88.4 % during 1992–1995 to 91.1 % during 2000–2007 [3], and the most recent data from the Surveillance Epidemiology and End Results (SEER) Database suggest that mortality may also be decreasing, from a peak of approximately 4.3 % in 2001 to 4.0 % in 2008 [11]. At present 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 mortality gains. Further study is needed to better characterize the relationship between downward stage migration and overall kidney cancer mortality, particularly with respect to SRMs.

Heterogeneity of Renal Cortical Tumors

RCTs represent a diverse group of biologic entities with varying cytogenetic defects, histologies, and biological aggressiveness. While any RCT, benign, indolent, or malignant, can display growth over time, a 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, 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 and as a result it is not widely utilized [14, 15]. Determining the malignant potential of RCTs, particularly small RCTs, from cross-sectional imaging is also limited. Work is ongoing to develop imaging modalities able to better differentiate benign from malignant lesions, and a radiolabeled I^{124}-cG250 chimeric antibody that binds to carbonic anhydrase IX and can be detected by PET has demonstrated a 94 % sensitivity and 100 % specificity for detecting clear cell carcinoma in a prospective study of 26 patients [16]. While these results are encouraging, the assay is still under investigation and not available for widespread use. As a result of these limitations, a significant number of patients with RCTs that are thought to be malignant undergo nephrectomy for lesions that are ultimately found to be benign on final pathology. Contemporary series of patients undergoing nephrectomy for RCTs suspected to be malignant have demonstrated that 10–30 % of lesions are in fact benign [17–22]. Clearly, techniques are needed for determining a lesion's histologic identity prior to surgery, so as to more accurately gauge a patient's risk and more appropriately counsel them regarding management.

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 [23]. 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 [24]. 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)[25]. 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 in size.

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, as well as surgeon fear of uncontrolled intraoperative hemorrhage, delayed bleeding, urine leak, and fistula formation. Textbooks published between 1937 and 1970, almost 100 years after the first PN was successfully performed, do not even mention the procedure [23]. 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, and 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 [26].

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 [1]. Herr and Licht are credited as the first to publish follow-up data on 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 [23]. And 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 are now routinely managed by a variety of techniques developed over preceding decades. Intraoperative ultrasound allows for determination of tumor multifocality, depth of invasion, and location respective to critical structures [27]. Nearness to vessels and the collecting system is 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 [28]. Complication rates for PN are comparable with RN and can usually be managed conservatively [29]. Previously, desire for 1-cm surgical margin, deemed necessary for adequate oncologic control, meant that 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, and several large series have demonstrated rates of freedom from local, regional, or metastatic recurrence in PN equivalent to RN [30]. 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. These technical advances, along with data regarding long-term renal functional outcomes and cardiovascular outcomes, have coalesced to validate PN as the surgical procedure of choice for the management of SRMs.

Despite the excellent oncologic control provided by surgery and low rates of complications, various epidemiologic and histopathologic data have prompted interest in active surveillance (AS) as an alternative to surgery in certain carefully selected patients. Because renal masses have historically been treated with prompt surgical excision, there is little longitudinal data regarding their growth rate and propensity for metastasis or predictors of metastasis over time. Most data at present is limited to small single-institution series with short follow-up, and as such there are no clearly defined or agreed-upon parameters to determine which patients with which lesions are most appropriate candidates for AS. What data is available does suggest that cT1a lesions tend to demonstrate slow growth rates and infrequent metastasis [31–33], and in appreciation of the potentially indolent clinical course that these lesions may display, some have questioned the survival benefit afforded by treatment in more elderly patients with competing mortality risk from other comorbidities [34]. However, given the limited ability to definitively predict preoperatively which lesions are at high risk of metastasis and a general paucity of large patient cohorts with long-term follow-up, AS remains an alternative treatment to the reference standard of surgical excision.

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 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 %. Lee et al. published follow-up results of a

retrospective analysis of 262 nephrectomies, 30 % of which were PN, performed for pT1a RCC [35]. 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 vs. 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 vs. PN in 164 pairs of patients matched for tumor grade, pathologic stage, tumor diameter, age, gender, and year of surgery [36]. At 15-year follow-up, they found no significant difference in overall survival, cancer-specific survival, metastasis-free survival, or local-recurrence-free survival. The 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 [37].

Additional studies have shown similar results for stage pT1b masses. A collaborative study between the Mayo Clinic and Memorial Sloan-Kettering Cancer Center of 1,159 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 vs. RN [38]. 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 [39–41]. Clearly, given the retrospective nature of these studies, they are likely to be subject to significant selection bias. Recently, however, the European Organization for Research and Treatment of Cancer Genito-Urinary Group (EORTC-GU) published results of a randomized phase three clinical trial comparing RN to PN for the treatment of a solitary renal mass <5 cm and found nearly equivalent 10-year CSS rates of 75.2 % for PN vs. 79.4 % for RN ($p=0.07$). This is the only prospective randomized study comparing PN to RN, and as such this finding helps to confirm results from other retrospective cohorts.

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 % [42, 43]. 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. With a median follow-up of 3.4 years, including a 5-year follow-up in 33 % of the cohort and a 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 [42]. In a multivariable analysis, positive margin status did not predict 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 [44]. 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 recurrence-free survival, 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 [45]. Despite these findings, the risk of recurrence is likely still 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 [46]. 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 and should be strived for 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 [47]. Most recently, 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 [48]. 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.

Renal Functional Outcomes in Partial Nephrectomy

The central concept driving contemporary interest in nephron-sparing approaches for the treatment of RCTs is the growing 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 the need for renal replacement therapy such as dialysis or transplantation. This misconception 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 [49, 50]. However, there are significant differences between the population of patients undergoing donor nephrectomy and the population of patients with renal masses. 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 significant comorbidities known to affect renal function, such as hypertension, diabetes, vascular disease, and 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 at increased risk for medicorenal dysfunction. This along with the aforementioned comorbidities means that many patients with renal tumors are likely to harbor significantly depressed baseline renal function in the nonneoplastic parenchyma of their kidneys.

Several large 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 two normal functioning kidneys [51]. This study, however, was remarkable in the fact that the 26 % was found in patients with preoperative serum creatinine concentrations in the normal range. More recently, Clark similarly found a 22 % rate of CKD in a population of patients presenting for PN for SRMs. These findings highlight one of the central tenets behind the rationale for PN – that serum Cr alone is an insensitive test for the detection of CKD – and suggests that clinicians may under-recognize CKD if only the serum creatinine concentration is used to estimate kidney function. Equations such as MDRD or the CKD-EPI should be utilized whenever possible to more fully appreciate a patient's renal function.

Further evidence of the high rate of underlying renal dysfunction in the RCT patient population can be found in a clinical and pathological study from Harvard Medical School, in which the nonneoplastic normal tissue adjacent to the tumor in nephrectomy specimens from patients who underwent PN or RN for a renal mass was examined for histologic evidence of medicorenal disease [52]. In this study it was found that only 10 % of patients who underwent surgery had completely normal adjacent renal tissue and 28 % were found to have histologic evidence of vascular sclerotic changes. In the remaining 62 % of cases, evidence of significant intrinsic renal abnormalities, including diabetic nephropathy, glomerular hypertrophy, mesangial expansion, and diffuse glomerulosclerosis, was noted. Taken in aggregate, these studies provide clinical and pathologic evidence to suggest that a significant number of patients who undergo surgical treatment for RCTs have significant underlying, and potentially unrecognized, renal dysfunction.

A substantial body of evidence from numerous large institution- and population-based studies has demonstrated that 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 [53]. 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 MSKCC in 2002, both of which demonstrated the detrimental effects RN has 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 [36]. 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 mg/dL) was 22.4 % in the RN group vs. 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 10-year follow-up data that was available and found that the cumulative 10-year incidence in chronic renal insufficiency was almost twice as high in RN vs. 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 [54]. With a mean follow-up of 26 months, they demonstrated a significantly higher postoperative creatinine in the RN group vs. PN group (1.5 mg/dL vs. 1.0 mg/dL) despite no difference between groups in preoperative creatinine. Nine percent of the patients in the RN group developed a creatinine >2.0 vs. none in the PN group, and Kaplan-Meier analysis demonstrated that 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 has on long-term postoperative renal function in patients undergoing surgery for RCTs [51]. This study from MSKCC included 662 patients who underwent RN or PN for a unilateral RCT <4 cm, 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 1,500 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 or other commonly

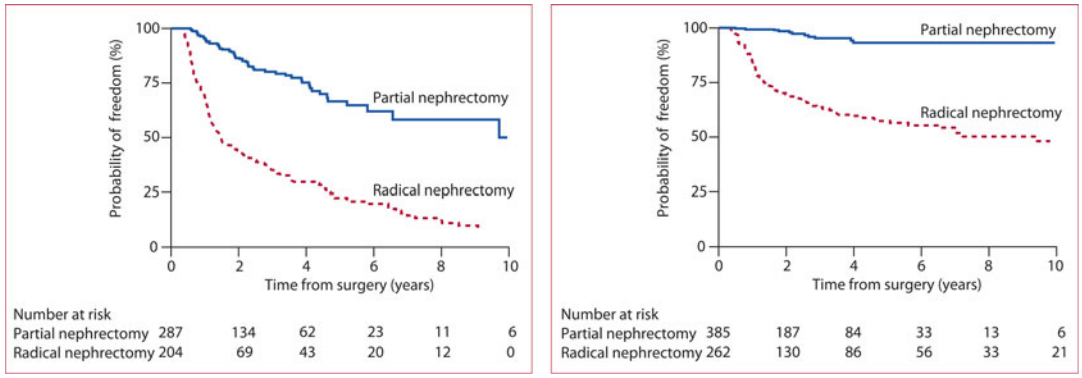
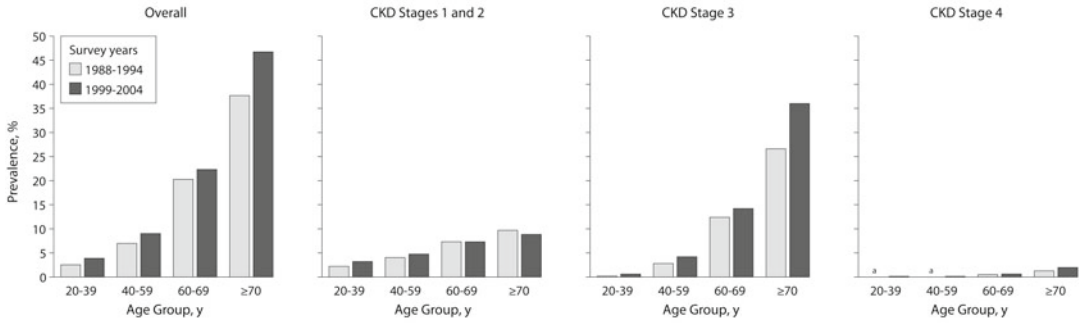


Fig. 11.2 Probability of freedom from new onset of GFR lower than 60 (*left panel*) and 45 (*right panel*) mL/min per 1.72 m [2], by operation type (Adapted from Huang et al. [51])

used equations [55–57]. 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, use of the MDRD equation revealed a 26 % rate of stage 3 CKD (eGFR <60 mL/min per 1.73 m [2]) according to the National Kidney Foundation (NKF) criteria, 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 per 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 per 1.73 m [2] were 95 % (91–98) and 64 % (56–70; $p<0.0001$), respectively (see Fig. 11.2). Multivariable analysis showed that RN remained an independent risk factor for patients developing new onset of eGFR lower than 60 mL/min per 1.73 m [2] (hazard ratio 3.82 [95 % CI 2.75–5.32]) and 45 mL/min per 1.73 m [2] (11.8 [6.24–22.4]; both $p<0.0001$). This trend was similarly demonstrated in a different cohort of 510 patients with cT1b renal masses from the Cleveland Clinic [58], with similar results demonstrated in other population-based cohorts [59]. At present, all available data have clearly demonstrated that RN has a measurable detrimental effect on renal function and puts patients at significant risk for new-onset CKD when compared with PN.

Chronic Kidney Disease, Morbidity, and Mortality

Chronic kidney disease is a significant and growing public health concern in the United States. Currently, it is estimated that CKD affects over 26 million Americans, or approximately 13 % of the US adult population [60, 61] (see Fig. 11.3). The prevalence and incidence of CKD has progressively risen in the last decade, and a person today is over five times as likely to be diagnosed with CKD than they were 20 years ago. It is projected that by the year 2030, more than two million patients will develop the most severe form of CKD, or end-stage renal disease (ESRD), and will require chronic hemodialysis or renal transplantation [62]. 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 [63]. 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 of CKD can reach upward of $20,000 per person per year, and in 2008 CKD accounted for $31 billion, or 14 %, of total Medicare expenditures [62]. Increasing prevalence of conditions that contribute to CKD, such as diabetes, obesity, and hypertension, means that CKD will continue to be a significant US public health issue.



NHANES indicates National Health and Nutrition Examination Surveys.
[a]There were no cases in 1988-1994.

Fig. 11.3 Prevalence of chronic kidney disease (CKD) stages by age group in NHANES 1988–1994 and 1999–2004 (Adapted from Coresh et al. [61])

Beginning in 1999, the National Kidney Foundation began to recognize that a significant number of patients in the US 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 [64]. As part of this effort, they developed a 5-stage classification system for CKD, which utilizes markers of kidney damage, specifically albuminuria, as well as an estimated glomerular filtration rate (eGFR) to diagnose and classify CKD. In this system, the presence of CKD is defined as kidney damage or an eGFR <60 mL/min per 1.73 m [2] for at least 3 months. The eGFR is calculated using the Modification of Diet in Renal Disease (MDRD) study equation, an easy-to-use equation based on serum creatinine level, age, sex, and race. The MDRD equation was developed using data from 1,628 patients enrolled in the MDRD randomized trial. Levey et al. used stepwise regression to generate the MDRD equation which they then tested against measured GFR using ^{125}I-iothalamate, measured creatinine clearance, and several other commonly utilized equations, such as Cockcroft-Gault. These researchers found the MDRD equation to be a more accurate estimate of measured GFR in this population and that several of the other methods to estimate GFR resulted in overestimates of the true measured GFR [55]. While other studies have demonstrated that the MDRD equation may demonstrate less accuracy in certain populations, namely, younger patients with type 1 diabetes and kidney donors in which it tends to underestimate GFR, it is reasonably accurate in nonhospitalized patients known to have chronic kidney disease; in general, GFR estimates appear to provide a substantial improvement over the measurement of serum creatinine alone in the clinical assessment of kidney function [56, 65]. The MDRD equation, in part because of its ease of use and ability to more accurately detect early stages of CKD, has been widely adopted by caregivers to estimate renal function. Recently, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) proposed an alternative equation that applies different coefficients to the same four variables in the MDRD equation. This equation has been evaluated in large numbers of patients and various clinical settings and may prove to be a better method for determining eGFR, especially in patients without preexisting CKD [66, 67].

It has been known since the 1970s that the risk of adverse cardiovascular events is dramatically increased in patients who are on renal replacement therapy [68]. Mortality rates for patients

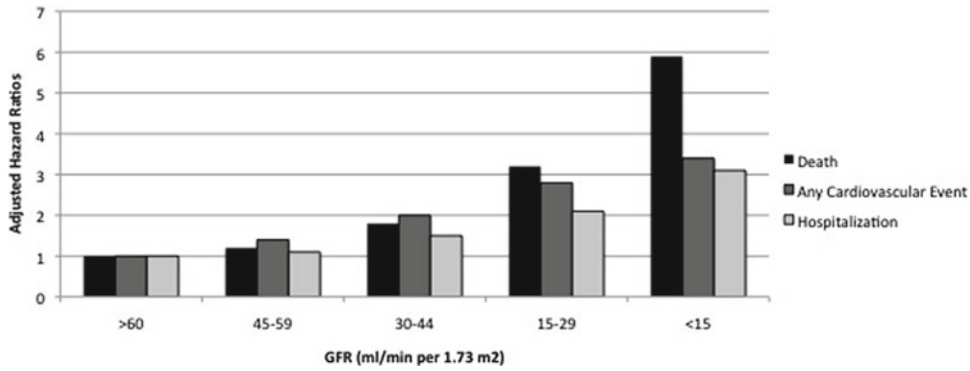


Fig. 11.4 Adjusted hazard ratio for death from any cause, cardiovascular events, and hospitalization among 1,120,295 ambulatory adults, according to estimated GFR (Adapted from Go et al. [69])

requiring maintenance hemodialysis approach 20 %, with more than 50 % of deaths attributable to cardiovascular disease. However, until 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 [69]. These investigators estimated the longitudinal GFR among 1,120,295 adults within a large, health-care 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 as the GFR decreased below 60 mL/min per 1.73 m [2]: the adjusted hazard ratio for death was 1.2 with an eGFR of 45–59 mL/min per 1.73 m [2] (95 % CI: 1.1–1.2), 1.8 with an eGFR of 30–44 mL/min per 1.73 m [2] (95 % CI: 1.7–1.9), 3.2 with an eGFR of 15-29 mL/min per 1.73 m[2] (95 % CI: 3.1–3.4), and 5.9 with an eGFR of less than 15 mL/min per 1.73 m[2] (95 % CI: 5.4–6.5). The adjusted hazard ratio for cardiovascular events also increased inversely in a dose-dependent fashion with the eGFR: 1.4 with an eGFR of 45-59 mL/min per 1.73 m[2] (95 % CI: 1.4–1.5), 2.0 with an eGFR of 30–44 mL/min per 1.73 m[2] (95 % CI: 1.9–2.1), 2.8 with an eGFR of 15–29 mL/min per 1.73 m[2] (95 % CI: 2.6–2.9), and 3.4 with an eGFR of less than 15 mL/min per 1.73 m[2] (95 % CI: 3.1–3.8) (see Fig. 11.4). The adjusted risk of hospitalization with a reduced eGFR followed a similar pattern. This study was groundbreaking in that it was the first to demonstrate significantly increased risk of death in patients whose eGFR was only moderately decreased (<60 mL/min per 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 [70–74]. Other researchers have found an eGFR <60 mL/min per 1.73 m [2] to be a risk factor for morbidity and death from other, non-cardiovascular causes in elderly populations [74]. It is clear that CKD places patients at increased risk for both cardiovascular and non-cardiovascular morbidity and mortality.

The connection between CKD and cardiovascular disease has been an active 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 [75]. Evidence for this was noted in a retrospective case-control study evaluating pre- and post-nephrectomy aortic calcium volume scores (ACS) [76]. 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 to controls and that age, postoperative GFR, and time since nephrectomy were independent predictors of ACS on multivariate regression. As a cause or consequence of this atherogenesis, evidence of oxidative stress and a state of microinflammation 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 [77]. 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 [78, 79]. Other serum abnormalities such as altered apolipoprotein patterns with increased Lp(a) have been found in patients with renal disease even when insulin clearance was still normal [80]. 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 kidney surgery can have on overall 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, it remains unclear if surgically induced CKD leads to increased risk of adverse cardiovascular events and worsened overall survival.

Several retrospective studies have examined the relationship between surgery and non-oncologic 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 [81]. When analyzed as a whole, investigators found no significant association between 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. By doing so, they found that in patients <65 years old, RN was significantly associated with an increase 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 substantiated 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 [82]. In this study, Huang et al. identified 2,991 patients older than 66 years who were treated with RN or PN for renal tumors 4 cm or less between 1995 and 2002 and found in multivariate and Kaplan-Meier analysis 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. 11.5). Several subsequent studies have supported these findings. Using SEER data from 1998–2004 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 to PN for cT1a masses [83]. Most recently, 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 ($p < .001$) when compared with RN [84] (See Fig. 11.6). This corresponded to a number-needed-to-treat of 7 at the 8-year time point. In

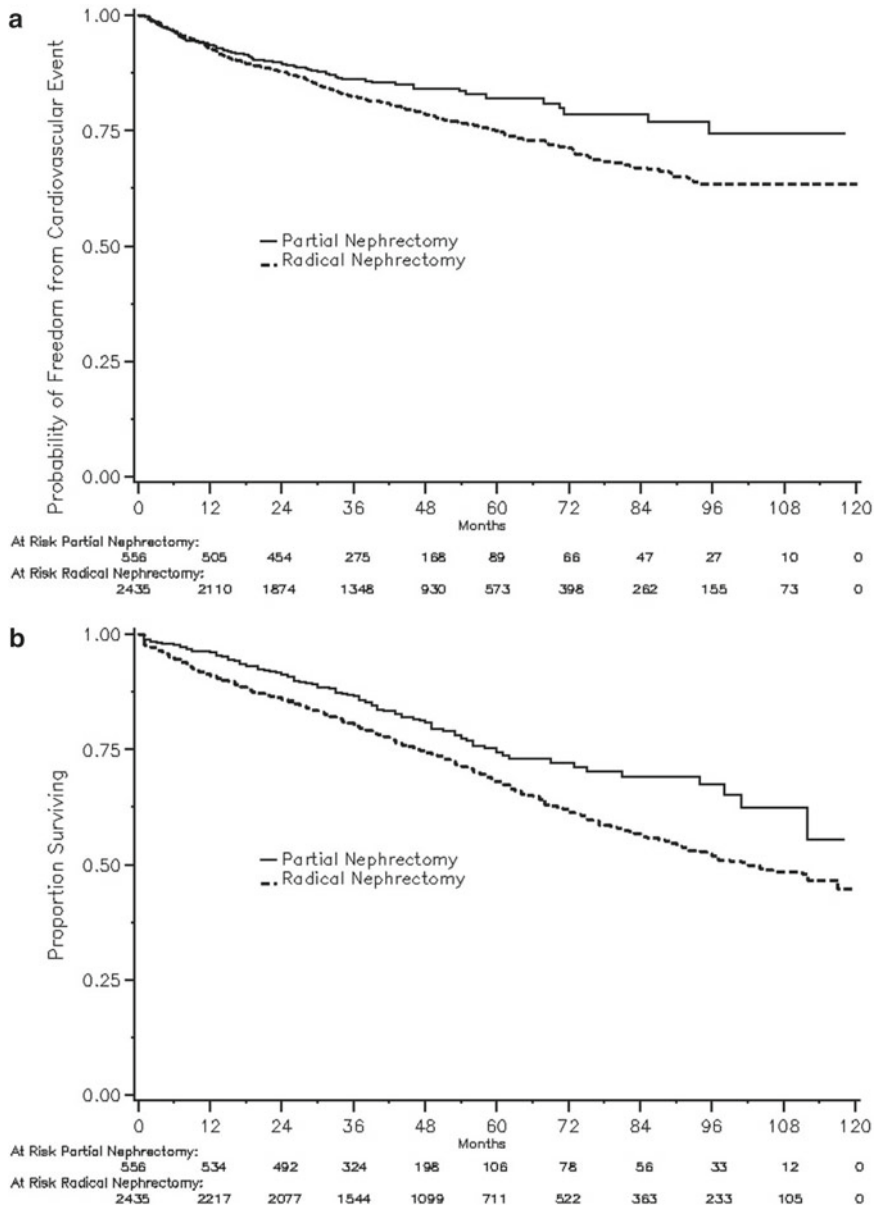


Fig. 11.5 Probability of freedom from cardiovascular events (*panel A*) and freedom from death (*panel B*) by surgery type (Adapted from Huang et al. [82])

other words, treating seven 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 1,004 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 [58, 85]. The results of these studies suggest that RN carries with it a significant risk of increased postoperative mortality when compared with PN and serve as one of the key pieces of evidence supporting the use of PN in the treatment of SRMs.

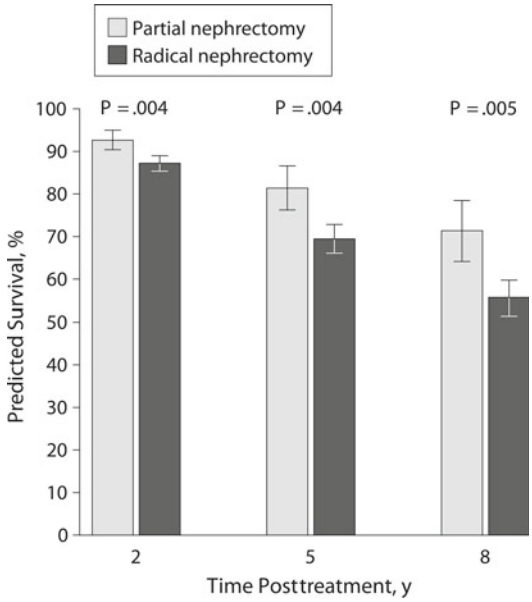


Fig. 11.6 Predicted survival probabilities at 2, 5, and 8 years after treatment with partial or radical nephrectomy (Adapted from Tan et al. [84])

Recently, however, the European Organization for Research and Treatment of Cancer Genito-Urinary Group (EORTC-GU) published the results of the only randomized prospective clinical trial comparing RN to PN for the treatment of a solitary renal mass <5 cm. In the intention-to-treat analysis of this study, investigators found that RN had a slightly higher 10-year overall survival rate when compared with PN 81.1 % vs. 75.7 % ($p=0.03$, test for superiority) [86]. 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. This finding, however, has been questioned by many because of concerns about the study design and methodology. First, the study was closed prematurely because of poor accrual and was thus statistically underpowered. Second, while designed as a non-inferiority 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 surgery centers) and a number of patients randomized to PN ultimately underwent RN (unequal crossover). Most critically, data regarding functional outcomes are unpublished, and as such, any inferences regarding the connection between renal functional outcomes and overall mortality in the study population are not possible at this time. The authors themselves acknowledge that their findings are perplexing, inconsistent with the existing observational data, and continue to recommend PN when feasible.

While substantial evidence exists to demonstrate that RN puts patients at increased risk for cardiovascular events when compared with PN, there is also preliminary 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 the development of osteoporosis and non-pathologic fractures [87]. 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, as well as prospectively evaluate 51 patients, all of whom underwent RN or PN for localized RCTs [88]. 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 vs. 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 [89]. 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 [90]. 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.

The increasing incidence of SRMs has prompted interest in evaluating cost-effectiveness of the management of these lesions. Chang et al. developed a Markov model designed to compare the cost-effectiveness of several management strategies in the treatment of an asymptomatic SRM [91]. In this analysis they found that when comparing immediate LPN vs. observation and possible delayed intervention vs. observation alone, immediate LPN had the highest incremental cost-effectiveness ratio in an otherwise healthy 65-year-old patient, with OPN being the second most cost-effective option. This finding held true across a wide range of probabilities for postoperative complications, QOL adjustments, and recurrence rates. These investigators also determined that in older patients or those with medical comorbidities, surveillance with possible delayed percutaneous ablative treatment was the most economically efficient strategy. Finally, their model also demonstrated that for poor surgical candidates and patients with limited life expectancy (less than 3 years), observation was the preferred alternative management strategy.

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 % [22, 92], 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 [28, 29]. In two large studies of complications graded using a standardized 5-tiered scale, investigators from the Cleveland Clinic and Memorial Sloan-Kettering Cancer Center (MSKCC) found that 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 [28, 29]. 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 [28, 29, 93]. Hemorrhage is generally managed expectantly with observation, bed rest, and transfusion as needed. Bleeding that cannot be controlled with these modalities prompts angioembolization or, rarely, re-exploration. Urine leak is treated with percutaneous image-guided drainage and ureteral stent placement, as indicated. Prolonged fistulization 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 %) [29].

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 [29]. 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 1,800 laparoscopic PN (LPN) and open PN (OPN) demonstrated that LPN was independently predictive of greater rates of postoperative complications, hemorrhage, and need for reintervention [94]. A follow-up study from the same group, however, demonstrated that complication rates for LPN have decreased over time and that contemporary rates for LPN are equivalent to OPN [28]. 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 to centers that perform fewer PNs, again suggesting that experience and volume contribute to lower rates of complications [95].

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 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 [96]. Literature examining the initial experience with RPN reveals similar complication rates as LPN. In a large multi-institutional review of RPN vs. LPN, Benway et al. demonstrated that morbidity after RPN was equivalent to LPN [97]. Robotics is likely to become an increasingly utilized modality for the treatment of RCTs.

Utilization of Partial Nephrectomy

Despite strong evidence demonstrating safety, oncologic efficacy equal to RN, and superior long-term renal function and other non-oncologic outcomes, there is substantial evidence that PN is currently underutilized in the management of surgically amenable RCTs [98]. While in high-volume tertiary-care centers such as ours approximately 90 % of pT1a lesions are treated with PN [99, 100], population-based studies suggest that PN accounts for only 20–40 % of all nephrectomies [101, 102]. 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 [102]. Follow-up studies capturing data through 2008 have demonstrated a 49 % increase in the PN as a proportion of all renal surgeries, such that at present approximately 25 % of renal surgeries for RCC are PN [103, 104]. Nonetheless, given that the majority of incident renal tumors are SRMs likely amenable to PN, it is probable that a substantial number of patients with SRMs who are candidates for PN continue to be treated with RN.

The reasons for the underutilization of PN are unknown, but a number of factors have been indentified 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 [101, 102]. This may be unsurprising given that present guidelines do not recommend PN for tumors >7 cm [105] and also because 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 likelihood of receiving PN [106, 107].

Older age has been found in multiple studies of both US and European populations to predict a decreased likelihood of undergoing PN [100, 101]. 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 [108, 109]. Female gender has also been demonstrated to be significantly associated with a decreased likelihood of receiving PN [100, 101]. One postulated explanation for this 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 is especially troubling given that women are more likely to have a benign renal mass [21]. The presence of comorbidities has been shown to be associated with a decreased risk of being treated with PN [103]. Again, the reasons for this 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 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.

Robust research in this area has identified a number of variables as risk factors for being treated with a non-nephron-sparing approach, including rural hospital setting, nonacademic institution, and lower nephrectomy surgical volume [101–103]. 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 [98, 110]. What does appear certain, however, is that at present PN continues to be underutilized in the treatment of SRMs, despite clear and unequivocal evidence of its oncologic efficacy, superior non-oncologic outcomes, and proven safety.

Candidate Selection

The absolute indications for PN, many of which have been recognized as early as the 1800s [26], 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.

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 R.E.N.A.L. score and should plan procedures with the aim of complete tumor resection as the primary goal, with preservation of functional parenchyma as secondary. However, given the known association between RN and new-onset postoperative CKD, surgeons less confident about their ability to excise complex cT1 lesions using PN should consider referral to a center with specialized experience in PN. 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 [111]. 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 [112]. On multivariate analysis, type of nephrectomy did not predict overall survival. A single-institution study of eight patients in whom PN was performed for tumors presumed preoperatively 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 [48]. 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. The use of PN in the treatment of renal masses is evolving. While at present it is clear that the procedure is effective and safe in cT1 renal masses and appears to result in superior non-oncologic outcomes when compared with RN, further studies are needed in order to prove whether PN is an appropriate treatment for larger lesions.

Conclusion

The increasing incidence of SRMs means that increasing numbers of patients in the United States and abroad will undergo intervention for

curative treatment of their disease. 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. Additionally, there is a substantial and ever-growing body of evidence demonstrating that RN puts patients at an increased risk for CKD and its attendant morbidity, including adverse cardiovascular events and death, when compared with PN, while providing no additional oncologic benefit. As such, 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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Objectifying Complexity of Kidney Cancers: Relationships of Tumor Anatomy and Outcomes

12

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Introduction

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 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 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

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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 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 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 greater than 5 mm from the hilum [36, 37]. Some authors have suggested that hilar location is the most influential factor in deciding between open or minimally invasive approach for nephron-sparing surgery [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) ndophytic/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. 12.1). 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 less than 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. 12.1). 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 since the mass is often out of plane with the polar line on coronal views. As such, 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. 12.1). 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 low complexity, 7–9 – moderate, and greater than 9 – high complexity renal masses (Fig. 12.2). 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

	1pt	2pts	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)

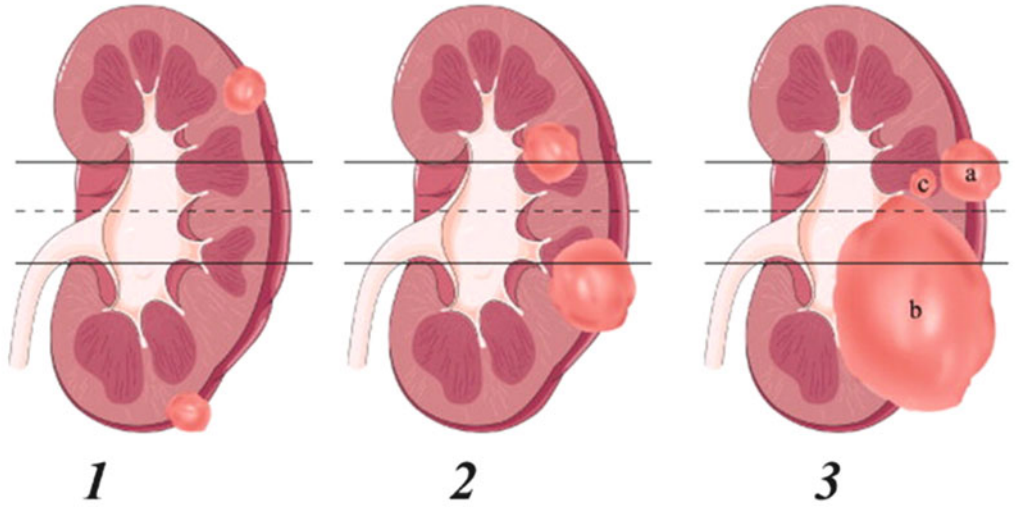

Fig. 12.1 RENAL nephrometry score with scoring of (L) ocation component. Polar lines (*solid lines*) and axial renal midline (*broken line*) are depicted on each sagittal view of kidney. Numbers 1 to 3 represent points attributed to each category of tumor [23]

nephrometry sum. The RENAL NS system has been operationalized 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, percent 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 2 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

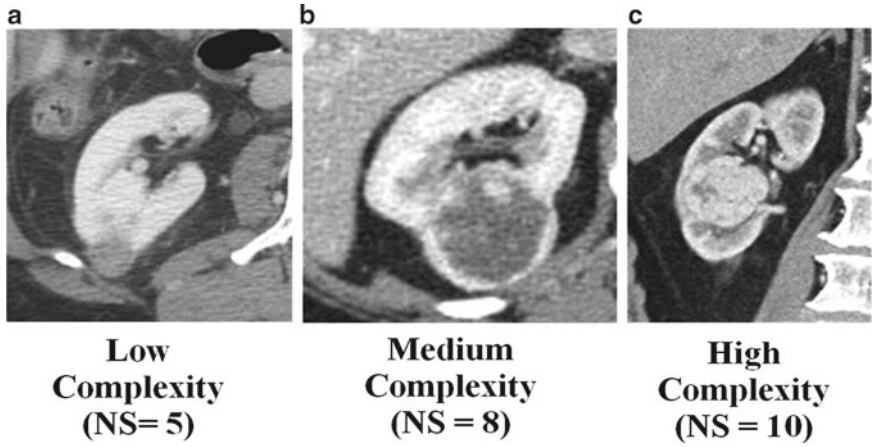

Fig. 12.2 Examples of tumor complexity based on RENAL nephrometry score [23] (**a**) Low complexity mass, treated with robotic-assisted partial nephrectomy; (**b**) medium complexity mass, treated with robotic-assisted partial nephrectomy; (**c**) high complexity mass, treated with open partial nephrectomy

Table 12.1 RENAL nephrometry and PADUA classification scoring systems [44]

	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	No points given. Mass assigned a descriptor of a, p, or x		
(L)ocation relative to the polar lines[a] [a]Suffix "h" assigned if the tumor touches the main renal artery or vein	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

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

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 12.1 [44].

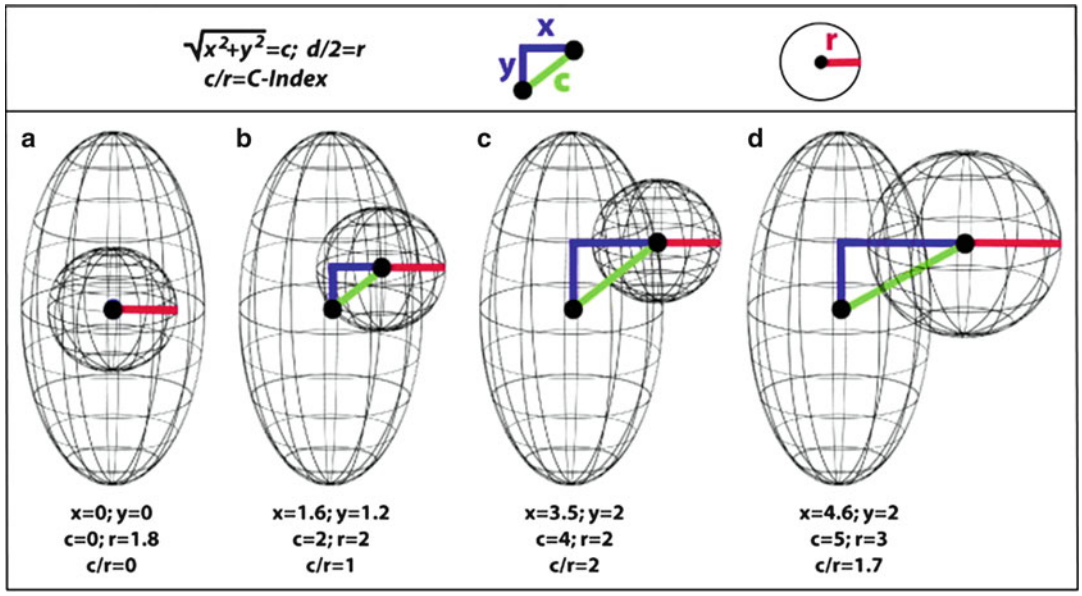

Fig. 12.3 A to D, in C-Index model c (*green lines*) is hypotenuse of triangle formed by sides x and y (*blue lines*). C-Index is calculated by dividing c by r (*red lines*) [45]

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. 12.3). This system was initially reported in the context of a laparoscopic NSS cohort, focusing on its ability to predict intraoperative outcomes and perioperative complications.

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. Inter-observer 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 is somewhat surprising since 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 GFR via MDRD formula, demonstrating greater than 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].

Conclusions

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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Open Partial Nephrectomy

13

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and John A. Libertino

Introduction

Despite broader acceptance of active surveillance and ablative approaches, surgical excision remains the standard of care for locally confined renal cell carcinoma (RCC). Historically, radical nephrectomy (RN) has been 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 2009 American Urologic Association and 2010 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].

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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 (1824–1876), 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

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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 pathologic studies demonstrating the non-invading, 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 the 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 RCC patients with normal contralateral renal function. As often true of 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 recently 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. Recently, 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]. Currently, urologists are focused on techniques to minimize ischemic injury and also lessen surgical morbidity by minimally invasive approaches.

Epidemiology of Small Renal Masses

Kidney cancer is the 13th most common malignancy worldwide with 270,000 new cases in 2008 [14]. In the United States, there will be an estimated 64,770 new cases and 13,570 deaths from renal tumors (including RCC and urothelial renal pelvis tumors) in 2012 [15]. For cases with pathologic 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 USA and Europe) [19], race (lower in Asian/Pacific descendent in the USA) [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 other 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 Data Base between 1993 and 2004 showed a significant increase in Stage I RCC with a corresponding decrease in Stage II–IV RCC [25]. Further, 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 USA [16, 18]. However, 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 a distinct 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 experience, 6.3 % of tumors greater than 7 cm were benign compared to 46.3 % of tumors less than 1 cm [27]. Further larger tumor size is associated with an increased risk of high-grade compared to low-grade RCC and clear cell compared to papillary RCC [27]. For renal masses less than 4 cm treated surgically, upstaging to T3 and advanced grade was both associated with increasing tumor size, especially for tumor greater than 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 is evident in the probability of de novo asynchronous metastatic RCC in postsurgical treated patients [31].

Oncologic Efficacy of Partial Nephrectomy

Traditionally, RN has been 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 in order to avoid dialysis dependence. Consistent with trends across other surgical disciplines favoring organ preservation, the American Urologic Association [1] and European Association of Urology [2] have recommended 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 and 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 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 to RN in elective cases with unilateral RCC with a normal contralateral kidney. Each group contained 164 patients and was matched for tumor size, pathologic stage (97 % T1), grade, age, sex, and year of surgery.

Table 13.1 TNM staging of renal cancer [109]

T1: Tumor <7 cm in greatest dimension, confined to kidney
T1a: Tumor <4 cm, confined to kidney
T1b: Tumor between 4-7 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

There was no difference in oncologic outcomes as 10-year cancer-specific survival (96 % RN vs. 98 % PN) and metastasis-free survival (95 % RN vs. 98 % PN) were similar between the two groups. There was no difference in 10-year overall survival as well (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. Prior to discussing the results, the study's shortcomings should be addressed. Foremost, the analysis was underpowered due to poor accrual (541 patients enrolled with 1,300 patients required) and there was a >10 % crossover rate following randomization. Also, the small number of total deaths (117) and cancer-related deaths [12] limited meaningful comparative statistics relating to survival. In the intent to treat analysis, unexpectedly, RN had superior overall survival compared to the PN (81.1 % vs. 75.7 %, $p=0.03$). In secondary analysis of RCC patients only, and clinically and pathologically eligible patients, the trend in overall survival was no longer 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 supports 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 to RN based on primary tumor stage (Table 13.1). Table 13.2 summarizes many of the studies reporting oncologic outcomes in T1 RCC.

T1a Tumors

A competing-risk population-based SEER analysis comparing oncologic outcomes after PN ($n=1,622$) versus RN ($n=5,658$) for T1aN0M0 was recently published. There was no difference in the 5-year cancer-specific mortality rate after adjusting for other cause 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 to 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) [34–37, 39–41, 110]

	Study	# of patients	Follow-up (months)	Local recurrence	Five-year disease-specific survival
T1a	Crepel et al.	1,622	24	NR	98.2 %
	Patard et al.	314	51	0.8 %	97.8 %
	Antonelli et al.	176	59	0.6 %	96.1 %
	Lee at 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 %	

Table 13.3 Oncologic outcomes of open PN for > T1 RCC [42, 43, 111]

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

T1b Tumors

A recent SEER population-based analysis of T1bN0M0 RCC compared matched PN (n=275) and RN (n=1,100) 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 for RN vs. PN: 1.97, p=0.079) [38]. 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

Although not widely considered standard of care, PN plays a vital role in treating certain 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 in experienced centers [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 ($n=567$) to PN ($n=34$) for locally advanced RCC. The RN group had larger tumors with more advanced pathologic 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 [42]. 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 [43].

The preceding data supports 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.

Preserving Renal Function: The Rationale Behind PN

The relative risks and benefits of localized RCC treatment options 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 [44]. 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 to matched populations [45–47]. The donor nephrectomy and RCC populations are considerably different, however, as kidney donors tend to be young and lack medical comorbidities. On the contrary to kidney donors, 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 [48, 49]. Pathologic studies of nonneoplastic parenchymal tissue in nephrectomy specimens also show frequent changes associated with underlying comorbidities. In a study of 110 specimens, only 38 % had normal renal parenchyma, of which a majority exhibited pathologically evident vascular disease [50]. A greater decrement in renal function 6 months after surgery was demonstrated in patients with substantial pathologic abnormalities compared to those with normal renal parenchyma [50]. 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.

In 2004 Go et al. published their landmark paper demonstrating a graded association between the degree of CKD and the risk of cardiovascular events, hospitalization, and death [44]. This study included 1,120,295 adult patients in the Kaiser Permanente Renal Registry with a follow-up

Table 13.4 National kidney foundation disease outcomes quality initiative CKD classification [112]

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)

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/1.73 m^2 was used as the reference. As GFR decreased, the risk of death increased: hazard ratio (HR) = 1.2 for GFR 45–59 mL/min/1.73 m^2, HR = 1.8 for GFR 30–44 mL/min/1.73 m^2, HR = 3.2 for GFR 15–29 mL/min/1.73 m^2, and HR = 5.9 for GFR <15 mL/min/1.73 m^2. The adjusted hazard ratios for cardiovascular events and hospitalization also increased inversely with respect to GFR [44]. 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 m^2 (odds ratio for 0, 1, and 2 risk factors = 1, 3.7, 10.4, respectively, $p \leq 0.001$) [51].

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, 52]. More recently, 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. RN compared to PN was associated with a lower 3-year postoperative probability of freedom from both GFR <60 mL/min/1.73 m^2 (35 % vs. 80 %, $p < 0.0001$) and GFR <45 mL/min/1.73 m^2 (64 % vs. 95 %, $p < 0.0001$). RN was an independent risk factor for the development of both GFR <60 mL/min/1.73 m^2 (ratio = 3.82, $p < 0.0001$) and GFR <45 mL/min/1.73 m^2 (hazard ratio = 11.8, $p < 0.0001$) [12].

Recently, 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 2,547 RN patients and 556 PN patients with T1a RCC. On multivariable analysis, RN was independently associated with an increased risk of cardiovascular events (hazard ratio = 1.4, $p < 0.05$) and overall mortality (hazard ratio = 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, RN compared to PN was not associated with worse 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 several factors including comorbidities, preoperative creatinine, and year of surgery [53]. The trend toward improved overall survival with PN compared to RN has been studied in T1b renal tumors as well. Weight et al. reported a retrospective study of 212 PN and 298 RN patients with preoperative GFR > 60 mL/min/1.73 m^2 and a normal contralateral kidney. New onset CKD was defined as postoperative GFR <60 mL/min/1.73 m^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 (hazard ratio = 0.47, $p = 0.03$) and graded stratification of postoperative renal function ($p = 0.003$) independently predicted overall survival when controlling for pathologic 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]. The limitations of this study are discussed in detail in the previous section. In brief, the small number of overall deaths and lack of reported renal function outcomes clouds the interpretation of the results relating to the effects of renal function on overall survival. Also, 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 % [54]. There was a trend toward increasing PN use over the study interval ($p < 0.001$) [54], and also the overall percentage of PN increased from a previous Nationwide Inpatient Sample study from 1988 to 2002 [55]. 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 the most recent Nationwide Inpatient Sample data. 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. Six thousand four hundred and sixty (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 with women, elderly, rural, earlier year of surgery, and larger tumor size all having statistically significant adverse effect in predicting PN [56].

Compared to 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 [57]. Investigators from Memorial Sloan Kettering report 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 [58]. Future endeavors aimed at understanding the underlying rationale for PN underutilization and addressing these issues are paramount for widespread acceptance of PN throughout the urologic community.

Objective Analysis of Tumor Complexity

In the 2009 AUA small renal mass guideline, it was stated that for clinical T1 renal masses, "nephron sparing approaches should be used whenever feasible"[1]. Partial nephrectomy feasibility was not defined. Differences in opinion between surgeons regarding the feasibility of partial nephrectomy may contribute to the variability in the 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 [59]. Traditionally, tumors were described with non-standardized, 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 anatomical 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 [60–62]. The RENAL nephrometry scoring system was described by Uzzo in 2009 (Table 13.5) [60]. 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).

Table 13.5 RENAL nephromery 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 [60]

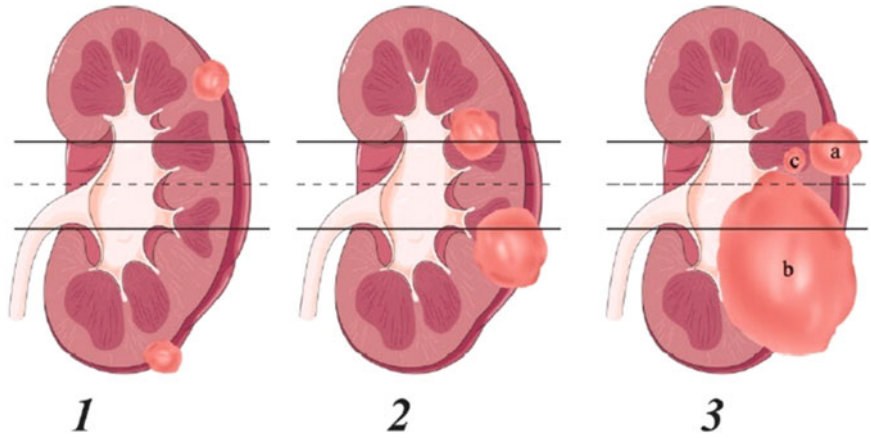

Fig. 13.1 The L component of RENAL nephrometry score characterizes a tumor location relative to the polar lines. A sagittal depiction of the kidney demonstrates the polar lines (*solid*) and renal axial midline (*dashed*), with the points (1, 2, or 3) that would be assigned to each tumor (Permission to reprint is pending from Kutikov A and Uzzo RG [60])

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 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 [62]. 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 Centrality index (C index) also aims to quantify the complexity of renal masses, but does so with a geometric approach [61]. The Centrality 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 the 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 the distance from the kidney center to the tumor center (c).

Table 13.6 The PADUA classification scoring schema [62]

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

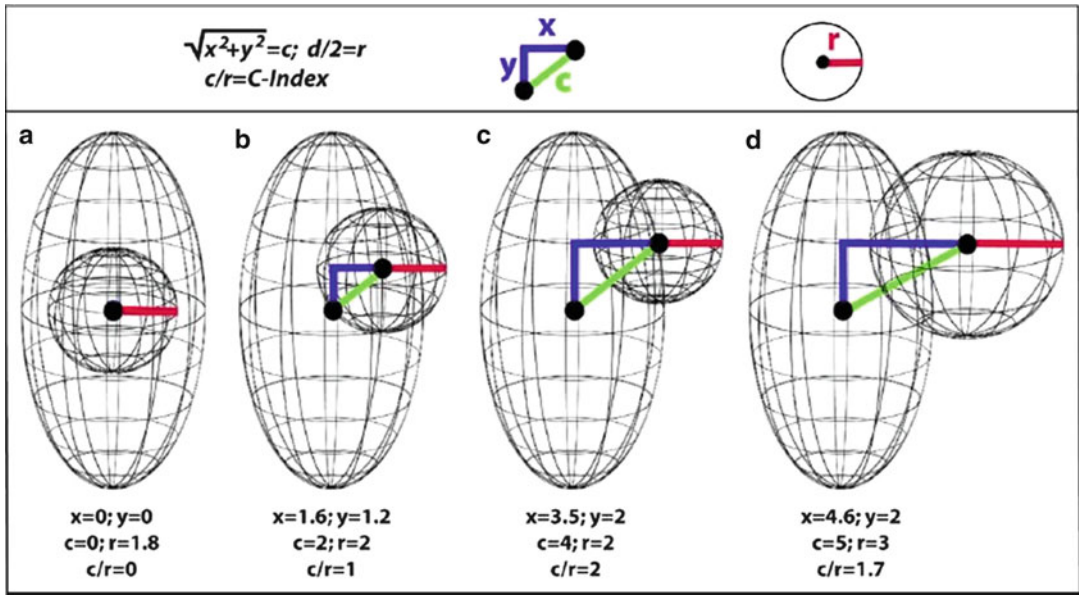

Fig. 13.2 The C index method uses the Pythagorean theorem to measure the distance between kidney center and tumor center, *c* (*green line*), which is the hypotenuse of a triangle formed by *x* and *y* (*blue lines*). Dividing *c* by *r* (*red line*) yields the C index (Permission to reprint is pending from Simmons et al. [61])

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, in particular 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 the members of the American Urologic Association, respondents were shown 8 tumors with RENAL nephrometry scores ranging from 4 to 10 [59]. 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 [63]. 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 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 as opposed to partial nephrectomy and open as opposed to minimally invasive partial nephrectomy [64, 65].

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 [66–69]. 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 [69]. 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 [62, 66, 67, 70, 71]. 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 %, $p<0.01$) [67].

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, identification and treatment of 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 [72]. 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 [73].

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 [74, 75].

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 h are both independent predictors of pulmonary complications [75]. 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 [74]. 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 open 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-h creatinine clearance, radionuclide imaging such as technetium-99 diethylenetriamine pentaacetic acid, or estimating GFR using equations such as the Modification of Diet in Renal Disease (MDRD) equation [76]. Although serum creatinine and estimates of GFR based on serum creatinine such as the MDRD equation may not be as accurate as a 24-h 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 at most centers. CT angiography is noninvasive and provides detailed anatomical images by incorporating arteriography, venography, excretory urography, and CT data into a single imaging modality. CT can delineate renovascular anatomy including the subsegmental branches supplying the tumor as well as renal tumor location, depth, and proximity to the collecting system [77]. In addition, preoperative imaging helps identify surgically relevant anatomical 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 prophylaxis (intermittent pneumatic compression devices or compression stockings) in all patients undergoing open surgery and consideration of pharmacologic prophylaxis in patients with elevated risk for VTE [78, 79]. The use of pharmacologic VTE prophylaxis in partial nephrectomy is controversial [80].

Surgical Techniques

Broadly speaking, the steps of performing open partial nephrectomy are the 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 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 [81]. 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 [82]. 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 indentified 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.

Mannitol is given intravenously 5–10 min before temporary renal arterial occlusion [83–85]. Anticoagulation to prevent intrarenal thrombosis is not necessary. The renal vein is not clamped, which may permit some oxygenation despite arterial occlusion [86–88]. In open partial nephrectomy, the kidney is cooled immediately after clamping to protect against ischemic renal injury. The entire kidney is surrounded by ice slush for 10–15 min to obtain a core kidney temperature of approximately 20° C, which permits as much as 3 h of ischemia time [85]. 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 min have recently been advocated as safe [84, 89]. Nonetheless, some data suggests 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 [90].

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, heminephrectomy 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 [91]. 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 [92–95]. When enucleation is employed, it may be beneficial to ablate the resection margin to reduce the risk of recurrence [96]. 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 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 [97, 98]. 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 [99].

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 beam 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 polyglactic sutures, ensuring that the renal vessels are not kinked or obstructed. These can be secured with knots or with a Weck clip (Pilling Weck Canada, L.P., Markham, ON, Canada) and a Lapra-Ty® clip (Ethicon Endo-Surgery, Cincinnati, OH, USA). If the renal artery was clamped, 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 [100].

Addressing the Adverse Impact of Ischemia

Partial nephrectomy can be associated with a postoperative decline in renal function [86, 101, 102]. 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 [86, 101, 102]. Modifiable factors that contribute to decreased GFR include reduction in functional renal parenchyma and ischemic injury [83, 90, 102–104]. Even when accounting for the percent of functional renal parenchyma preserved after partial nephrectomy, renal ischemia is independently associated with postoperative renal dysfunction [104]. 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 to partial nephrectomy without clamping [89].

To address the adverse impact of renal ischemia, several investigators have proposed performing partial nephrectomy with the kidney fully perfused [48, 105–108]. We, thus far, at the Lahey Clinic have performed 839 open non-clamping partial nephrectomies and have demonstrated that this can be safely performed for complex lesions. In addition we have compared this patient population to 380 patients who had renal artery clamping, and the observations with regard to blood loss, pre- and post-op creatinine levels, urine leaks, and oncologic outcomes are recorded (Table 13.7). In an open non-clamping series in 158 patients with solitary kidney, 16 % of patients had previous ipsilateral nephron-sparing surgery, 33 % of tumors were characterized as hilar/central, and mean tumor size was 3.6 cm. The maximum tumor size in the series was 13 cm, and while the median number of tumors resected was 1, the series included patient who underwent multiple partial nephrectomy of as many as 13 tumors [48].

Table 13.7 Clamp versus non-clamp

	Clamp	Non-clamp
	380 Pts	839 Pts
Blood loss (med)	250	600
Creatinine (avg)	pre-op 1.16	pre-op 1.15
	latest 1.8	latest 1.4
Urine leak (pts)	8 (2 %)	31 (4 %)
Regional/local Recurrence	12 (3 %)	24 (3 %)
Other metastasis	23 (6 %)	36 (4 %)

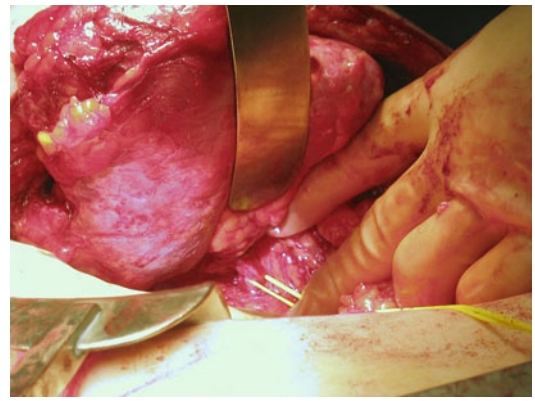

Fig. 13.3 Vascular control

The open non-clamping technique has been described in detail [48, 105]. The kidney is mobilized as described above. Similar to clamping partial nephrectomy, the hilar vessels are dissected out and non-occlusive 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.

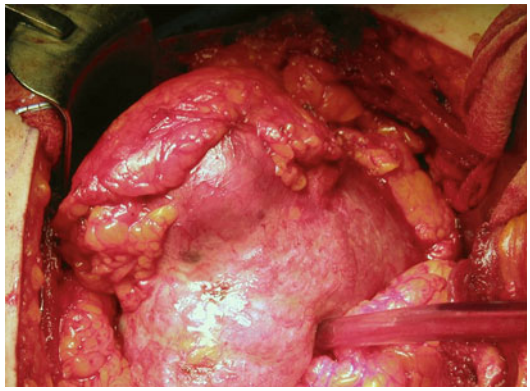

Fig. 13.4 Preservation of perinephric fat

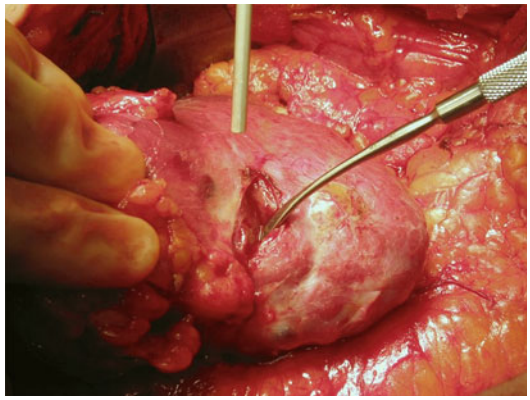

Fig. 13.5 Cleavage plane between tumor and normal parenchyma

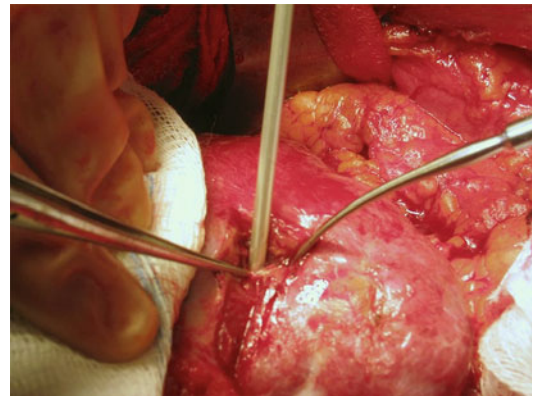

Fig. 13.6 Coagulation of small arteries at the corticomedullary junction

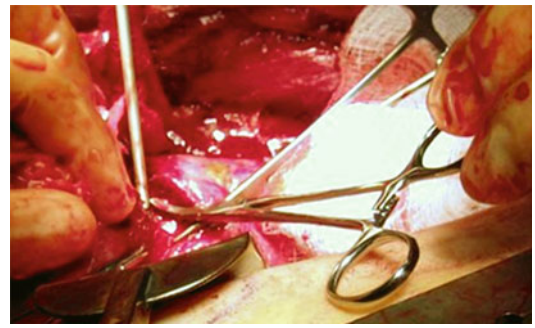

Fig. 13.7 Ligation of larger intrarenal arteries at tumor base

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. 13.6). 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; 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. On 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.

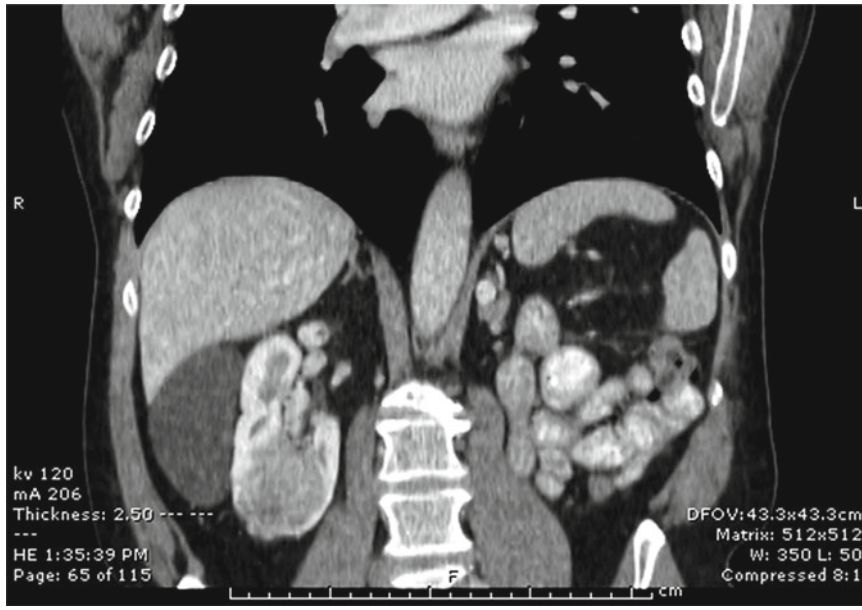

Fig. 13.8 Lower pole tumor – solitary kidney

In non-clamping partial nephrectomy series, in 158 solitary kidneys, there was a trend toward lower percentage decrease in nadir GFR when measured between 7 and 100 days postoperatively in the non-clamping cohort versus the clamping cohort (11.0 % vs. 16.1 %, $P=0.08$) [48]. The data suggest a progressive renal insult after 100 days in the clamping group. **When measured 101 and 365 days after surgery in comparison to preoperative values, there was a 27.7 % decrease in GFR in the clamping group compared to 11.8 % in the non-clamping group** (***P*=0.01**). A multivariate analysis that included tumor size, location, and focality as well as CKD risk factors was performed. Clamping was the only significant covariate. A limitation is that this multivariate analysis did not account for percent of functional parenchyma preserved, though another series suggests that ischemic injury remains an important determinant of postoperative renal failure even when accounting for percent of parenchyma that is preserved [104]. There was no difference in median estimated blood loss between the non-clamping and clamping groups (900 vs. 1,000 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 does not translate into better margins. In patients with two functioning renal units, margin rates were similar between the clamping and non-clamping groups (6 % vs. 4.7 %)[105].

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14 Minimally Invasive Partial Nephrectomy and Ablative Procedures for Small Renal Masses

Casey G. Kowalik, David Canes, and Ali Moinzadeh

Introduction

Concurrent with the increased incidence of small renal masses (SRMs), there has been an expanding role for minimally invasive (laparoscopic and robotic assisted) partial nephrectomy (MIPN) and ablative management [5]. Partial nephrectomy is considered a standard treatment for most renal tumors ≤4 cm [1]. The technical challenge of laparoscopic partial nephrectomy (LPN) has precluded its widespread use. The robotic platform has increased the number of robotic-assisted laparoscopic partial nephrectomies (RALPN) performed [6]. 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 [7]. When discussing treatment options for SRMs, consideration should be given to ablative therapies, including cryoablation and radiofrequency ablation. Less commonly available (and not FDA approved) ablative techniques include microwave therapy and high-intensity focus ultrasound [8, 9]. Numerous factors play a role in choosing the optimal treatment for each patient. Although beyond the scope of this chapter, active surveillance is a reasonable option in select patients with SRMs [1]. In this chapter, we describe the surgical technique for MIPN and provide an overview of alternative ablative strategies for SRMs.

Partial Versus Radical Nephrectomy

Equivalent cancer control between partial nephrectomy and radical nephrectomy has been established for clinical T1-T2 tumors [10–12]. The added benefits of performing partial nephrectomy include preserved renal parenchyma and less overtreatment of benign renal tumors.

Most studies comparing radical and partial nephrectomy oncologic outcomes are retrospective and therefore have several inherent issues with study validity, most notably selection bias. In a review of Surveillance, Epidemiology and End Results (SEER) cancer registry data, partial nephrectomy was associated with reduced mortality and decreased number of postoperative cardiovascular events compared to radical nephrectomy [13]. Van Poppel and colleagues compared radical and partial nephrectomy in a multicenter, randomized controlled trial of 451 patients with T1-T2 renal tumors [10]. At a median follow-up of 9.3 years, the total number of cancer-related deaths was 12, and 21 patients had disease progression with no significant difference between the two groups. Excluding patients with multifocal disease at the time of

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surgery, there was no difference in 10-year overall survival between the groups concluding that partial nephrectomy provides a valuable and, in select cases, superior option for the treatment of T1-T2 renal tumors.

Open Versus Minimally Invasive Partial Nephrectomy

The goal of minimally invasive technology is to minimize perioperative morbidity while maintaining oncologic principles. The established benefits of laparoscopic over open partial nephrectomy are shorter hospital stay, faster convalescence, and decreased narcotic requirements [14]. In the largest retrospective study to date, Gill et al. [4]. compared open and laparoscopic partial nephrectomy in 1,800 patients with a unifocal clinical T1 renal tumor. Patients in the laparoscopic group had significantly shorter operative times and less blood loss, but longer warm ischemia time than open partial nephrectomy. Each procedure had a small number of intraoperative complications precluding statistical analysis. LPN had a total of 14 and open partial nephrectomy (OPN) had ten intraoperative complications including vascular ($n=10$), ureteral ($n=8$), spleen ($n=1$), and bowel ($n=1$) injuries. Sixteen (2.1 %) cases converted to open. The LPN group was three times more likely to undergo a secondary procedure, which was attributed to the higher rate of postoperative hemorrhage. Patients undergoing LPN had a shorter hospital stay by an average of 2.2 days. There was no difference in postoperative serum creatinine and oncologic outcomes with a median follow-up time of 1.2 years.

Excellent long-term oncologic outcomes have been established by Lane and Gill [2] in their comparison of LPN to OPN for T1 tumors. Seven-year metastasis-free survival was 93 % and 95 % ($p=0.7$), for LPN and OPN, respectively. Seven-year cancer-specific survival was equal between the groups at 95 %. Equivalent renal functional and oncologic outcomes, with the benefits of shorter hospital stay, underscore the effectiveness of LPN as an option for experienced surgeons.

Laparoscopic Partial Nephrectomy in Solitary Kidneys

Tumor in a functional or anatomic solitary kidney poses a unique clinical challenge. While oncologic control remains the most important goal, preservation of renal function and avoidance of long-term hemodialysis are also crucial [15]. To accomplish these goals, nephron-sparing surgery, if technically possible, is imperative.

In the largest published series to date, Haber et al. [16] report their experience with 78 patients with a solitary kidney undergoing LPN. There were four intraoperative complications, all requiring open conversion. The postoperative complication rate was 22.9 %, which is consistent with the range of postoperative complications after MIPN published in other series [4, 17–20]. Lane et al. [21] compared OPN ($n=169$) to LPN ($n=30$) in patients with solitary kidneys. LPN had longer warm ischemia time by an average of 9 min. Patients in the LPN were 2.54-fold more likely to have a postoperative complication. Three patients undergoing LPN required renal replacement therapy acutely, and two required permanent hemodialysis within 1 year. The small sample size and retrospective nature of these studies are inherent limitations. Nonetheless, MIPN in this subset of patients is feasible although with the potential for renal functional morbidity.

Minimally Invasive Partial Nephrectomy

Patient Selection

When planning for LPN or RALPN, careful consideration must be given to appropriate patient selection. A thorough history and physical examination to identify any factors that may impede a laparoscopic approach is necessary. Prior abdominal surgery is not a contraindication to laparoscopic surgery, but care should be taken as extensive intra-abdominal adhesions may be encountered. The surgeon should consider the

proximity of the scar to the initial access site and surgical field as well as the nature of the prior surgery, i.e., suppurative processes where there is likely to be adhesion formation. Obese patients may pose additional difficulties as the anatomic landmarks may be shifted and obesity is associated with an increased number of comorbidities [22]. Studies have demonstrated that laparoscopic (transperitoneal or retroperitoneal approach) renal surgery can be performed safely and without increased morbidity in obese patients [23, 24]. Pulmonary and cardiac disease may prevent patient tolerance of pneumoperitoneum. Patients with severe chronic obstructive pulmonary disease are at risk for developing severe hypercarbia with resultant acidosis [25]. The increased intra-abdominal pressure induced by peritoneal insufflation is transmitted to the thoracic cavity decreasing cardiac performance [26]. The potential for conversion to an open procedure should be discussed with every patient. All patients receive preoperative bowel preparation with magnesium citrate and a clear liquid diet the day prior to planned surgical procedure.

Imaging should be carefully reviewed to identify number of vessels, exact tumor location, and its proximity to the collecting system, along with the presence of lymphadenopathy. We prefer dedicated cross-sectional imaging (CT scan or MRI) with three-dimensional reconstruction to better assess precise tumor location as well as vascular anatomy. Calculation of RENAL nephrometry score may provide a standardized system of classifying the complexity of renal lesions, useful for research purposes [27].

Patient Positioning

After initiation of general endotracheal anesthesia, it is the authors' preference to place an ipsilateral ureteral catheter in patients prior to proceeding with MIPN. The ureteral catheter allows for retrograde injection of dilute methylene blue during the case for identification and closure of the collecting system. Alternatively, Bove et al. [28] demonstrated no difference in terms of postoperative urine leak rate whether a ureteral catheter was used during LPN. The patient is then placed in a 45° modified flank position (transperitoneal approach) or full flank position (retroperitoneal approach) with the table maximally flexed. The ipsilateral arm and contralateral arm are placed on padded arm boards parallel to the floor in such a position to avoid stretching of the brachial plexus. An axillary roll is used in nearly all patients except the morbidly obese with a significant axillary fat pad. Pillows are placed between the legs with the contralateral leg bent to 90° and ipsilateral leg straight. Careful padding of all bony prominences (hips/knees/ankles) is performed as needed. Sequential compression devices are routinely utilized on the bilateral lower extremities. Flank and shoulder supports are placed on the posterior aspect to allow table rotation. The hips and shoulders are secured with tape to the table to ensure no movement with table rotation. Neutral positioning of the head is confirmed. A universal time-out involving all team members is performed after positioning and prior to draping to ensure correct laterality. Careful patient positioning is paramount to prevent neuropathies and rhabdomyolysis (Fig. 14.1). Despite proper positioning, rhabdomyolysis has been reported [29, 30]. The patient's abdomen and flank are prepped widely in preparation for efficient conversion to open surgery if needed.

Laparoscopic Access

Transperitoneal

For the transperitoneal approach, five or six trocars are generally utilized. A 12 mm incision is made at the ipsilateral border of the rectus muscle at a midpoint between the umbilicus and anterior superior iliac spine. Intraperitoneal access is obtained via Hassan (open) or Veress technique depending on surgeon preference, and pneumoperitoneum is achieved to 15 mmHg [31]. Remaining trocars are placed under direct vision. A 12 mm subcostal port for the surgeon's right (if left-sided tumor) or left (if right-sided tumor) hand is placed. An intervening 12 mm camera

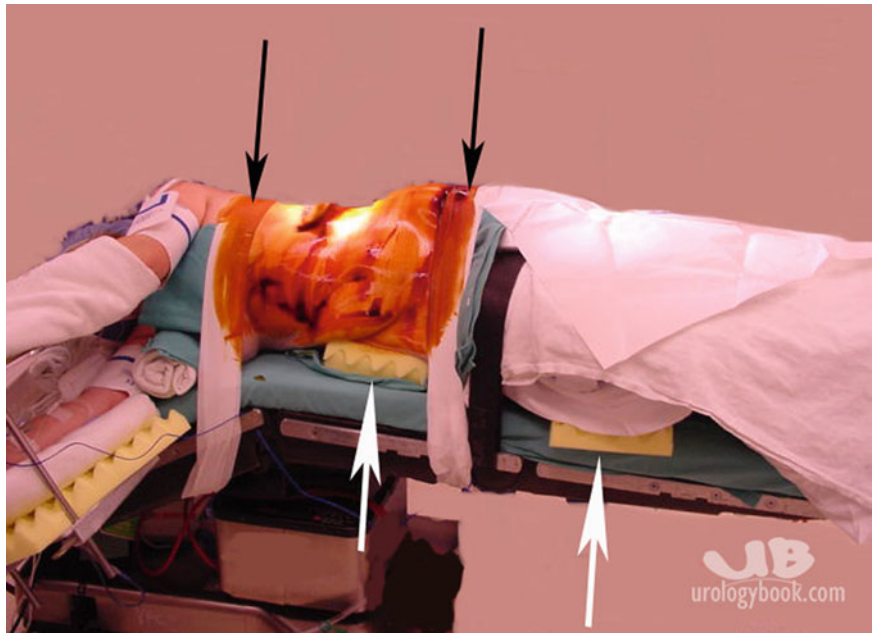

Fig. 14.1 *Patient positioning for left renal surgery*. Table is maximally flexed. Patient is at 45° modified flank position. *White arrows*: pressure points padded at knee and hips. *Black arrows*: tape securing patient to bed. Arms are placed in padded double arm boards (*Image courtesy of use*, www.urologybook.com)

trocar is placed just medial and caudal to the subcostal trocar. A 12 mm trocar along the anterior axillary line is placed for use by the assistant. For a right-sided tumor, a 5 mm subxiphoid trocar is inserted for liver retraction (Fig. 14.2).

Retroperitoneal

For the retroperitoneal approach, the patient is in the full flank position. A 12 mm incision in the posterior axillary line between the iliac crest and tip of the 12th rib is made. Using blunt dissection, a working space is created and a blunt tip trocar is inserted through the incision. Three additional trocars are used: a 5 mm port placed at the tip of the 12th rib, a 12 mm port at the level of the umbilicus in the anterior axillary line, and a 12 mm port just superior to the umbilicus in the midaxillary line [32]. Retroperitoneal access is best suited for posterior tumors or a patient with multiple prior abdominal procedures. The limited working space reduces visualization and makes suturing more technically challenging if performed laparoscopically. Comparisons of transperitoneal and retroperitoneal LPN have shown similar blood loss, perioperative complication rates, and postoperative creatinine [33].

Hand-Assisted

Hand-assisted laparoscopic (HAL) partial nephrectomy offers the benefit of tactile feedback, similar to open surgery, while maintaining a more cosmetically appealing incision. It is the authors' preference not to employ hand assistance for partial nephrectomy cases as typically a large extraction incision is not necessary. Usually, the surgeon's nondominant hand is inserted through a periumbilical working port. The exception is when right-handed surgeons operate on right-sided tumors, the hand incision is made in the right lower quadrant. The optimal length of the working port incision corresponds to the width of the surgeon's hand to prevent gas escaping. Two or three additional ports are utilized and location may vary. One example of trocar placement is as

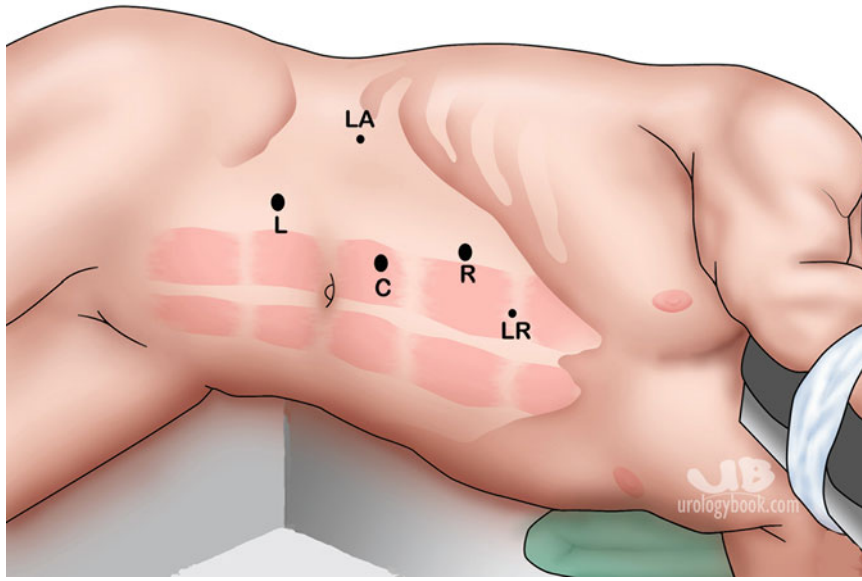

Fig. 14.2 Laparoscopic access for right transperitoneal partial nephrectomy. *LR* 5 mm liver retraction port placed subxiphoid, *R* right-hand working trocar, *C* camera trocar, *L* left-hand working trocar, *LA* 5 mm lateral assistant trocar (*Image courtesy of use*, www.urologybook.com)

follows: 12 mm camera port is placed midline between the epigastrium and umbilicus and a 10/12 mm working port in the midclavicular line lateral to the umbilicus [34].

Procedure

Once transperitoneal access is safely obtained, the ascending (right) or descending (left) colon is mobilized medially. On the right, using blunt dissection, the hepatic flexure is mobilized and the duodenum is Kocherized. On the left side, 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 for left-sided renal dissection then traced proximally to the renal hilum. For right-sided procedures, the gonadal vein is preserved medially adjacent to the inferior vena cava while the ureter is retracted laterally. Significant dissection of the ureter is avoided to minimize the risk of devascularization. The renal artery and vein are dissected to allow adequate placement of clamps. In patients with multiple veins and/or arteries, intraoperative Doppler ultrasound may be used to help identify their location. In a study of 53 consecutive patients undergoing RALPN by Hyams et al. [35], utilization of Doppler ultrasound reduced mean hilar dissection time and aided in the detection of accessory vessels not seen on preoperative imaging. Gerota's fascia is then incised and the tumor is identified. If possible, a portion of Gerota's fascia is preserved over the tumor to allow for T3 staging as well as serving as a handle during excision of the tumor. The adrenal gland may be separated from the upper pole in sparing procedures or included en bloc for upper pole medial tumors [36]. The 2010 European Association of Urology update on renal cell carcinoma guidelines [37] does not recommend routine adrenalectomy unless preoperative imaging reveals an abnormal-appearing adrenal gland or operative findings include a grossly abnormal adrenal gland or adrenal nodule.

The role of lymph node dissection in renal cell carcinoma remains controversial [38, 39]. In patients with stage 1 renal cell carcinoma and clinically negative lymph nodes, lymph node

dissection offers no survival benefit [40]. Despite this, some continue to advocate lymph node dissection in patients undergoing radical nephrectomy and partial nephrectomy with larger T1b tumors because of the minimal added morbidity and chance for cure in patients with micrometastatic disease [41].

Hilar Clamping

Depending on surgeon preference, various devices can be utilized for hilar clamping. A Satinsky clamp can be used for en bloc clamping or bulldog clamps for selective clamping. Significant variation in clamping technique exists. Gong et al. [42], in a retrospective case-controlled study, reported their experience of artery-only clamping in 25 patients compared to artery and vein clamping in 53 patients. Each group had similar blood loss. The artery and vein group had a significant increase in their postoperative creatinine, while the artery-only group had no significant change. Of the patients without preexisting kidney disease, there was no difference in the number of patients from each group developing renal insufficiency.

Renal hypothermia and administration of diuretics prior to hilar clamping have been employed to theoretically reduce cellular oxidative damage during renal ischemia and renal perfusion. A combination of mannitol and/or Lasix may be given prior to clamping. Methods of renal hypothermia including renal arterial perfusion with cold crystalloids, [43] retrograde transurethral saline infusion [44], and kidney cooling with intraperitoneal ice slush [45] are not routinely utilized given the technical challenges.

Early unclamping represents a significant technical improvement in reducing warm ischemic times. Utilizing this technique, the kidney is reperfused immediately after placement of the initial central running suture and prior to placement of mattress or bolster sutures [46]. Our preference is to use a barbed unidirectional suture for this running anastomosis (V-Loc, Covidien, Mansfield, MA, USA). With the kidney unclamped, Vicryl (Ethicon, Somerville, NJ, USA) sutures are then placed on bleeding vessels until hemostasis is obtained. In their series of 100 patients, Nguyen et al. [46] compared early unclamping to the standard technique and found similar intraoperative blood loss. The average clamp time in the early unclamping group was 13.9 min, which was about 6 min shorter than clamping times for open partial nephrectomy published in Gill's [4] comparison of open and laparoscopic partial nephrectomy. There was a trend towards fewer postoperative complications in the early unclamping group, although this was not statistically significant. The group hypothesized that early unclamping exposes bleeding that would otherwise not be exposed with clamped vessels. This allows for directed suture placement by the surgeon, which may translate into a reduced incidence of postoperative hemorrhage.

Guillonneau et al. [47] published an initial retrospective comparison of clamping ($n=16$) and non-clamping ($n=12$) LPN. In the non-clamping group, tumor excision was performed using ultrasonic shears and bipolar electrocautery for hemostasis of the tumor bed. Oncologic control was not compromised as all patients had negative margins. Both groups had the same number of complications demonstrating the feasibility of non-clamping LPN. Rais-Bahrami and colleagues [48] report their experience in off-clamp LPN in 126 patients. The off-clamp group had significantly more blood loss, but did not require more transfusions than the on-clamp cohort. At 6 months postoperatively, serum creatinine was found to be significantly less changed in the off-clamp group suggesting the potential for improved renal functional outcomes. Performing off-clamp MIPN for more complex (central or hilar) tumors is typically not feasible given excessive blood loss and poor visualization.

Gill et al. [49] described microdissection of tumor-specific arterial branches to eliminate global renal ischemia with the aid of preoperative 3-D CT imaging and color Doppler ultrasonography when needed. Clamping of select renal artery segment(s) supplying the tumor allows for partial nephrectomy while maintaining perfusion to the remaining kidney (Fig. 14.3). Given its recent introduction, reproducibility of this technique and its benefits on renal functional outcomes are not yet clear.

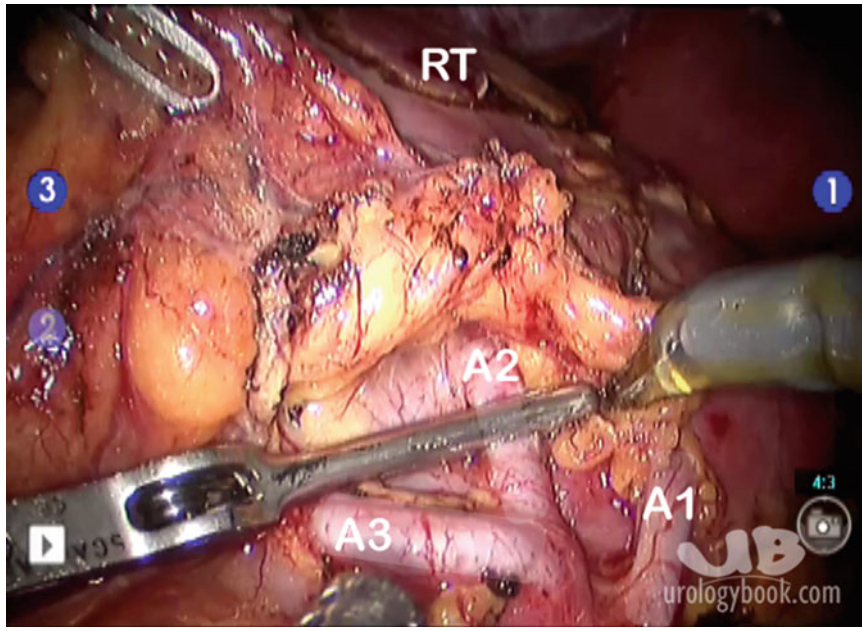

Fig. 14.3 Selective clamping of one of three right-sided secondary renal artery branches (*A1–A3*) during robotic-assisted laparoscopic partial nephrectomy. Intraoperative ultrasound with Doppler was performed demonstrating *A2* as the renal artery branch supplying area of renal tumor (*RT*) (*Image courtesy of use*, www.urologybook.com)

Tumor Resection

Once the kidney is fully mobilized and access to the renal pedicle isolated, intraoperative ultrasound is utilized to confirm tumor location and depth, as well as the absence of other renal tumors. Using electrocautery, the tumor is demarcated circumferentially with ultrasound guidance. Tumor excision then proceeds with cold cutting with the goal of obtaining a small surrounding rim of normal renal tissue. The excised mass should be placed in a specimen retrieval bag to be removed prior to fascial closure. Data suggests that only minimal normal peritumor renal parenchyma is necessary for adequate local control [50]. The reported rate of positive surgical margins after MIPN ranges from 0.7 % to 5.7 % [51]. Data on the effect of positive surgical margin on local and distant disease recurrence appears to show minimal risk [52, 53], but long-term data on the effect on overall survival is lacking. The utility of frozen section in decreasing positive margins is also controversial with several studies reporting discrepancies with final pathology results [53–55]. Frozen section of random tissue samples from the tumor bed is low yield given the small sampling size. The surgeon's gross inspection of the resected specimen seems to provide an accurate assessment of margin status [56]. Frozen section may have a role in confirming suspicion that tumor was left in the tumor bed based on gross inspection of both the renal defect and the specimen.

Reconstruction of the Collecting System

Tumors abutting or invading the collecting system may require direct collecting system entry. Retrograde filling with methylene blue through an open-ended ureteral catheter or intravenous administration of indigo carmine if the kidney is perfused aids in identification and repair. Closure of the collecting system can be accomplished by closure in layers using 2-0 Vicryl or a 3-0 unidirectional barbed suture with a Lapra-Ty (Ethicon Endo-Surgery, Cincinnati, OH, USA) at the end. Other techniques of collecting system closure have been explored. Bylund et al. [57] employed

a fibrin glue absorbable gelatin sponge sutured in place with no formal reconstruction of the collecting system in 104 patients. Two patients experienced a urine leak that was treated with conservative management.

Hemostasis of the Tumor Bed

Achieving hemostasis is crucial during LPN as the most common postoperative complication requiring secondary procedure is delayed hemorrhage [4]. Several techniques have been described. Following excision of the tumor, a central running Vicryl suture is placed in the resection site to oversew any bleeding vessels. If bleeding persists, then directed suture placement is done. If the collecting system was entered, this is closed in a watertight fashion. Renorrhaphy with or without the use of a bolster and hemostatic agents is performed by placing 2-0 Vicryl sutures with a Weck Hem-o-lok clip (Teleflex Medical, Kenosha, WI) on one end. Depending on the size of the tumor bed, 4–6 sutures are placed in mattress fashion through the renal parenchyma and secured by placing a Weck Hem-o-lok clip. Tsivian and colleagues [58] describe a primary closure of the renal parenchyma without the use of hemostatic agents in 34 patients with tumor size ranging from 1.7 to 8.5 cm with one case of delayed hemorrhage postoperatively. The surgeon may use a bloster composed of oxidized cellulose polymer (Surgicel, Ethicon, Somerville, NJ, USA) along with a gelatin matrix (FloSeal, Baxter Healthcare Corporation, Fremont, CA, USA) injected between the bolster and tumor bed (Fig. 14.4). Alternatively, when apposition of renal bed sides is possible, the bolster may be avoided.

Closure

After hemostasis is confirmed, Gerota's fascia is re-approximated. The specimen is extracted. Pneumoperitoneum is resumed and hemostasis is reconfirmed. A Jackson-Pratt drain is brought out through the most lateral port. All trocars are removed under direct vision. Local anesthesia is injected into each of the port sites. The extraction site fascia is closed with 0 Vicryl in interrupted or running fashion. The remaining 12 mm trocar sites are closed using Carter-Thomason device with 0 Vicryl. Skin is closed with Monocryl (Ethicon, Somerville, NJ, USA), and tissue adhesive can be applied if desired.

Robotic-Assisted Laparoscopic Partial Nephrectomy (RALPN)

Robotic-assisted laparoscopic partial nephrectomy (RALPN) is emerging as an alternative to LPN. At the authors' institution, we have performed RALPN almost exclusively over LPN since 2007. Advantages of the robot-assisted approach over pure laparoscopic include articulating instruments that allow full range of motion and 3-D vision that enhances dexterity and precision.

Comparison of RALPN to LPN

A systematic review of the literature by Aboumarzouk et al. [59] compared robotic and laparoscopic partial nephrectomy. Outcome measures including operative time, intraoperative blood loss, rates of conversion, length of hospital stay, postoperative complications, and positive margins were similar between the two groups. One significant finding was that the robotic group had a shorter warm ischemia time. RALPN is still emerging, so long-term oncologic data is lacking, but early results indicate oncologic outcomes comparable with LPN [18, 60–62].

Procedure

The techniques described for transperitoneal laparoscopic partial nephrectomy can be translated for use with the da Vinci (Intuitive Surgical, Sunnyvale, CA, USA) robotic surgical system. The use of articulating arms may decrease challenging angles necessary during renal surgery, such as closing the collecting system or placing

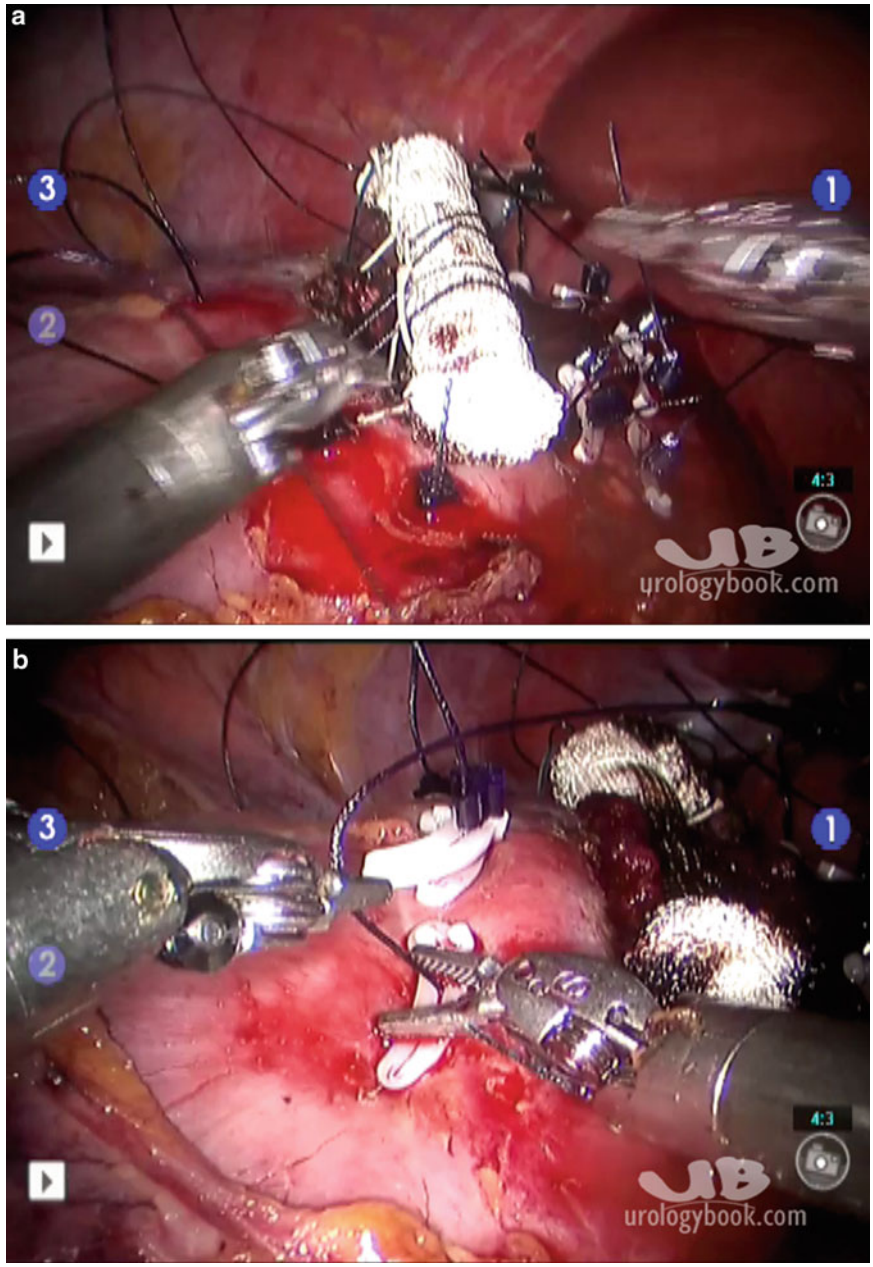

Fig. 14.4 (**a**) Placement of Surgicel bolster under 0 Vicryl mattress parenchymal sutures. Early unclamping has been performed, hence perfused renal parenchyma. (**b**) Bolster sutures are cinched down using slip technique of Hem-o-lok (*Image courtesy of use*, www.urologybook.com)

renal parenchymal sutures. Patient positioning is the same as for the transperitoneal laparoscopic approach with patients placed in the 45° modified flank position with the table maximally flexed [63]. Rather than being centered on the table, the patient's posterior is closer to the side where the robot is docked so as to decrease the reach of the robotic arms over the patient's torso. Typically there are four robotic ports and an assistant port placed between the camera trocar and the left robotic working trocar, with an additional subxiphoid liver retractor for right-sided tumors.

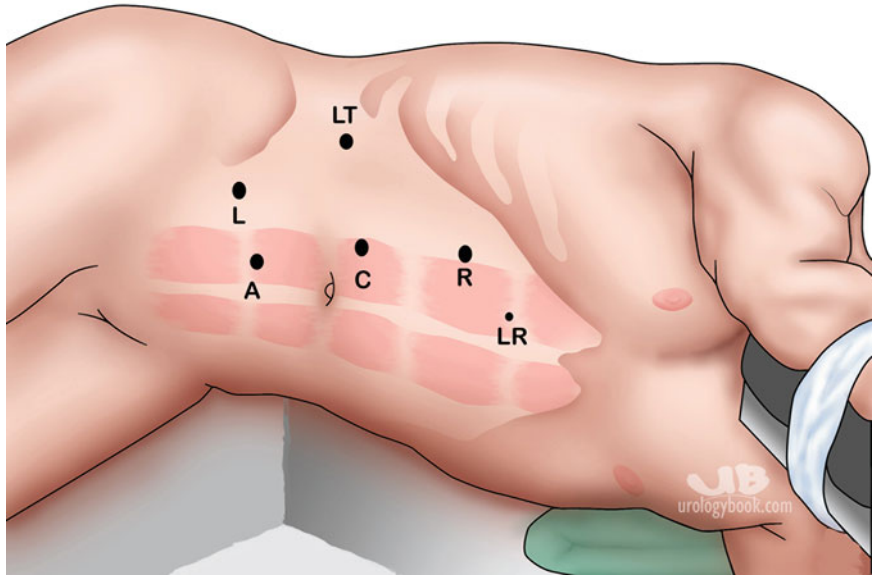

Fig. 14.5 Trocar placement for robotic-assisted laparoscopic partial nephrectomy. *LR* 5 mm liver retractor port, *R* robotic right arm, *C* robotic camera, *L* robotic left arm, *LT* robotic lateral trocar (*Image courtesy of use*, www.urologybook.com)

When selecting trocar sites, attention must be paid to ensuring adequate distance between sites so that there is sufficient working room for the instruments. Robotic trocars and the camera should be placed at least 8 cm away from each other. Initially, a 12 mm incision is made lateral and cephalad to the umbilicus, where the 30°-down laparoscope is placed. Three additional 8 mm ports are placed at the ipsilateral edge of the rectus muscle, midline about 3 cm below the umbilicus (robotic left arm for right-sided renal tumors), and cephalad to the camera port (robotic right arm for right-sided renal tumors). The robot is docked at nearly 90° to the table. We place one robotic arm in the later almost position on the abdomen during transperitoneal cases. The ideal location for this arm is determined after the robot has been docked. In this way, the least amount of arm clashing can be determined. The fourth arm with a prograsper may be used to provide counter retraction during bowel takedown and hilar dissection. With alternative instruments, the fourth arm may be used for kidney and tumor dissection. The bedside assistant is responsible for suctioning, retraction when needed, delivery of sutures, and placement of clips on sutures. Depending on the method of hilar clamping, this may also be the assistant's responsibility (Fig. 14.5).

Laparoendoscopic Single-Site Partial Nephrectomy

Laparoendoscopic single-site surgery (LESS) is gaining momentum in the urologic community pushing the limits of minimally invasive surgical techniques. A recent literature review suggests that transumbilical LESS is feasible for experienced laparoscopists [64]. Autorino et al. [65] reported their experience with LESS, which included 133 partial nephrectomies. The majority (61 %) of cases were converted to reduced port (52.6 %), traditional laparoscopy (6.8 %), or open (1.5 %). More revealing is that LESS partial nephrectomy was performed successfully in 52 patients, the largest of any series. Six patients had intraoperative complications with an overall complication rate of 9.8 %. Four patients had major complications defined as either requiring an additional procedure or experiencing single

organ dysfunction. A comparison of laparoscopic to LESS partial nephrectomy has yet to be performed, but this data will be essential in establishing functional and oncologic outcomes. Standard laparoscopic LESS is also being extended into the robotic arena where specialized instrumentation is being conceived to improve dexterity [66]. It remains to be seen if LESS provides any benefit over multitrocar minimally invasive procedures.

Natural Orifice Translumenal Endoscopic Surgery (NOTES)

Another avenue in exploration of minimally invasive surgery is incision-less surgery with natural orifice translumenal endoscopic surgery (NOTES). NOTES involves the use of an endoscopic camera into a hollow organ where a transvisceral incision is made to access the peritoneal cavity. Boylu et al. [67] described a transgastric partial nephrectomy using thulium laser in a porcine model. This was a non-clamping technique. The specimen was retrieved using a wire loop and removed via the gastrotomy. Ideally a specimen sac would have been used to prevent possible tumor seeding; however, one was not available that could pass through the working port of the gastroscope. According to the authors, the most challenging aspect was manipulating the laser fiber within the gastroscope. Robotic NOTES partial nephrectomy through vaginal access was performed in the porcine model with no intraoperative complications [68]. Besides the improved cosmetic effect, NOTES eliminates surgical site infections and incisional hernias. More study is needed, but the limits of NOTES are being explored and whether there will be more applications in the future is uncertain.

Postoperative Management

Postoperatively, patients are admitted to the medical surgical floor and continued on intravenous fluids. Pain control is managed with intermittent intravenous analgesics. Laboratory data is checked postoperatively and the following morning. Perioperative antibiotics are continued for 24 h. For deep vein thrombosis prevention, sequential compression devices are worn at all times and early ambulation is encouraged. The following morning, patients are started on a clear liquid diet and ureteral stent is removed. Once tolerating liquids, analgesic medications are given orally. The drain is monitored for output, and if high, fluid is checked for creatinine. If drain output remains low, the Foley catheter is then removed and the drain is removed prior to discharge from the hospital. On average, length of hospitalization is 2.2 days at our institution. Patients advance diet as tolerated once they have evidence of bowel function. Shah and Abaza [69] presented their clinical pathway for discharging patients on postoperative day 1 following robotic partial nephrectomy. In their series of 90 patients, 94 % ($n=85$) were discharged on postoperative day 1 with a readmission rate of 5 % ($n=4$). Minimal data exists, but in our empiric experience, antiplatelet agents can be safely resumed in 10 days.

Complications of Minimally Invasive Partial Nephrectomy

Reported complications for LPN and RALPN range from 11 % to 36 % and from 8.5 % to 35.3 %, respectively. Table 14.1 provides an overview of complications reported in select series of LPN and RALPN.

Intraoperative Complications

Vascular Injury

Injuries to the renal hilum can have significant mortality and morbidity if not managed rapidly and in a controlled manner. In cases of small venous bleeding, direct pressure with Surgicel (Ethicon, Somerville, NJ, USA) may be sufficient. Pneumoperitoneum must be turned down to ensure that hemostasis is achieved. Larger venous injuries may be oversewn with a 4-0 Prolene

Table 14.1 Summary of intraoperative complications of LPN and RAPN

	LPN or RALPN, no.	Overall complication rate, % (no.)	Intraoperative complication rate, % (no.)	Conversion, % (no.); indication if given	Postoperative complication rate, % (no.)	Transfusion, % (no.)	Vascular, % (no.); secondary procedure if given	Urine leak, % (no.)
Gill et al. [4]	LPN, 771	26.7 % (206)	1.8 % (14)	2.1 % (16); 15 OPN, one ORN; elective (4), hemorrhage (6), vascular injury (4), uncertain margin (1), tumor identification (1)	24.9 % (192)	5.8 % (45)	4.2 % (32); angioembolization (10), re-exploration (6), nephrectomy (3)	3.1 % (24)
Gong et al. [17]	LPN, 76	22.4 % (17)	7.9 % (6)	7.9 % (6); six OPN; hemorrhage (3), difficulty accessing tumor (2), positive margin (1)	22.4 % (17)	6.6 % (5)	6.6 % (5); emergent nephrectomy (2)	1.3 % (1)
Benway et al. [18]	LPN, 118	11 % (13)	0.8 % (1)	4.5 % (5); 2 HALPN for failure to progress, 2 LRN because nephron-sparing not possible; 1 ORN for hemorrhage	10.2 % (12)	1.7 % (2)	0.8 % (1); AV malformation requiring angioembolization	3.4 % (4)
	RALPN, 129	8.5 % (11)	0	1.6 % (2); 2 OPN; adhesions (1), uncertain margin (1)	8.5 % (11)	0.8 % (1)	2.3 % (3); AV malformation (2), nephrectomy (1)	2.3 % (3)
Kaouk et al. [19]	RALPN, 400	18 % (72)	2.7 % (11)	1.8 % (7); 4 LPN, 2 OPN, 1 RRN	15.3 % (61)	7.3 % (29)	0.3 % (1); angioembolization	0.5 % (2)

LRN laparoscopic radical nephrectomy, *OPN* open partial nephrectomy, *ORN* open radical nephrectomy, *RRN* robotic radical nephrectomy, *AV* arteriovenous

(Ethicon, Somerville, NJ, USA) suture. If significant injury to the hilar vessels occurs, it may be necessary to proceed with radical nephrectomy.

Injury to Intra-abdominal Organs

Bowel injury etiologies include traumatic (e.g., during access) and sharp or thermal dissection. The method of repair of bowel injuries depends on the severity, original cause of the injury, and whether it is recognized at the time or in the postoperative period. In instances of an immediately identified minor thermal bowel injury, simple imbrication may be sufficient. Major thermal injuries should be managed with bowel resection and re-anastomosis or, rarely, diversion. In such a case, it would be prudent to obtain general surgery or colorectal surgery consultation depending on institution routine. If the bowel injury is identified in the postoperative period, depending on the clinical circumstances, this may require reoperation with bowel resection. Clinical signs and symptoms of bowel injury vary widely and include peritonitis, nausea, vomiting, tachycardia, fevers, and sepsis.

Pancreatic injuries during laparoscopic renal surgery most often occur at the pancreatic tail during left-sided procedures [70]. Pancreatic injury identified in the postoperative period may present with increasing drain output, and confirmation is by fluid and serum amylase and lipase. If identified postoperatively, management includes total parenteral nutrition, nasogastric tube placement, somatostatin to suppress pancreatic exocrine function, and percutaneous drainage.

Injuries to the spleen can often be treated with argon coagulation and/or use of hemostatic agents. Rarely, in instances of significant splenic laceration, a splenectomy is performed.

In laparoscopic renal surgery, inadvertent diaphragm injury has a reported incidence of 0.4 % [71]. Billowing of the diaphragm is a noticeable sign of pleural entry. Repair can be performed laparoscopically in a technique similar to open repair [71].

Postoperative Complications

Hemorrhage

Delayed hemorrhage is the most common complication requiring secondary procedure after LPN [4]. Depending on the severity, postoperative hemorrhage is managed with a combination of transfusion, selective angioembolization, or re-exploration with local control versus completion nephrectomy.

Urine Leak

A urine leak is a result of collecting system entry with tumor resection. Depth and size of the lesion is associated with collecting system entry, but this does not necessarily translate to increased likelihood of postoperative urinary leak [72]. Typically, a drain is left in place in the operating room, which can aid in diagnosis and treatment of urinary leakage. The clinical presentation may include rising serum creatinine, increasing drain output, ileus, or worsening flank pain. Diagnosis is confirmed by an elevated drain fluid creatinine. Most cases of urinary leakage are treated conservatively with ureteral stent, percutaneous drain, and bladder drainage. Antibiotics should be initiated in the patient who is febrile or has a leukocytosis. If the urine leak does not heal with these measures, the patient may need a percutaneous nephrostomy tube for complete urinary diversion and extremely rarely a second surgical procedure to close the defect.

Alternative Minimally Invasive Nephron-Sparing Options

Minimally invasive ablative therapies for renal tumors can be performed percutaneously or laparoscopically and are typically performed with real-time imaging guidance. These techniques are technically less challenging than partial nephrectomy as there is no need for hilar clamping,

Table 14.2 Reported oncologic outcomes of minimally invasive nephron-sparing procedures for T1 renal tumors

Study	Procedure	No.	Follow-up (months)	OS	CSS	RFS
Lane et al. [2]	OPN	332	80.4 (median)	93.5 at 7 year	95 % at 7 year	95 % at 7 year
	LPN	145	74.4 (median)	83.1 at 7 year	95 % at 7 year	93 % at 7 year
Kyllo et al. [62]	RALPN	124	29 (median)	97.3 % at 3 year	99 % at 3 year	94.9 % at 3 year
Aron et al. [78][a]	LCA	80	95 (median)	84 % at 5 year	92 % at 5 year	81 % at 5 year
Goyal et al. [77][a]	PCA	141	36.1 (mean)	77.7 % at 5 year	98 % at 5 year	95.6 % at 5 year
Ji et al. [83][a]	LRFA	106	32 (mean)	100 %	100 %	97.8 %
Zagoria et al. [84][a]	PRFA	41	61 (median)	58.5 %	97.6 %	88 %

OS overall survival, *CSS* cancer-specific survival, *RFS* recurrence (local and metastatic)-free survival, *OPN* open partial nephrectomy, *LPN* laparoscopic partial nephrectomy, *LCA* laparoscopic cryoablation, *PCA* percutaneous cryoablation, *LRFA* laparoscopic radiofrequency ablation, *PRFA* percutaneous radiofrequency ablation

[a]Included patients had biopsy-proven renal cell carcinoma prior to treatment

collecting system reconstruction, renorrhaphy, or adjacent organ dissection. Ablative therapy is typically limited to clinical T1 tumors and patients with increased surgical risks [1]. The majority of patients undergo renal biopsy prior to ablative procedures to confirm presence of malignancy [73, 74]. It is the recommendation of the American Urological Association [1] that all patients undergo percutaneous renal biopsy prior to ablative procedures. The two most commonly studied and utilized methods are cryoablation 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 occurs. 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 [75–77]. In patients with recurrent disease, ablative therapy did not preclude radical nephrectomy [74, 78].

A number of studies have compared MIPN (LPN or RALPN) to laparoscopic cryoablation (LCA) [75, 79–82]. These studies have demonstrated similar short-term oncologic outcomes; however, longer-term data is needed. Aron et al. [78] present 80 patients who underwent LCA with a median follow-up of 93 months (range 60–132). In patients with biopsy-proven renal cell carcinoma, 5- and 10-year disease-specific and recurrence-free survival was 92 % and 81 % and 83 % and 78 %, respectively. Midterm oncologic outcomes of radiofrequency ablation for SRMs are published [74, 83, 84]. Tracy et al. [74] report 208 patients undergoing either laparoscopic or percutaneous radiofrequency ablation with a mean follow-up of 27 months. There were nine local recurrences with 5-year recurrence-free survival of 93 %. The overall 5-year survival was 85 %. These outcomes are inferior to published disease-specific survival data for extirpative therapy for T1a tumors [2]. A meta-analysis comparing cryoablation to RFA suggests that patients undergoing RFA have higher local tumor progression, but no direct comparisons of the two modalities exist [85]. Table 14.2 provides a comparison of oncologic outcomes of minimally invasive nephron-sparing procedures for T1 tumors reported in the literature. The largest series with the longest follow-up were selected. 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 [81]. At the present time, minimally invasive ablative procedures should be reserved for patients requesting treatment, but are high-risk surgical candidates.

New treatment modalities such as high-intensity focused ultrasound (HIFU) and microwave

therapy remain investigational. An international group has reported their experience with extracorporeal and laparoscopic HIFU demonstrating its feasibility and safety [9, 86]. Castle et al. [87] reviewed their experience with ten patients undergoing microwave therapy, which showed high postoperative complication rate (40 %) and high recurrence rate (38 %) for the cohort. Further trials and longer-term follow-up are needed to demonstrate the oncologic safety of these novel techniques.

Future Directions

Efforts to further reduce warm ischemia time to normal renal parenchyma have led to zero-ischemia techniques with superselective blood flow interruption of tertiary or higher-order arteries via clamping or embolization [49, 88]. Our institution developed a technique for angiographic delivery of a reverse thermosensitive polymer (Lumagel, Pluromed Inc., Woburn, MA, USA) to reliably interrupt blood flow to tumor-specific arteries [89]. The polymer contains a contrast agent and works by increasing viscosity when warmed to body temperature upon injection into the targeted artery and returns to its less viscous state upon recooling. A recent randomized study comparing hilar clamping to selective arterial branch occlusion using Lumagel in porcine models demonstrated success in performing bloodless partial nephrectomy [90]. At 6 weeks necropsy was performed which showed no evidence of gross or microscopic damage to the remaining ipsilateral kidney or endothelium at the prior plug location.

Lastly, significant data heterogeneity exists among reports for minimally invasive nephron-sparing treatment. If evidence-based decisions are to be made on the available literature, more standardized reporting is necessary. More authors are utilizing the Clavien classification for reporting postoperative complications and the nephrometry scoring for complexity of lesions [27, 91]. Going forward, using these classification structures will help with future meta-analysis. Standard definitions of intraoperative complications have not yet been established.

Conclusion

Since the first transperitoneal laparoscopic partial nephrectomy performed in 1993 by McDougall et al. [92] in a porcine model, significant advances in minimally invasive nephron-sparing techniques, along with development of new instrumentation, have led to the performance of safe and effective MIPN. It is established that MIPN has a shorter hospital stay compared to open [4]. Long-term outcomes following MIPN are not yet available. The current trend using the robotic platform has expanded the role of MIPN to include more complex tumors.

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Surgery for Renal Cell Carcinoma with Thrombus Extension into the Vena Cava

15

Chad Wotkowicz and John A. Libertino

Introduction

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 and 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 our outcomes data from 300 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.

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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 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 authors have proposed a variety of classification systems, the primary outcome in most cases will depend on surgical experience and confidence.

Renal cell carcinoma has long been called the internist's tumor because of the myriad of symptoms this particular malignancy can present with (Chart 1) [7]. More concerning are the symptoms that tumor thrombi can produce (Chart 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).

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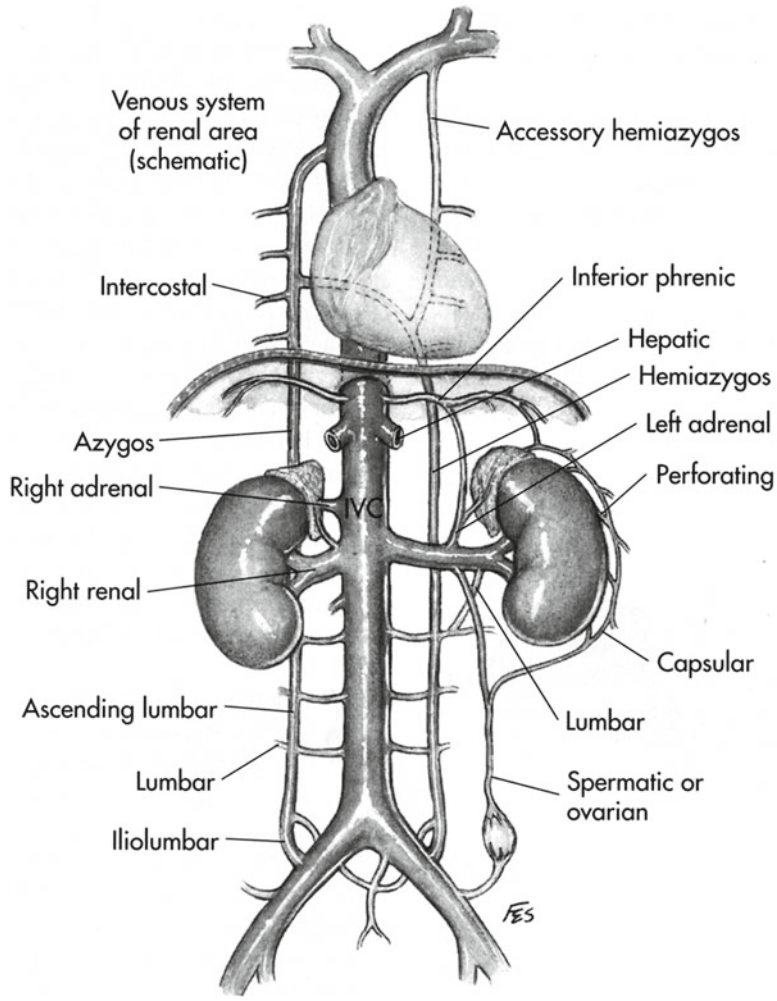


Fig. 15.1 Relevant venous anatomy of the kidney and retroperitoneum

The presentation and diagnostic evaluation of RCC and tumor thrombus has been described elsewhere in this text and will not be discussed 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 performes at the time of preoperative renal artery embolization (Fig. 15.3). Additionally we employ preoperative TEE and coronary angiography to assess the potential for cardiac revascularization which can be performed concomitantly. The primary goal with preoperative imaging is to determine the extent of 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 provide improved survival rates [9].

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 4 weeks prior to planned neph-

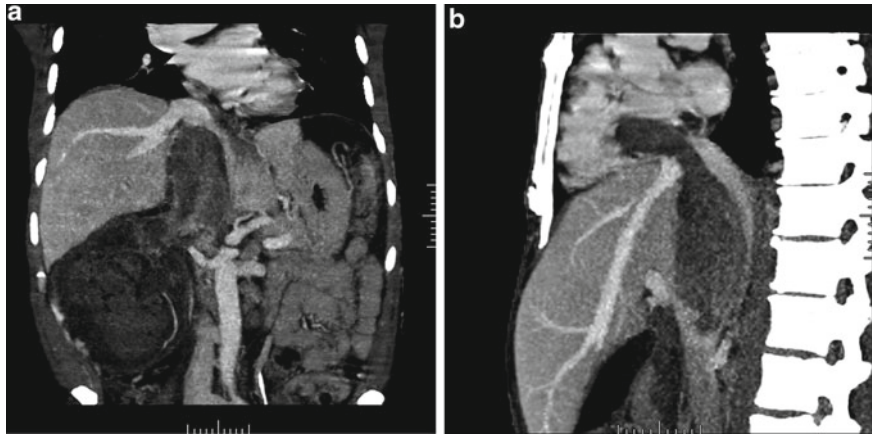


Fig. 15.2 Imaging reconstructions demonstrate extension of a large right renal cell carcinoma with tumor extension into the right atrium

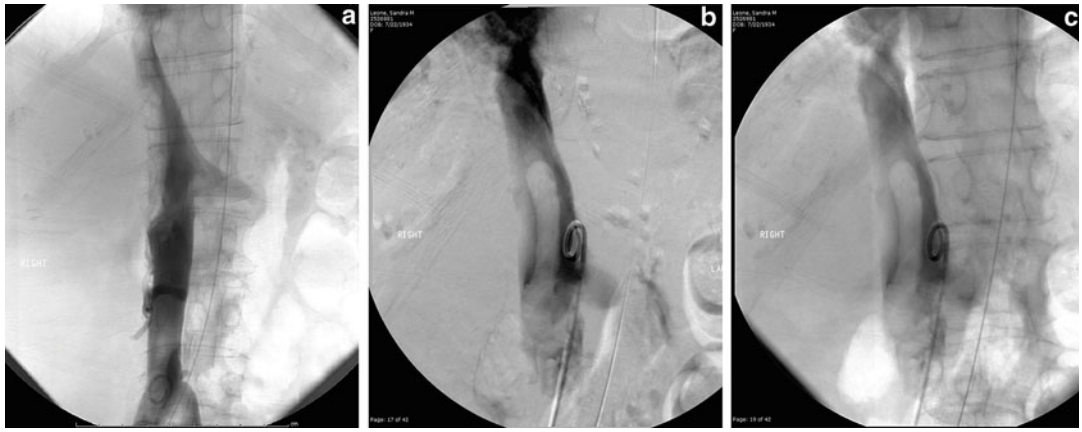


Fig. 15.3 Cavagram series demonstrating thrombus within the inferior vena cava. MRI is used in conjunction to differentiate tumor from bland thrombus

rectomy (Fig. 15.4). The primary purpose of this technique is to provide some insurance against excessive blood loss and 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 may activate 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 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

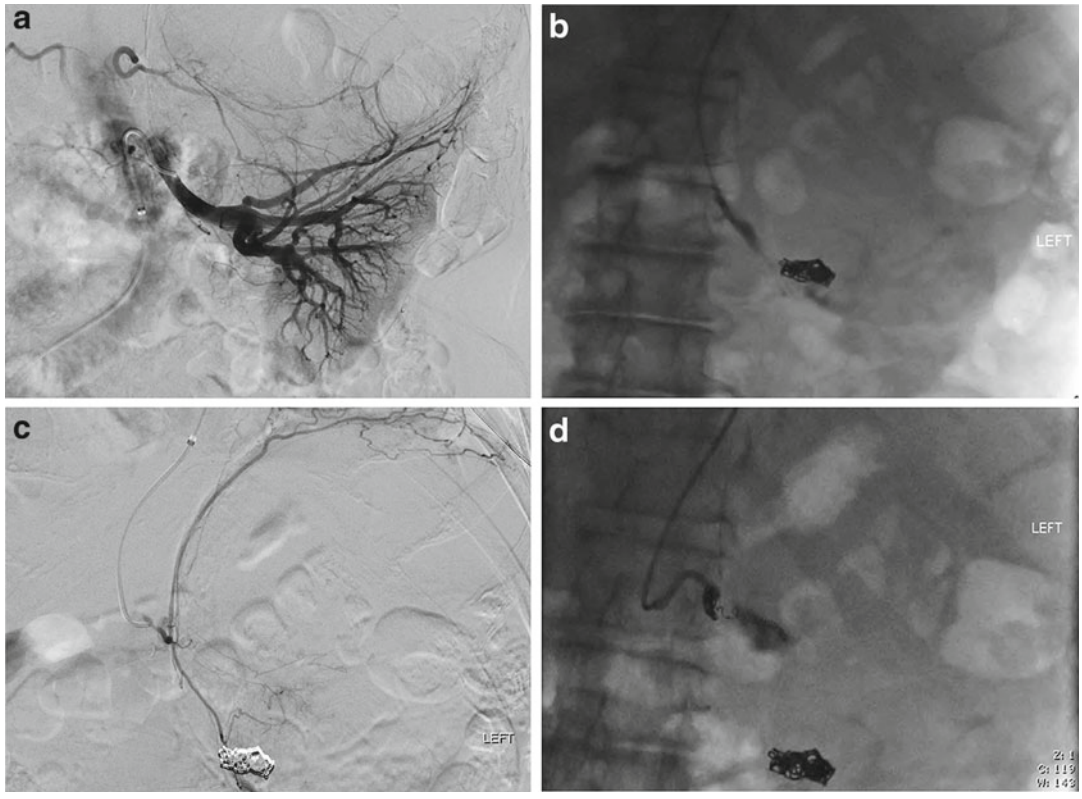


Fig. 15.4 (**a**) Left aortogram demonstrating hypervascular left renal mass. (**b**) Left brachial artery was accessed for embolization of left renal artery using purified ethanol followed by platinum coils. (**c**) Inferior phrenic artery was cannulated and demonstrated tumor vascularity. Embolization performed with purified ethanol and coils. (**d**) Successful embolization of inferior phrenic artery with diminished flow to left kidney

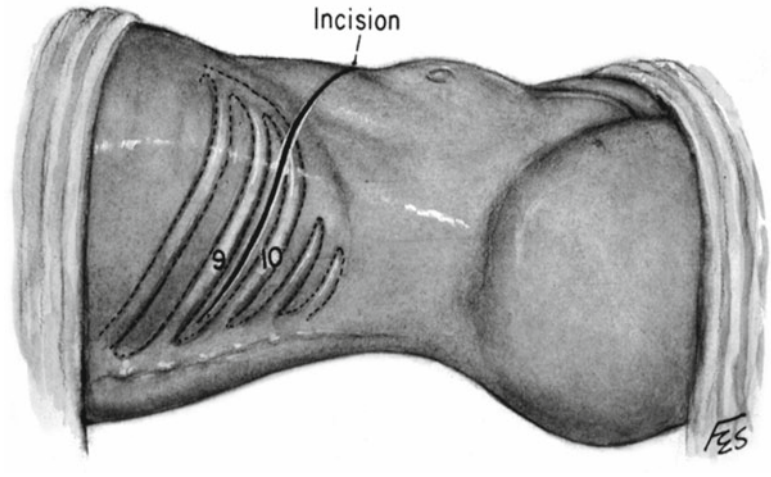


Fig. 15.5 Thoracoabdominal incision for renal vein tumor thrombus. Curve-linear supratenth incision extending to the midline

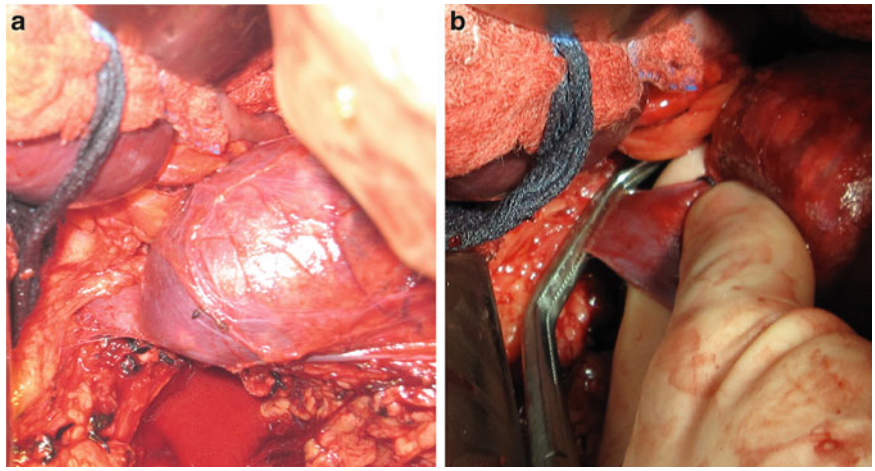


Fig. 15.6 Large renal vein thrombus is milked back to expose the confluence of the RV/IVC for placement of the Satinsky clamp

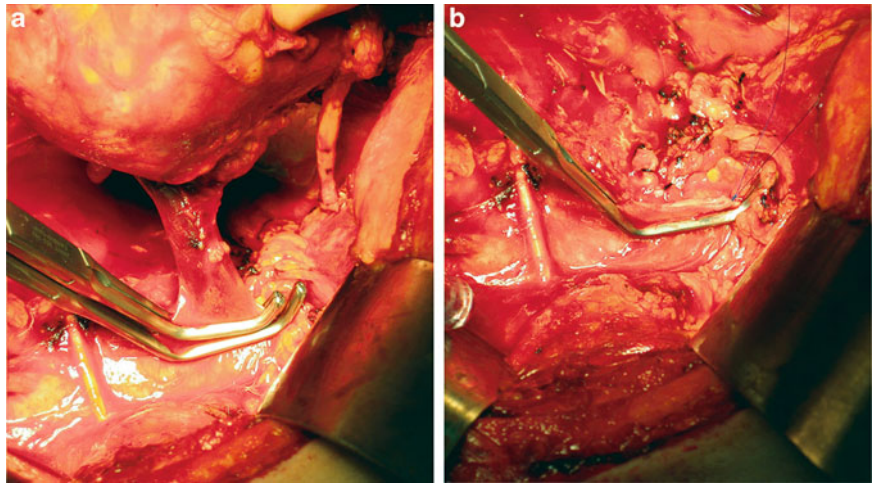


Fig. 15.7 A second Satinsky clamp is placed taking caution not to limit the circumference of the IVC following caval reconstruction

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 the second clamp in place to facilitate reconstruction of the IVC with 4-0 polypropylene suture in a running fashion (Figs. 15.6–15.9).

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

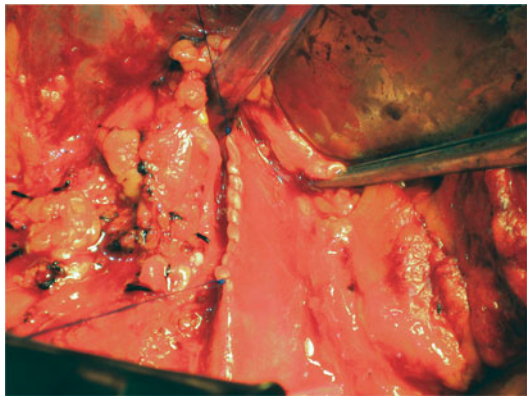


Fig. 15.8 Closed cavatomy with running 4-0 polypropylene (Prolene)

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 angioinfarction prior to resection. It should be mentioned here 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 porta hepatis. Perforating minor hepatic veins can be sacrificed 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 occur if one performs enough resections, and these injuries are best dealt with utilizing gentle pressure proximally and distally. We advocate utilizing sponge sticks 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.

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 artery to rule out incomplete embolization. If any question exists, one can utilize intraoperative Doppler. If there is still concern, we strongly advocated isolation, ligation, and division of the renal artery before tumor thrombectomy with large Hem-o-Lok clips or suture ligation.

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. 15.11–15.17). 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 cavatomy is almost always due to a missed lumbar vein. An Allis clamp can serve as a tag while placing figure-of-eight stitch 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 reconstruction

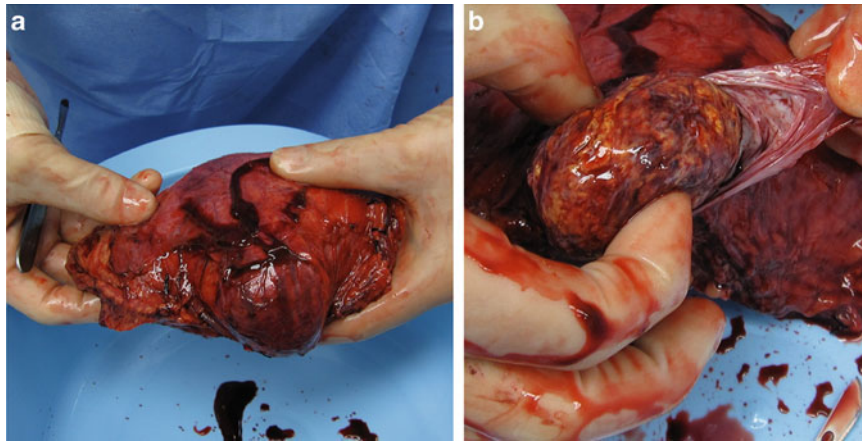


Fig. 15.9 Kidney specimen with thrombus in the renal vein

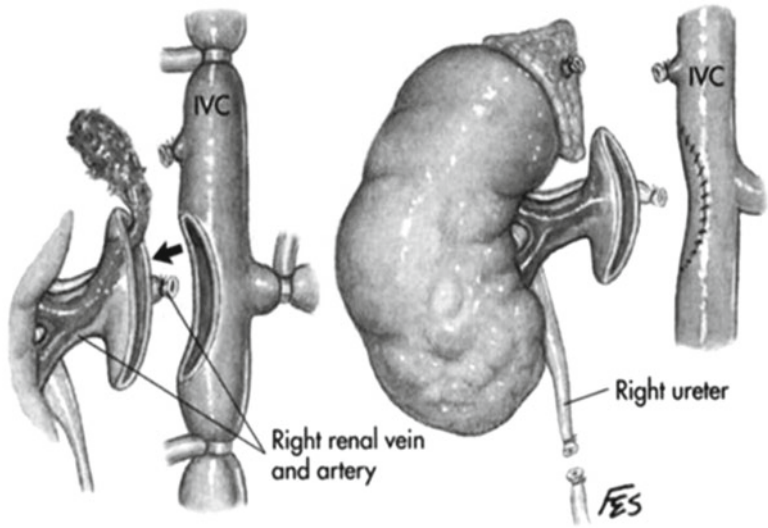


Fig. 15.10 Removal of infrahepatic tumor thrombus demonstrating placement of the Rummel tourniquets. Occasionally large lumbar veins will need to be dissected and treated with tourniquets as well

or 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 arrest and 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 and within the right atrium. In addition to describing out technique, we would also like to highlight other surgical techniques utilized by our contemporary colleagues in managing

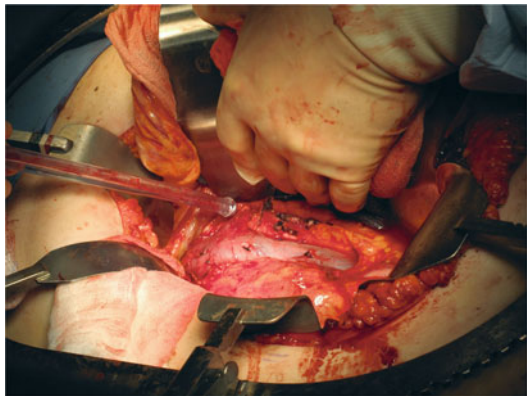


Fig. 15.11 Left renal cell carcinoma with tumor thrombus at the renal vein confluence. Patient had a previous caval filter placed precluding atraumatic placement of Satinsky clamps

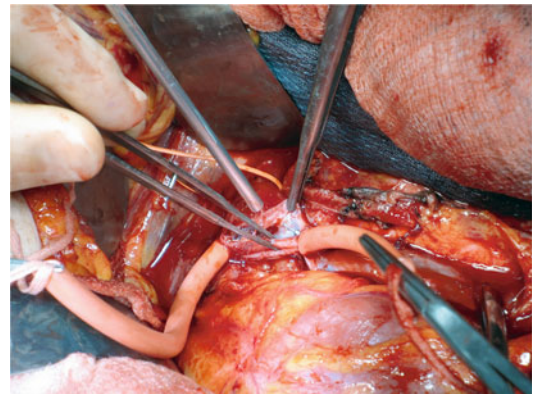


Fig. 15.14 Cavatomy demonstrates IVC filter

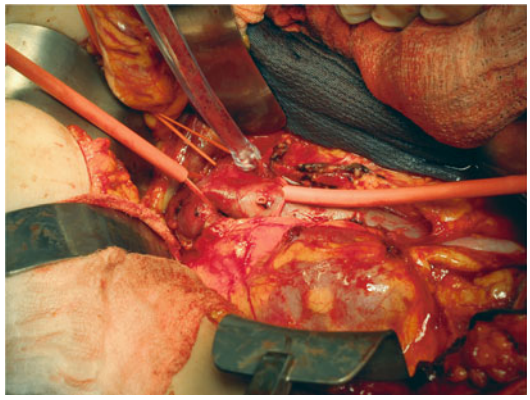


Fig. 15.12 Smaller *red* vessel loop in foreground isolated the contralateral retrocaval right renal artery. The caudal Rummel tourniquet is around the proximal portion of the inferior vena cava above the previous filter. Cephalad Rummel tourniquet encompasses the suprarenal IVC and contralateral right renal vein

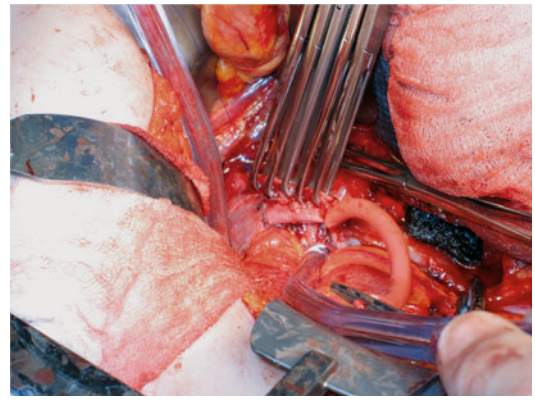


Fig. 15.15 After removal of thrombus and ligation of the left renal vein, Allis clamps are utilized to reapproximate IVC prior to reconstruction

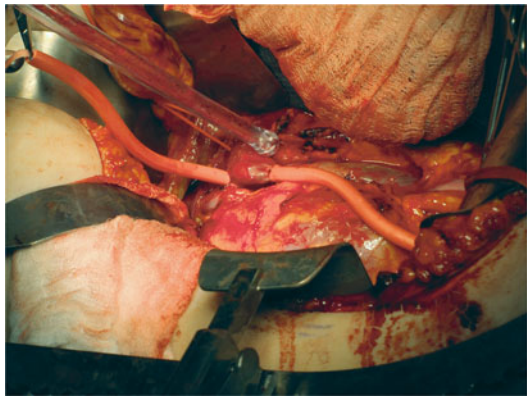


Fig. 15.13 Rummel tourniquets are cinched in place in preparation for anterior longitudinal cavatomy

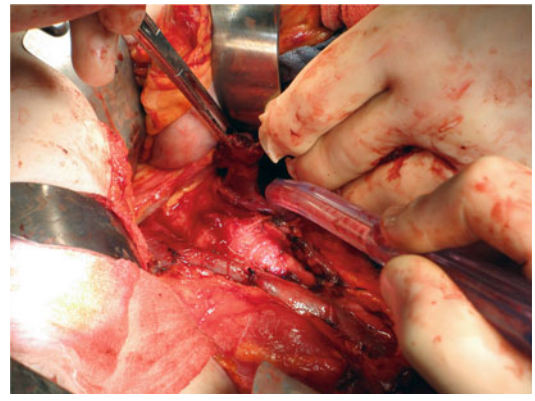


Fig. 15.16 Left renal vein with tumor thrombus noted in lumen. Cavatomy has been closed with running 4-0 Prolene suture

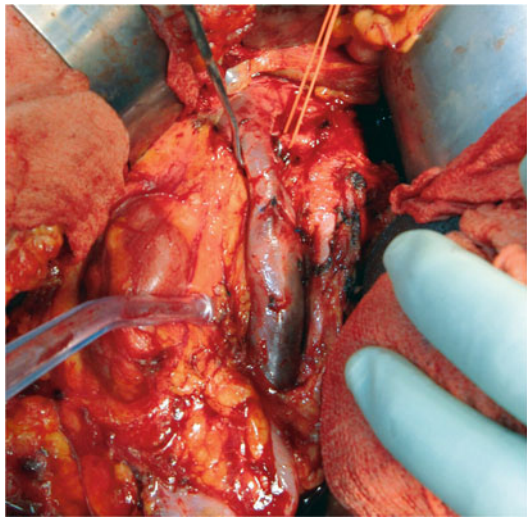


Fig. 15.17 Closed cavatomy

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 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 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 described, dividing the ligaments (falciform, triangular, superior coronary, and ligamentum teres) and 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 major 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 for any metastatic disease that

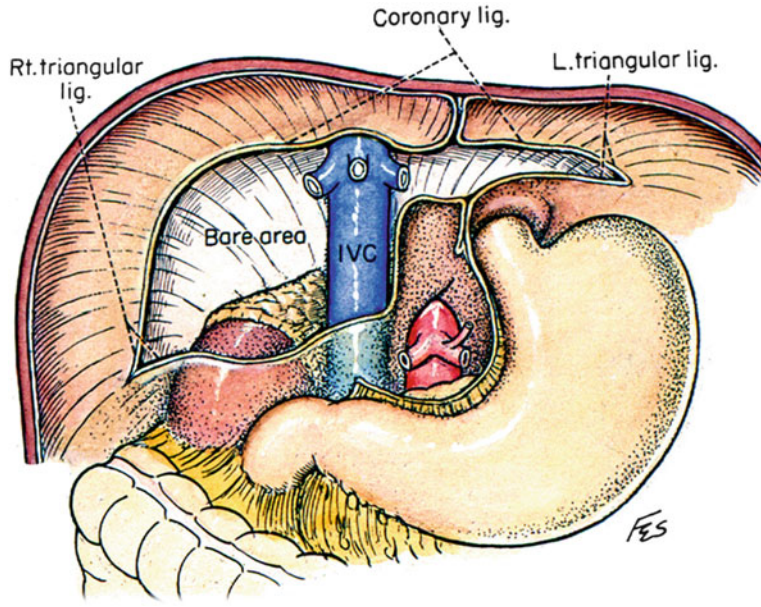


Fig. 15.18 Anterior schematic of the infrahepatic IVC demonstrating the relationship between the major hepatic veins and the diaphragm

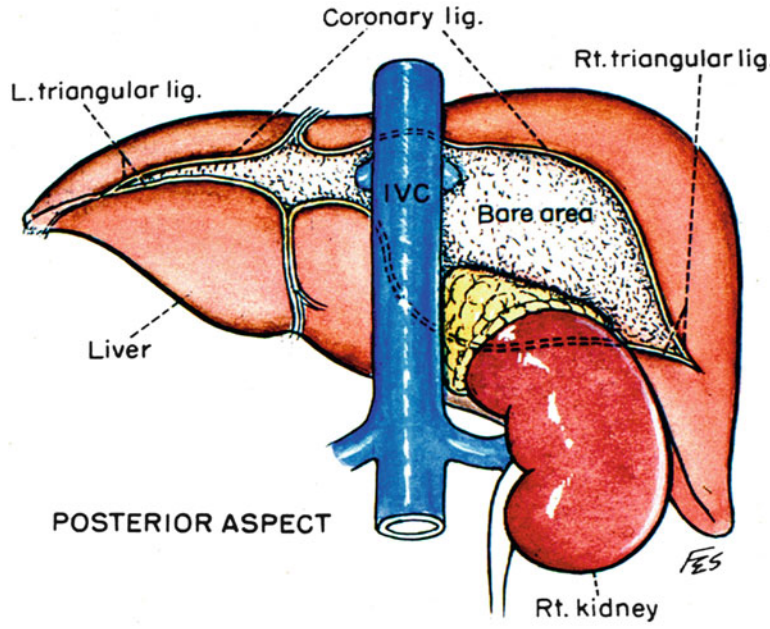
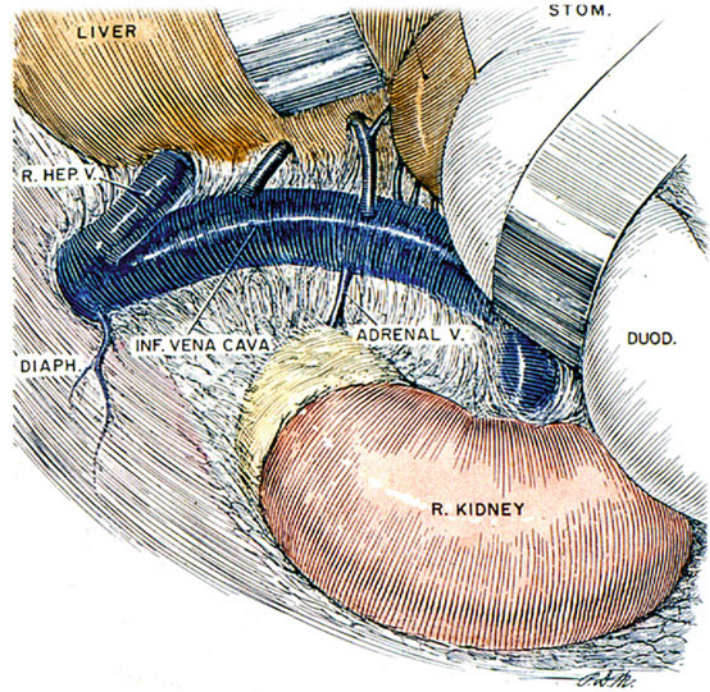


Fig. 15.19 Posterior view of the IVC

may have been undetected by preoperative imaging. 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

Fig. 15.20 Langenbeck



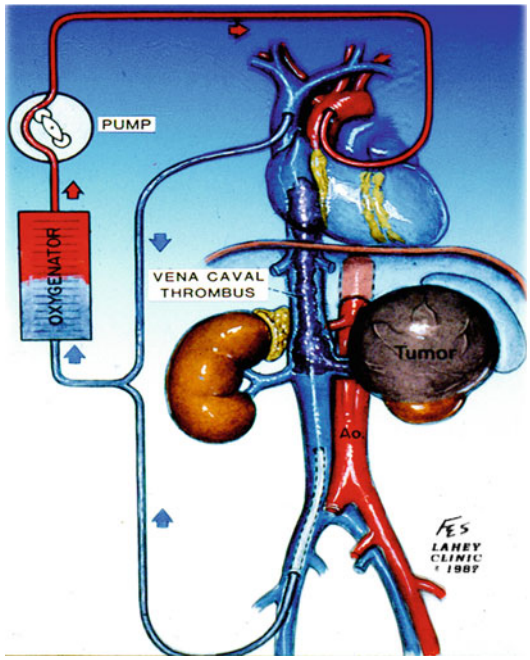


Fig. 15.21 Traditional cardiopulmonary bypass

common iliac bifurcation. The contralateral renal vein is also exposed to avoid damage during the cavatomy.

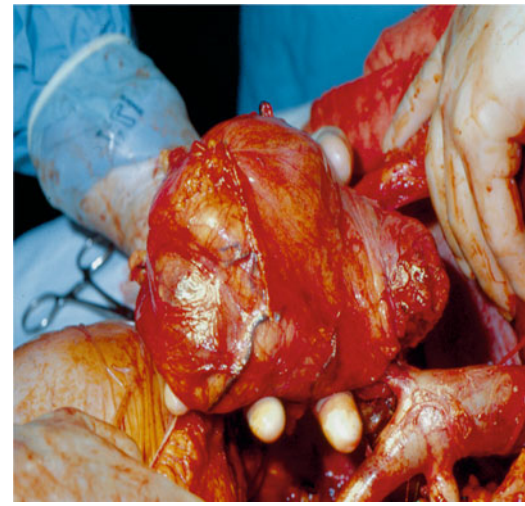


Fig. 15.22 Complete mobilization of the affected kidney with traditional cardiopulmonary bypass

At this time the patients are placed on systemic heparin and traditional bypass initiated with cannulation of the ascending aorta proving 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

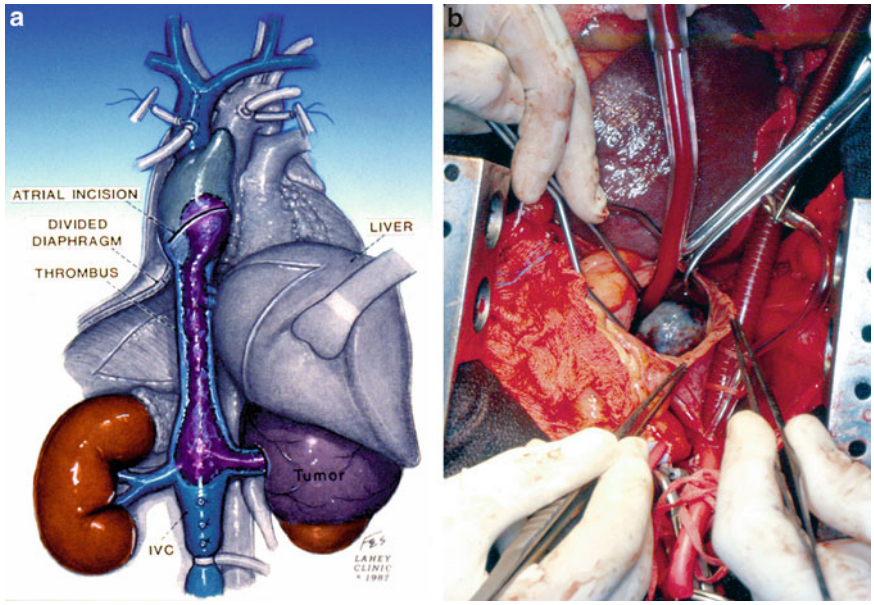


Fig. 15.23 Right atriotomy demonstrating tumor thrombus in the right atrium

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 extend 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 Trendelenburg's position and using positive pressure respirations. Ideally the thrombus and 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

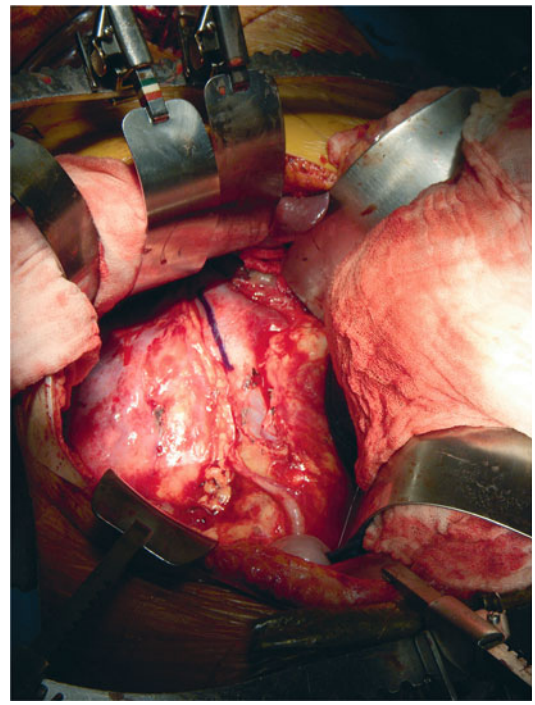


Fig. 15.24 Planned anterior longitudinal cavatomy for larger right renal cell carcinoma with caval tumor thrombus

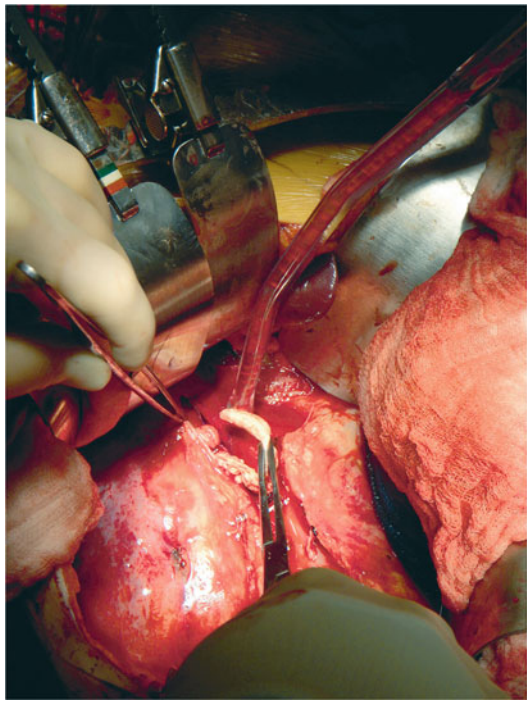


Fig. 15.25 Following cavatomy the thrombus is removed with a pair of forceps and the caval wall is inspected for invasion

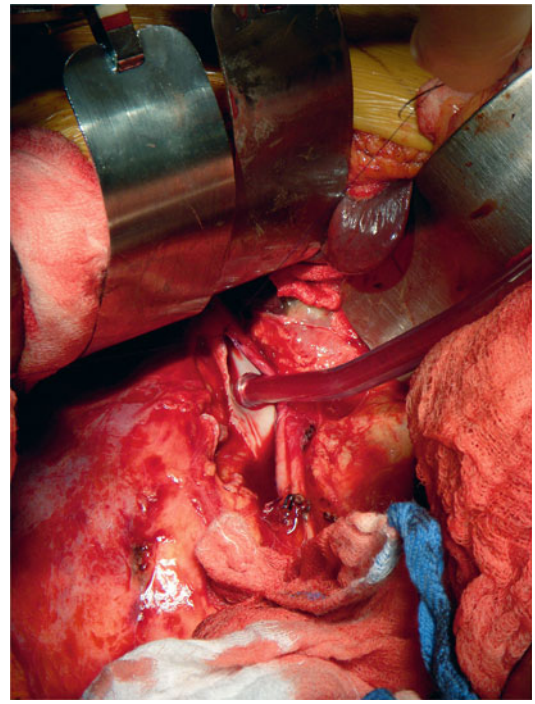


Fig. 15.26 The caval wall is inspected for any of caval wall invasion. A running 4-0 polypropylene suture is started at the cephalad portion of the cavatomy

replaced completely by the minimally invasive approach discussed next. If there is a need for coronary revascularization, the traditional approach should be employed.

Cardiopulmonary Bypass (Minimally Invasive)

First described at Lahey Clinic 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 mobilized along the entire anterior surface with minimal trauma and without mobilization of the kidney. 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 removed, 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 for venous return. 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 rewarmed and protamine sulfate, fresh frozen plasma, platelets, and desmopressin are administered in order to offset coagulopathies.

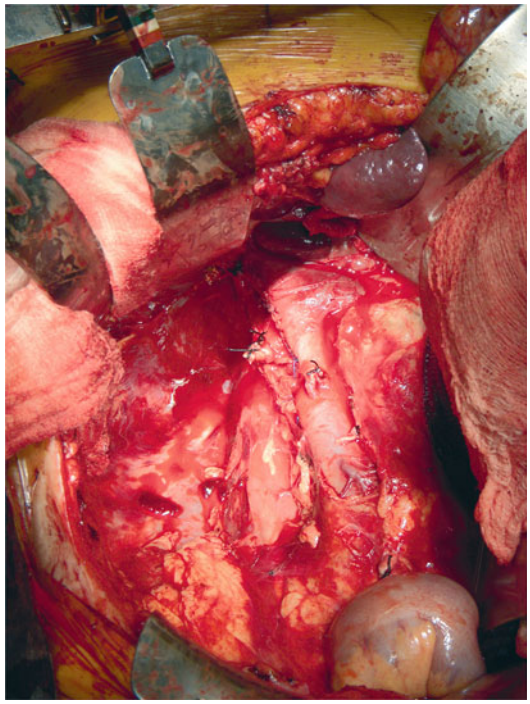


Fig. 15.27 The renal artery is double ligated with 0 silk suture and the cavatomy is closed without significant reduction in the lumen diameter. The gonadal vein has been sacrificed in the foreground

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 tumor thrombus level, one must inspect the caval wall for suspected invasion and perform 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 [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 suprarenal 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 laparoscopy 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 has published their results utilizing the da Vinci robot to treat five patients with tumor thrombi involving the inferior vena cava [22].

Partial Nephrectomy and Tumor Thrombus

At our institution we have an extensive experience utilizing partial nephrectomy to preserve renal function; however, we would only advocate this approach with tumor thrombus involving only major branch of the renal vein with a patent

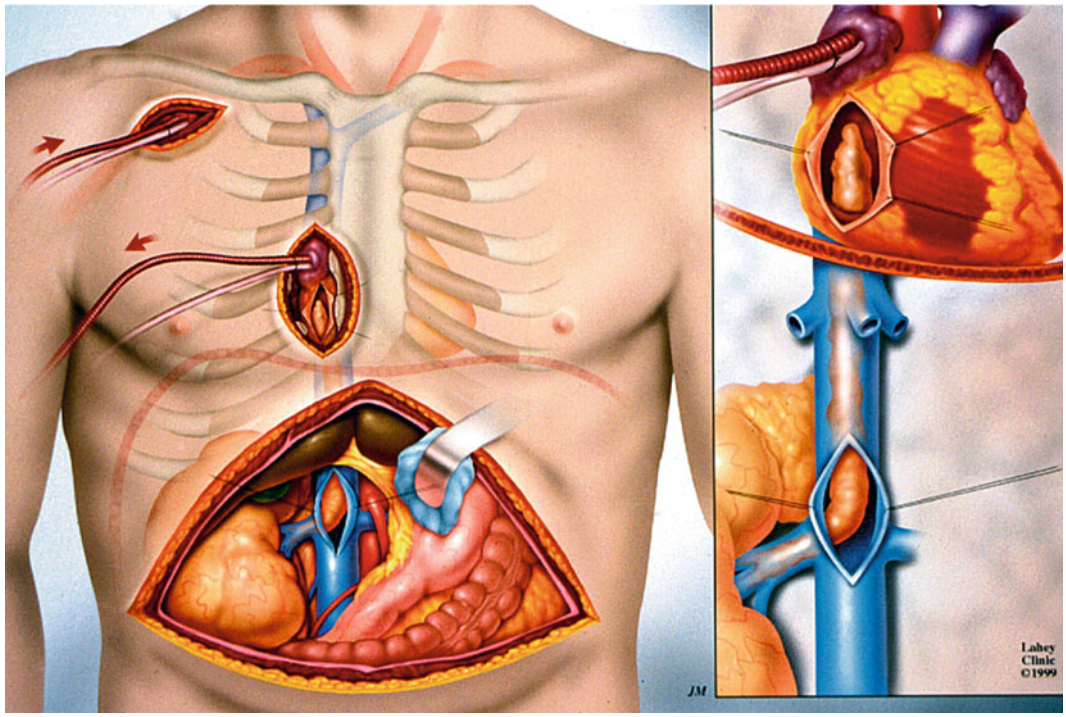


Fig. 15.28 Minimally invasive cardiopulmonary bypass for removal of a large right renal mass with tumor thrombus extending to the right atrium. Schematic demonstrates right subclavian artery graft and right atrial venous cannulation

main renal vein, in a patient with a solitary kidney. Kim and colleagues describe 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 [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, 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 of 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

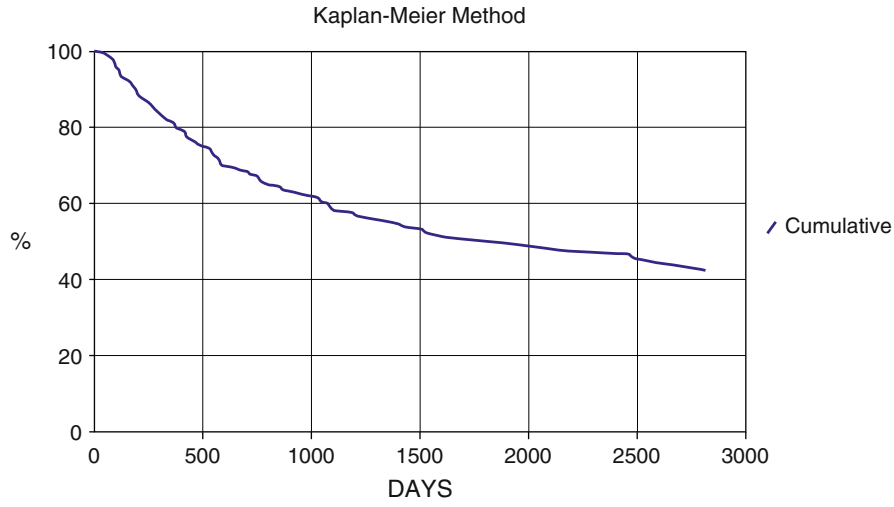


Fig. 15.29 Overall disease-specific survival ($n=300$) median – 18 months, mean – 44 months

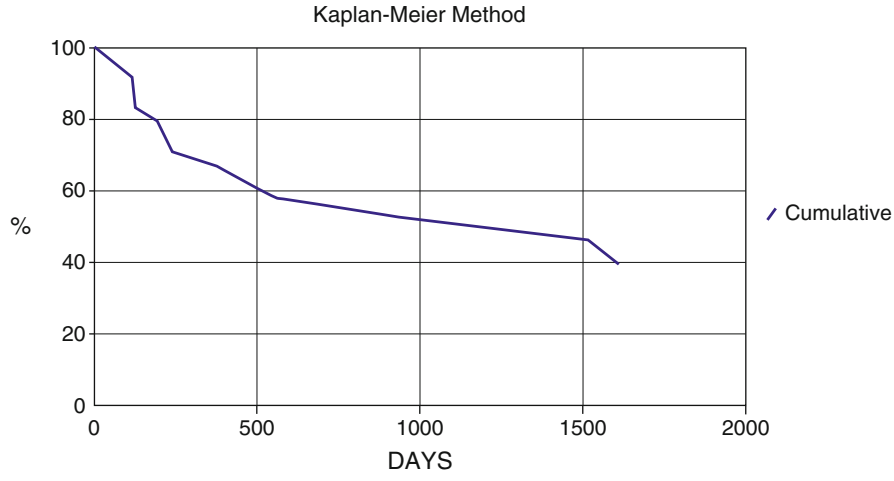


Fig. 15.30 Overall disease-specific survival – atrium ($n=31$)

clamps [26]. We remain optimistic that non-pulmonary 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.

Lahey Clinic Experience

We have treated over 300 patients with renal cell carcinoma and caval tumor thrombus (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. Tumor thrombus extension and survival data are illustrated in this section. Our complication and survival rates

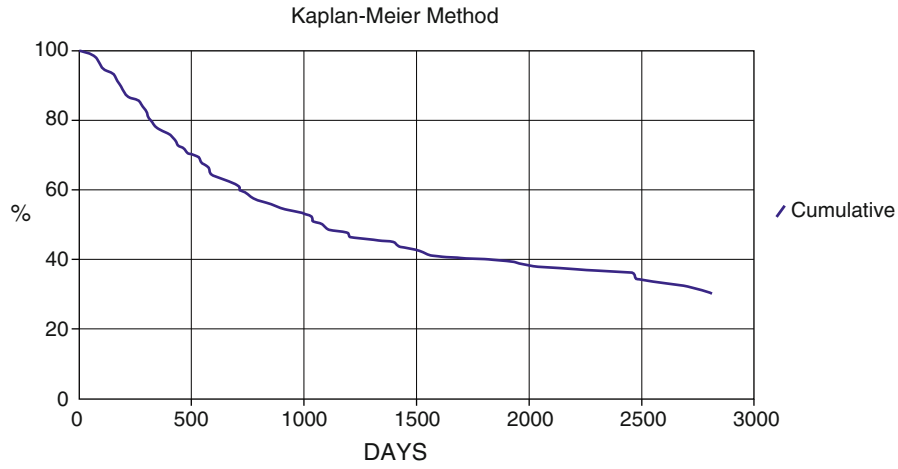


Fig. 15.31 Overall disease-specific survival – vena cava ($n = 146$)

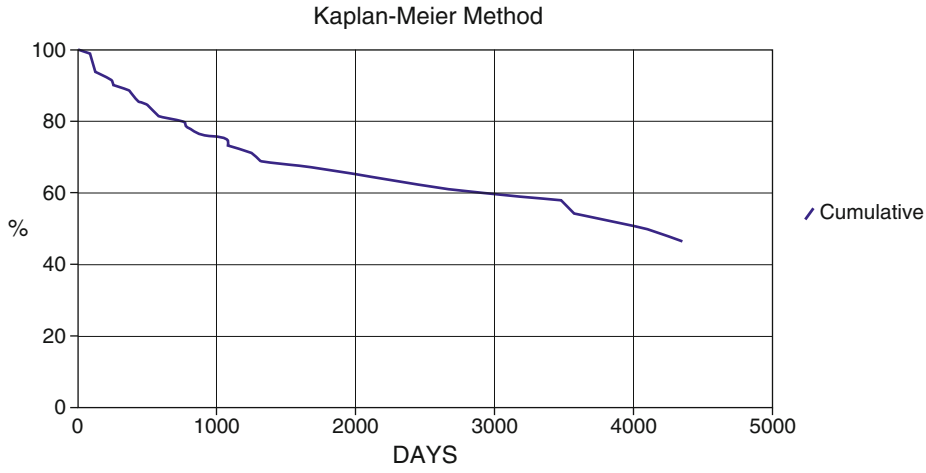


Fig. 15.32 Overall disease-specific survival – renal vein ($n = 123$)

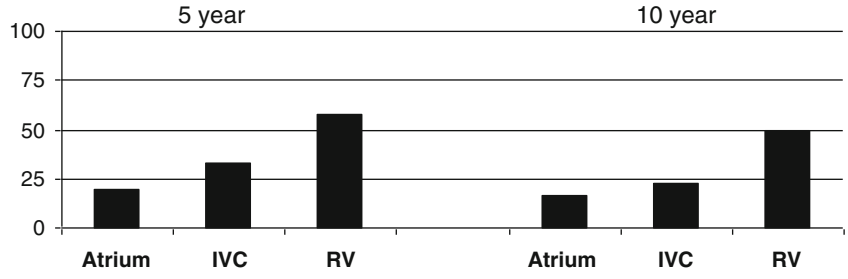


Fig. 15.33 Cancer-specific survival

are well within the average of our contemporary colleagues. 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 [27].

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

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

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Role of Lymphadenectomy

16

Hein Van Poppel

Introduction

To date, no data have clearly demonstrated which patients should undergo surgical extirpation of regional lymph nodes (lymphadenectomy or lymph node dissection, LND) in the treatment of renal cell carcinoma (RCC). Despite decades of evaluation, the therapeutic benefit of LND in the management of RCC remains controversial. The rising use of routine computerised 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 localised disease is small (1–5 %) [1–3]. The 5-year overall survival (OS) in these patients is poor and ranges from 15 % to 30 % [4–6]. The anatomic localisation of metastases is unpredictable due to the relatively heterogeneous metastatic spread of RCC through both haematogenous and lymphatic routes. The absence of a demonstrated therapeutic benefit, as reported in the European Organization for Research and Treatment of Cancer (EORTC) trial number 30881 [1], has created controversy regarding the necessity and extent of LND, formerly considered mandatory at the time of radical nephrectomy (RN) [7]. 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 [8]. 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

The patterns of renal lymphatic drainage were initially described by Parker in 1935, during anatomical studies of the posterior lymphatic channels of the abdomen. He found that the pathways of drainage could be quite variable [9]. Assouad et al. [10] 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). However, in one-third of the patients, renal lymphatics have been found draining directly into the thoracic duct [10]. Saitoh and colleagues [11], in an autopsy study of 1,828 cases of renal cancer, observed extremely wide variation in the anatomic localisation of lymph node metastases from RCC. There was a low incidence of metastases to the ipsilateral adrenal and renal hilar lymph nodes in nephrectomised cases [11]. Johnsen and Hellsten [12] in an autopsy study, analysing 554

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patients with renal cancer, 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, the 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 [12]. Another confounder is the predilection of RCC for early haematogenic dissemination without lymph node infiltration. Vasselli et al. [13] reported an incidence of 53 % of distant metastasis without lymph node invasion. 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 [14].

Extent of LND for RCC and Templates

There is no consensus on the anatomic extent of LND for RCC management. The limits of the extended LND during RN for RCC have changed over the years. In 1969 Robson and colleagues [7] included an extended LND 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 [7]. 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 [15].

Templates proposed for extended LND 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 [16]. Figure 16.1 shows an extended LND; a views after removal of the specimen (Fig. 16.1a) and the specimen with RN and "en bloc" LND (Fig. 16.1b).

Herrlinger et al. [17] evaluated in a retrospective study whether the extent of LND had any significant effect on patient survival. They compared the outcomes of 320 patients who underwent extended LND with data of 191 patients who underwent only "facultative" LND (removal of no or only a few nodes for staging purposes). Positive lymph nodes were found in 17.5 % of those undergoing extended LND and in 10 % of those undergoing facultative LND. OS improved for extended LND when compared with the OS for facultative LND from 58 % to 66 % after 5 years and from 40.9 % to 56.1 % after 10 years. The authors suggest that the improvement in survival may be due to the excision of undetected micrometastatic disease. They concluded that extended LND improves the prognosis of RCC patients without any additional morbidity and suggest that extended LND is superior over facultative LND [17].

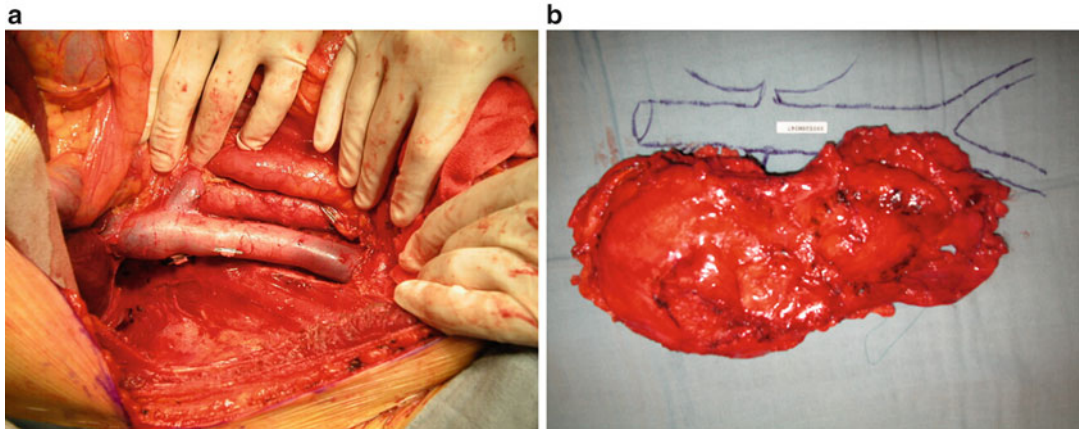

Fig. 16.1 (**a**) Extended lymph node dissection, view after removal of the specimen. (**b**) Specimen with radical nephrectomy and "en bloc" lymph node dissection

Several authors reported on the impact on survival of analysing the number of dissected nodes, instead of anatomical extension of the LND. For performing an accurate LND, some authors suggest a removal of minimum eight lymph nodes [18, 19]. However, according to Terrone et al. [20], at least 13 nodes should be excised to provide adequate staging. They reviewed the reports of 725 patients with RCC submitted for RN. LND was performed in 608 patients (83.8 %). The rate of lymph node metastases in these patients was 13.6 %. The patients were divided into five groups according to the number of nodes removed. When ≥13 lymph nodes were removed, the rate of pN+ increased from 10.2 % to 20.8 % ($P<0.001$). The authors observed that for organ-confined and locally advanced tumours, there was a statistically significant difference in the pN+ rate between patients with <13 and ≥13 nodes examined (3.3 % vs. 10.5 % and 19.7 % vs. 32.2 %, respectively). A minimum of 13 lymph nodes should be assessed for optimal staging and prognosis [20]. Schafhauser et al. [21] found a similar cut-off of 14 lymph nodes [21]. The required number of lymph nodes examined to provide optimal nodal staging is not well defined by the American Joint Committee on Cancer (AJCC). Joslyn et al. [22] retrospectively studied 4,453 RCC patients from the Surveillance, Epidemiology, and End Results (SEER) database who had undergone RN with or without regional LND. Overall, 1,558 (55 %) of the 2,831 patients with known lymph node removal status had had at least one lymph node examined. The authors assessed the extent of LND using the number of nodes examined and the nodal burden using the ratio of the number of positive nodes to the total number of nodes examined. They found an inverse correlation between the number of nodes examined and cancer-specific survival (CSS). An increase in the total number of positive nodes and in the nodal burden was associated with worse CSS, although they were not independent predictors of RCC-specific mortality [22]. 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 [23]. Recently, Crispen et al. [15] proposed a standard surgical template for LND based on locations of lymph node involvement (LNI). 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 a LND, the paracaval and interaortocaval lymph nodes are removed in patients with right-sided tumours and the para-aortic and interaortocaval lymph nodes are removed from the crus of the diaphragm to the common iliac artery [15]. Many surgeons attempt to decrease morbidity by limiting the extent of dissection. However, the extent of a limited regional LND for right and left kidney is still unclear. Regional LND for the right kidney may include the hilar, para- and precaval lymph nodes and for the left kidney the hilar, para- and preaortic lymph nodes [24]. Disagreement continues about the ideal limits of LND. More recently, Whitson et al. analysed the 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 ten nodes resulted in a 10 % absolute increase in CSS at 5 years in this subset of patients [25]. 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

The most common complications associated with the surgical treatment of RCC are lymphocoele, chylous ascites, bleeding from lumbar or major vessels and damage to adjacent organs [1]. 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 [1]. LND is still a highly complex procedure and should be performed by well-trained surgeons.

With the increased use of laparoscopic techniques in 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. An initial report of laparoscopic RN with hilar LND in patients with advanced RCC noted a mean of only 2.7 lymph nodes [26]. However, another report 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 extended LND. The overall risk of intraoperative and postoperative complications was similar between the group undergoing laparoscopic RN with LND and the group without LND [27].

Tumour, Node, Metastasis (TNM) Staging System

Currently, the most commonly used staging system for RCC is the tumour-node-metastasis (TNM) system. In the 2002 AJCC version, LNI is defined as pNx (unresected nodes because they cannot be assessed), pN0 (negative nodes), pN1 (one metastatic lymph node) or pN2 (>1 metastatic lymph node) [28].

Several studies reassessed the current nodal staging system for RCC [6, 29, 30]. The major adjustment in the AJCC v.7 nodal staging system is combining the previously named N1 (1 positive node) and N2 (>1 positive node) patients into a single group, pN1 (positive regional nodes) [31]. This change was based on the finding that although 5-year recurrence-free survival and CSS rates were poorer in pN+ than in pN0 patients, no survival difference was found between those with pN1 and those with pN2 [6, 29, 30]. Terrone et al. [6] tried to improve the clinical impact of the current TNM lymph node staging for RCC by considering an additional parameter, that is, lymph node density (ratio between number of positive lymph nodes and total number of lymph nodes retrieved). They evaluated the outcome in 618 patients who underwent lymphadenectomy along with RN for RCC. The rate of positive lymph nodes (pN+) was 14.2 % (88 of 618). Patients with lymph node density >60 % had worse OS on multivariate analysis. The study showed that the current TNM stratification of RCC patients with positive nodes is not correlated with clinical outcome and that classification as ≤4 or >4 positive lymph nodes involved, supported by lymph node density (>60 %), better reflects the impact of the disease on survival [6]. In addition, Dimashkieh and colleagues [29] showed that the presence or absence of extranodal extension may further improve the prognostic accuracy of the current pN classification. The study included 34 patients with pN1 metastases and 35 with pN2 metastases. The study showed no statistically significant association between the pN classification and death from RCC (pN2 vs. pN1 RR 1.05, 95 % CI 0.62–1.79, $P=0.846$). However, patients with extranodal extension were twice as likely to die of RCC compared with patients in whom the metastases did not extend outside of the lymph node capsule (RR 2.02, 95 % CI 1.18–3.45, $P=0.010$). The 5-year CSS was 18 % and 35 % following nephrectomy in patients with (41 %) and without extranodal extension (59 %), respectively ($P=0.01$) [29]. In contrast, Kwon and colleagues [30] found that extranodal extension and lymph node density, as well as the location of involved lymph nodes or the presence of lymphovascular invasion, did not significantly correlate with prognosis in RCC patients. The authors stratified 1,503 patients who had undergone nephrectomy according to the number, location and size of lymph node metastases. They found that lymph node size (<3 cm vs. ≥3 cm) better reflected the impact of the disease on survival. The therapeutic role of lymphadenectomy might be limited to diagnostic purposes and reducing local recurrence in patients with clinical or radiologic suspicion of lymph nodes with size <3 cm [30].

False-Positive and False-Negative CT Findings

Today, patients with micrometastases in normal-sized lymph nodes who might benefit from LND [32] cannot be visualised by the currently

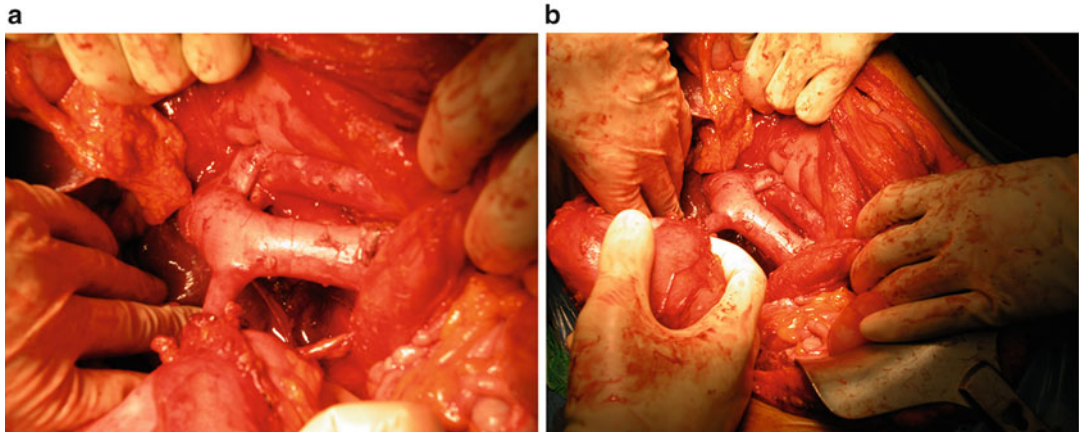

Fig. 16.2 (**a** and **b**) Lymph node dissection for CT-scan suspicious nodes, in conjunction with partial nephrectomy

available imaging techniques [33]. Therefore, the absence of any evident lymph node metastasis with modern imaging technology should not rule out a regional LND. Figure 16.2a, b shows a LND for CT-scan suspicious nodes, in conjunction with PN.

For microscopic LNI, CT scan gives both false-positive and false-negative images [34]. Studer et al. [34] 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 the other 25 patients (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 ($P=0.0044$) [34]. The study supports the need for extended LND in patients where accurate staging is important. Because current imaging techniques are unable to differentiate lymph node metastasis from enlarged inflammatory nodes, routine LND is recommended for any individual with radiologically identified lymphadenopathy [24].

Prevalence of Lymph Node Metastasis

The incidence of lymph node metastasis has decreased over time. The early study of Robson et al. [7] and the more recent EORTC 30881 study of Blom et al. [1] reported an incidence of positive lymph nodes of 22.7 % and 4 %, respectively [1, 7]. Giberti et al. [35] evaluated the LNI in RCC in 328 patients and found 20.4 % pN+ and 7.0 % pN+M0 patients. Stage pN+M0 occurred in 6.3 % of patients with pT1 stage ($n=32$), 5.2 % of patients with pT2 stage ($n=135$) and 9.7 % of patients with pT3 stage ($n=145$) [35]. In most historical series, incidence of positive lymph nodes among patients undergoing RN and lymphadenectomy ranges from 23 % to 35 % [3, 7, 36, 37]. In contemporary series smaller asymptomatic lesions are diagnosed with rising frequency, and the rate of positive lymph nodes has decreased significantly. Nowadays, the incidence of pathologically positive lymph nodes (pN+) in a low-risk population of clinically node-negative and metastasis-negative (cN0M0) patients ranges from 1 % to 5 % [1, 2, 38, 39].

Higher clinical stage and higher pathological tumour grade are associated with higher rates of positive nodes. Giuliani et al. (1990) reported 13.2 % and 36.1 % positive nodes in stage pT1–2 and pT3–4, respectively [40]. Pantuck et al. [3]

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 [3]. Blute et al. [2] noted on a multivariate analysis that the risk of dying from RCC was 7.87-fold higher with LNI at nephrectomy than without. Pantuck et al. [3] reported that patients who did not undergo LND were three times more likely to die than those who underwent the procedure. Recurrence rates were similar regardless of the extent of LND ($P=0.57$) [3].

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 [3, 7, 22, 35, 41]. The great challenge is to accurately identify those patients that would most benefit from LND.

Protocols and Nomograms

Blute et al. [2] retrospectively reviewed an institutional cohort of 1,652 patients from the Mayo Clinic surgically treated for clinically nonmetastatic (M0) clear cell RCC (68/1,652 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 [2]. 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 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 [15]. External validation of the protocol is needed to confirm these findings. The difficulty with the application of the protocol is that in routine clinical practice, the utility of the protocol is limited as frozen section analysis to determine the risk features is not available at all institutions [32].

Hutterer et al. [42] developed a preoperative nomogram based on patient age, symptom classification and tumour size to predict the probability of LNI. They evaluated the probability of nodal metastases in seven European centres ($n=2{,}522$) and externally validated it against patients of another five European centres ($n=2{,}136$). On multivariate analysis, only tumour size and symptom classification were independent predictors of nodal metastases. External validation demonstrated 78.4 % accuracy [42]. 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.

Intraoperative Lymph Node Assessment

In the EORTC study 30881, 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 [1]. Intraoperative 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 [43].

Sentinel Lymph Nodes

Sentinel node biopsy is widely used for nodal staging of melanoma and breast cancer. Bex et al. [44] were the first to explore the sentinel node technique for RCC. They evaluated the feasibility of intratumoural injection of radiolabelled technetium Tc 99 m nanocolloid under ultrasound guidance followed by lymphoscintigraphy and hybrid single-proton emission 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 visualisation of one or more nodes. In total, two retrocaval sentinel nodes and four interaortocaval sentinel nodes were found (including one hilar). One patient showed drainage to an extraperitoneal sentinel node, located along the internal mammary chain. In two patients no lymphatic drainage could be demonstrated. The authors conclude that sentinel lymph node sampling is feasible and safe, and its use may improve the insight in renal lymphatic drainage. Studies are necessary to further explore this technology [44]. Most of the nodes were within the template as described by Crispen et al. [15].

When to Perform LND?

Localised Disease (cT1–2N0M0)

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 randomised to undergo RN plus extended LND ($n=362$) 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 lymphadenectomy [1]. Comments on the study design of the EORTC 30881 study undermined the clinical applicability of its results: (1) low number of node-positive patients (majority of patients included would not need a LND), (2) the study is underpowered to conclude that the outcome in both arms is equivalent, (3) the number of nodes resected is not recorded, (4) too few patients with high-risk tumours and (5) the majority of the patients in the study would probably undergo PN today. The results of the EORTC 30881 study are not necessarily applicable to patients currently undergoing RN for locally advanced disease [33].

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) [1]. Patients staged cN0M0 preoperatively and then found to have palpable nodes at the time of surgery had an incidence of pathologically detectable lymph node metastases (pN+) of approximately 20 % as compared with less than 1 % ($P<0.00$) in patients with nonpalpable nodes at nephrectomy [1].

Pantuck et al. [3] retrospectively studied 900 patients who underwent nephrectomy for RCC. They divided the patients in four pathological groups including (1) those without metastases, (2) those with only regional lymph node enlargement, (3) those with only distant metastatic disease and (4) those with regional lymph node enlargement and distant metastatic disease. These groups were divided into subgroups that did and did not undergo retroperitoneal LND at nephrectomy. LND did not offer a survival benefit in patients without enlarged lymph nodes at diagnosis [3]. In the setting of patients with clinically localised, clinically node-negative RCC (cT1–2N0M0), LND would only be "useful" for staging and not for a proposed therapeutic benefit. If patients with low-stage (T1–T2) RCC show additional unfavourable characteristics (Fuhrman grade 3 or 4, sarcomatoid differentiation and the presence of coagulative tumour necrosis) at surgery, the risk of LNI significantly increases and makes LND a valid surgical procedure (level 2 evidence) [2, 3, 23, 24, 45].

Locally Advanced Disease (cT3–4N0M0)

The value of LND in patients with locally advanced disease (cT3–4N0M0) has not been adequately assessed in a prospective randomised study. Blute et al. [2] showed that patients with high stage (pT3a, pT3b, pT3c or pT4) were twice as likely to have regional LNI compared with low stage (pT1a, pT1b or pT2) RCC ($P=0.017$). Patients with high-grade (grade 3 or 4) clear cell RCC were more than five times (95 % CI 3.12–8.83) more likely to have regional LNI at nephrectomy compared with those with low-grade (grades 1 and 2) RCC ($P<0.001$) [2]. In the setting of patients with locally advanced clinically node-negative RCC (cT3–4 N0M0), 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

In a series including 200 consecutive RCC patients who underwent RN and extensive LND, 10 % of patients had positive nodes without distant metastases, and the 5-year survival rate in this group was 52 % compared with 7 % in those with distant metastases [40]. Similar findings were made by Giberti et al. [35]. They found a 5-year survival of 53.2 % in node-positive RCC patients without distant metastases and without venous involvement (pN+M0V0) who underwent RN with regional LND [35]. The University of California Los Angeles (UCLA) reported a retrospective study including 900 patients who underwent RN for renal cancer. Overall, 112 patients with positive lymph nodes and without distant metastases underwent nephrectomy with or without LND. LND was associated with an improvement in median survival of 5 months and a trend towards an improved response to immunotherapy [3]. The MD Anderson Cancer Center group reported a retrospective study including 40 patients with positive lymph nodes but without distant metastases who underwent nephrectomy with extended retroperitoneal LND. Median tumour size was 11 cm and pathologic stage was T3 and T4 in 80 % of patients. Nodal status was N1 in 30 % and N2 in 70 % of patients. Thirty percent of patients had no evidence of disease at a median follow-up of 17.7 months and median disease-specific survival was 20.3 months. The authors concluded that these patients may benefit therapeutically from resection of isolated positive lymph nodes [5]. A recent 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 %. This finding suggests that LND of positive nodal metastases in patients undergoing RN for RCC may be beneficial for some patients [39].

In the setting of patients with clinical node-positive RCC (cTanyN+M0), LND has a staging as well as a possible therapeutic benefit. In patients with clinical node-positive disease (Tany,N+,M0), aggressive resection should be offered and, if possible, complete extended LND [23].

Regional Lymph Node Recurrence

Therapeutically, LND might help reduce the incidence of local recurrences. Kwon et al. [30] followed 1,503 patients who had undergone nephrectomy for RCC and found that 2.4 % (36/1,503) had a local recurrence with the most common site being regional lymph nodes (30/36). 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). 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 [46]. Figure 16.3 shows salvage LND for recurrence after RN (Fig. 16.3a) and a view after removal of lymph node recurrence (Fig. 16.3b).

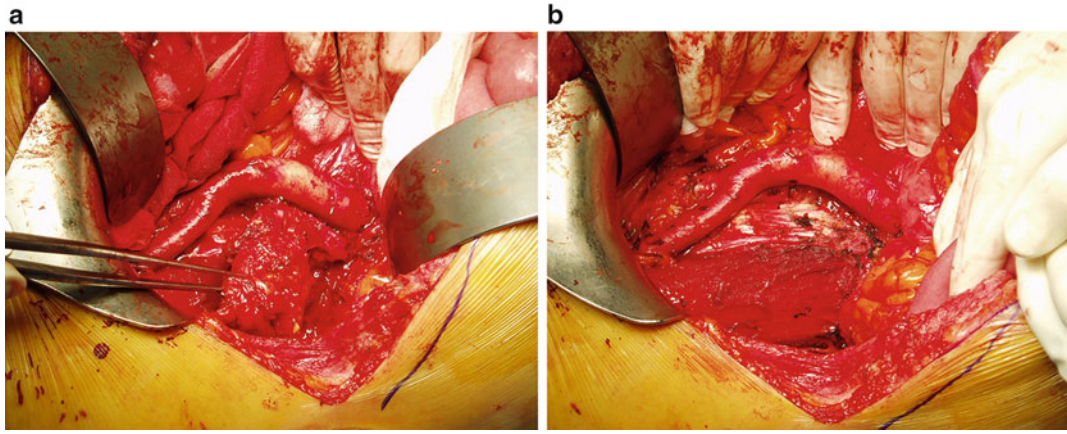

Fig. 16.3 (**a**) Salvage LND for recurrence after radical nephrectomy. (**b**) After removal of lymph node recurrence

Distant Metastasis and Cytoreduction (cTanyNanyM1)

The value of LND in patients with metastatic disease during cytoreductive nephrectomy has been assessed by a number of retrospective reviews in the era of immunotherapy [3, 13, 14, 41].

Vasselli et al. [13] evaluated the presence of lymphadenopathy (radiographic cN+) in 154 patients with metastatic RCC undergoing cytoreductive nephrectomy prior to treatment with interleukin-2 (IL-2). Eighty-two patients with pathologically negative lymph nodes (N0M1) survived longer (median 14.7 months) than the 72 patients with pathologically positive lymph nodes (N+M1) (median 8.5 months, $P=0.0004$). 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 [13]. Pantuck et al. [41] evaluated the impact of the presence of retroperitoneal lymphadenopathy on the survival and response to immunotherapy of 322 patients with metastatic RCC. The outcome of 236 patients with N0M1 disease and 86 patients with N+M1 disease was assessed. The authors showed a median survival of 20.4 months for all N0M1 patients compared with 10.5 months for N+M1 patients ($P=0.002$). Patients with N0M1 disease were reported to have a significant improvement in survival (median 28 months, $P=0.0008$) for those able to receive immunotherapy versus those who did not receive immunotherapy after nephrectomy. The median survival of patients with N+M1 disease was the same in those treated with and those treated without adjunctive interleukin-2 (IL-2)-based immunotherapy ($P=0.18$). N+M1 patients did not achieve a survival benefit from immunotherapy [41]. Pantuck et al. [3] 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 ($P=0.0002$). Patients who did not undergo LND were three times more likely to die than those who underwent the procedure. Recurrence rates were similar regardless of the extent of LND ($P=0.57$) [3]. Within the SEER database, Lughezzani and colleagues [14] identified 1,153 patients who were treated with cytoreductive nephrectomy for metastatic RCC, with LND (negative lymph nodes [N0] vs. positive lymph nodes [N1–2]) or without LND (unknown lymph node stage [Nx]). Of 797 patients treated with LND, 42.9 % were found to have lymph node metastases. At 3 years after cytoreductive nephrectomy, the cancer-specific mortality-free rates of N1–2 versus N0 versus Nx patients were 14.4 % versus 34.7 % versus 34.0 %, respectively. The findings

of the current population-based study indicate that lymph node stage should be considered in prognostic models [14].

In summary, in patients with T1–T2N0 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.

In high-risk patients (cT3–T4N0M0 or cTanyN+M0), the majority of the retrospective nonrandomised studies suggest a possible benefit of regional LND on CSS [2, 3, 23, 24, 45]. In high-risk patients (cT3–T4,N0 or cN1 or cM1), LND should be considered for more optimal staging and because of indirect evidence of a possible survival benefit (level 2 evidence). If RN or PN is planned, enlarged lymph nodes at either imaging or palpation during surgery should be resected when technically feasible [47].

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. High-risk patients with advanced or metastatic disease should undergo LND because they may benefit from a therapeutic effect. However, in my opinion there is no reason today not to do an easy LND in all RCC patients who could have microscopic nodal disease and not only in high-risk patients. This means LND should be performed in all patients at risk and certainly in the actually selected RN candidates. Definition of template and techniques requires 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.

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Postoperative Surveillance Protocols for Renal Cell Carcinoma

17

Megan M. Merrill and Jose A. Karam

Introduction

Cancers of the kidney and renal pelvis accounted for approximately 3–5 % of all malignancies diagnosed in the United States in 2012, with 65,150 new cases and 13,680 deaths expected in 2013 [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, and ablative therapies for RCC.

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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. 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].

Distant Recurrence

Lung

The most common site of metastasis from RCC is the lung, with a reported incidence of 3–16 %

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[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 CT chest 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 one 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 eight developed brain metastasis [14]. For pT2 and pT3 disease, the reported incidence ranges from 0 % to 15 % and from 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 followed 1,737 node-negative patients who underwent nephrectomy for RCC. They reported a 1.8 % incidence of isolated renal fossa recurrence at 5 years, with only 60 % of those patients being symptomatic upon diagnosis [24]. Margulis et al. [25] reviewed 2,945 patients who had a radical nephrectomy with curative intent and reported an isolated local recurrence in 54 (1.8 %) of those patients. Local recurrence was defined as any RCC, proven by pathology evaluation, localized in the renal fossa, ipsilateral adrenal gland, or ipsilateral retroperitoneal lymph nodes. In line with the Mayo series, 61.2 % of patients were symptomatic (28 patients with local symptoms and five 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 median survival of 111 months. Patients with only one risk factor ($N=9$) had median survival of 40 months, while patients with more than one risk factor ($N=11$) had median survival of only 8 months after resection. As noted, tumor size was one of the poor prognostic indicators, suggesting that earlier detection of such recurrence could lead to improved resectability and achieving 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 [26].

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 [27]. 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 [28].

Aside from the influence of size on recurrence patterns after partial nephrectomy, the effect of positive surgical margins (PSMs) has also been recently investigated. A study conducted by Memorial Sloan-Kettering Cancer Center and the Mayo Clinic reviewed 1,344 patients who underwent partial nephrectomy at one of these institutions between 1972 and 2005 [29]. 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 [29]. A retrospective

multi-institutional review collected data from 26 centers throughout Europe and North America and reported similar results [30]. 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 [30].

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 current 5-year overall survival rates are 81 % for stage T1, 74 % for T2, 53 % for T3, and 8 % for T4 [31]. 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 (reviewed in [32]). 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 [33]. 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 % versus 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 of 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 [33].

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, supraclavicular or axillary lymphadenopathy, and 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 urinalysis, complete blood count (CBC), coagulation profile, and a comprehensive

metabolic panel (CMP), which consists of liver function studies, lactate dehydrogenase (LDH), calcium, electrolytes, BUN, and creatinine.

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 % [34]. 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 [35]. CKD has been shown to be associated with a higher risk of morbidity and mortality [36]. 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 [37].

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 [38].

Tumor size has been demonstrated to be an independent predictor of disease-free survival [39–41]. 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 [42]. In a follow-up study, the MSKCC group also confirmed the importance of tumor size in predicting disease recurrence independent of pathological stage [43].

Histology by itself has also been shown in several studies to predict disease-specific survival. Of the four subtypes of RCC, chromophobe RCC confers a better prognosis than conventional (clear cell) RCC or papillary RCC [44]. Papillary type II, however, has been shown to independently predict poor survival [45, 46]. The presence of sarcomatoid dedifferentiation on final pathology indicates poor prognosis and has been utilized in risk stratification algorithms to predict disease recurrence [47, 48].

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 [43]. 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 [39, 49, 50]. 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 [49].

Authors from the 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 [51]. 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 2,517 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 [50].

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 17.1.

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 [52]. 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 subselect 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. Twelve 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 ten 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 eight recurrences were not isolated, but were associated with other findings.

Table 17.1 Surveillance guidelines after partial or radical nephrectomy

	Clinical assessment (history, physical exam, laboratory studies)	Chest X-ray	Abdominal CT
pT1			
Sandock [16]	Not specified	Not recommended	Not recommended
Hafez [13]	Yearly	Not recommended	Not recommended
Levy [14]	Yearly	Yearly	Not recommended
Ljunberg[a] [15]	Not recommended	Not recommended	Not recommended
Mickish [54]	Every 6 months for 3 years, then yearly from years 3–5	Every 6 months for 3 years, then yearly from years 3–5	Not recommended
Stephenson [56]	Yearly	Yearly	Not recommended
Kassouf [59]	Yearly	Yearly	At years 2, 5 (optional at 3 months)
pT2			
Sandock [16]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	Not recommended
Hafez [13]	Yearly	Yearly	Every 2 years
Levy [14]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	At years 2, 5
Ljunberg[b] [15]	At 3 and 6 months, then every 6 months until 3 years, then yearly	At 3 and 6 months, then every 6 months until 3 years, then yearly	Not recommended
Mickish [54]	Every 6 months for 3 years, then yearly from years 3–5	Every 6 months for 3 years, then yearly from years 3–5	Not recommended
Stephenson [56]	Yearly	Yearly	Not recommended
Kassouf [59]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	12, 36, 60, 80, 108 months
pT3			
Sandock [16]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	Not recommended
Hafez [13]	Yearly	Yearly	Every 6 months until 2 years, then every 2 years
Levy [14]	At 3 and 6 months, then every 6 months until 3 years, then yearly	At 3 and 6 months, then every 6 months until 3 years, then yearly	At years 2, 5
Ljunberg [15]	At 3 and 6 months, then every 6 months until 3 years, then yearly	At 3 and 6 months, then every 6 months until 3 years, then yearly	At 6 and 12 months (optional)
Mickish [54]	Every 6 months for 3 years, then yearly from years 3–10	Every 6 months for 3 years, then yearly from years 3–10	Every 6 months for 3 years, then yearly from years 3–10
Stephenson [56]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	At 6, 12, 24, and 36 months, then every 2 years
Kassouf [59]	Every 6 months for 3 years, then yearly	Every 6 months for 3 years, then yearly	At 6, 12, 18, 24, 36, 60 months, 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, then yearly until 10 years	Every 6 months for 3 years, then yearly until 10 years	At years 1 and 2, then every 2 years for 10 years
High risk	Every 6 months for 3 years, then yearly until 10 years	Every 6 months for 3 years, then yearly until 10 years	Every 6 months for 2 years, then yearly until 5 years, then every 2 years until 10 years
Nodal disease	At 3, 6, 12, 18, 24 months then yearly	At 3, 6, 12, 18, 24 months then yearly	At 3, 6, 12, 18, 24 months 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

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 in patients with pT1 disease. For patients with pT2 and pT3 disease, they recommended a history, physical examination, liver function tests, and chest X-rays every 6 months for the first 3 years, 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 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 [53] from Columbia University reported on 45 patients that were enrolled in an adjuvant autolymphocyte therapy trial for N+M0 high-risk patients. Twelve 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, 11 in the lung at 14.4 months, 5 in the liver at 14.9 months, 5 in bone at 11.9 months, 4 in the mediastinal nodes at 11.8 months, 3 in the renal fossa at 6.9 months, and 2 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 intra-abdominal metastasis without associated symptoms. All brain metastases presented with neurological symptoms that prompted further evaluation. In the eight pT1 patients with recurrent disease, 4 were in the chest (lung), 2 in bone, and 1 each in 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 bone, and 1 in 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 bone, five in lymph nodes (detected on physical examination), and 3 in 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. The authors recommended history, physical exam, laboratory studies, and chest X-ray at 12, 24, 36, 48, and 60 months after surgery for pT1, 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, Ljungberg and colleagues [15] from Umea 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 bone, 21 were intra-abdominal (11 liver, 7 local or retroperitoneal, 3 abdominal), 4 were brain, 3 were 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. Fourteen percent (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 one symptomatic) and 5 were in bone (all symptomatic). In patients with pT3, only 1 of 24 lung recurrences was symptomatic, while all 10 bone and all 5 liver, 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, Mickish and colleagues [54] 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, then yearly until year five. 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 [54].

In 2003, Frank and colleagues [55] from the Mayo Clinic retrospectively reviewed 1,864 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. Sixteen percent (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 [56] 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 four patients had an isolated local recurrence. Sixteen 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 (2 after partial nephrectomy, 1 after radical nephrectomy) and 1 symptomatic abdominal recurrences. Fourteen 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. Twenty-three 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 every 6 months for the first 3 years with history, physical examination, 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 afterwards.

In 2005, Lam and colleagues from the 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 – that has been shown to predict outcomes in patients post nephrectomy for RCC [51] (Fig. 17.1). This UISS model has been validated in subsequent studies [57, 58]. 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. 17.2). 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. Fifty-eight percent 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 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. 7 % of the chest recurrences were found on routine imaging after 5 years of follow-up. Abdominal recurrences including renal fossa, liver, and other abdominal organs together comprised 68.2 % of recurrences.

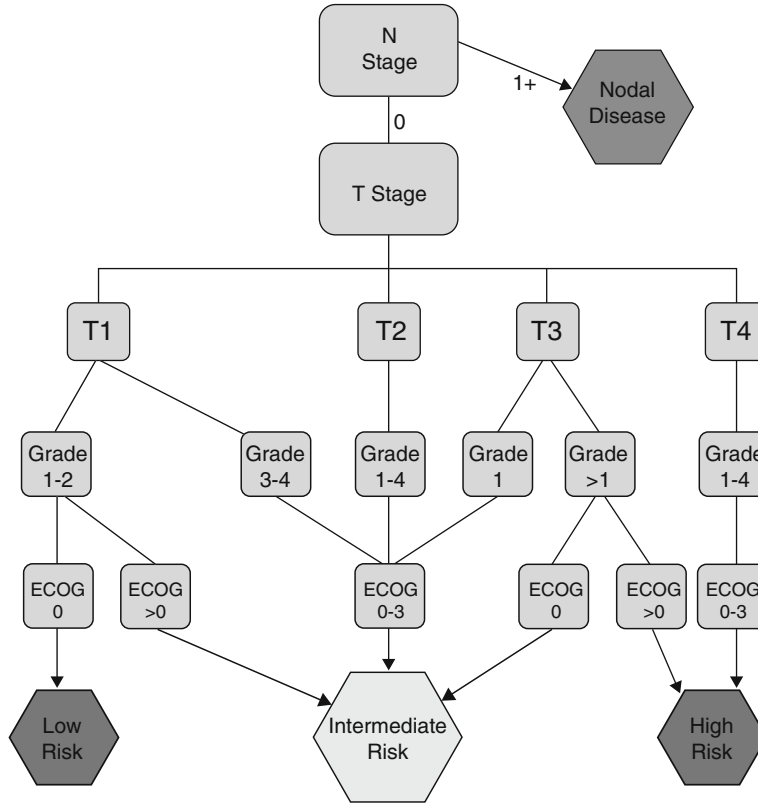

Fig. 17.1 Flow chart for UISS risk group assignment of patients with localized and locally advanced RCC. Progress from top to bottom using 1997 UICC N stage and T stage, Fuhrman grade, and ECOG-PS (Reprinted from Lam et al. Postoperative surveillance protocol for patients with localized and advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. J Urol. 2005;174(2):466–72, with permission from Elsevier)

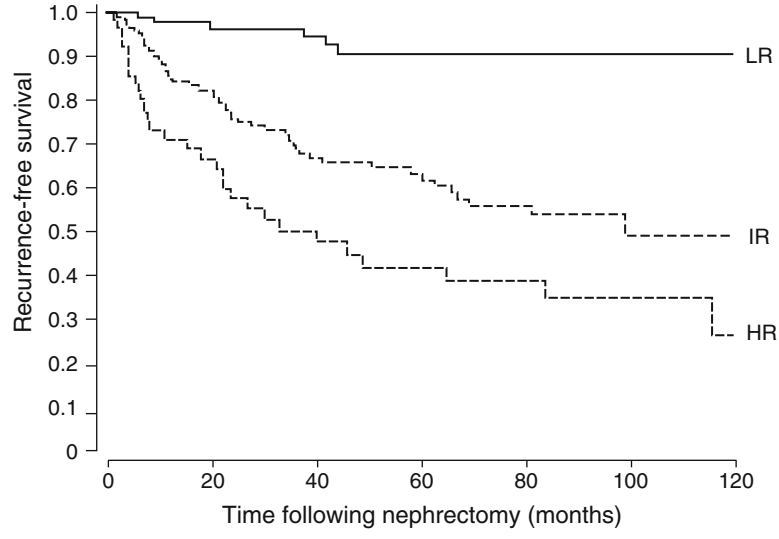

Fig. 17.2 Kaplan-Meier estimate of recurrence-free survival following nephrectomy among UISS risk groups (Reprinted from Lam et al. Postoperative surveillance protocol for patients with localized and advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. J Urol. 2005;174(2):466–72, with permission from Elsevier)

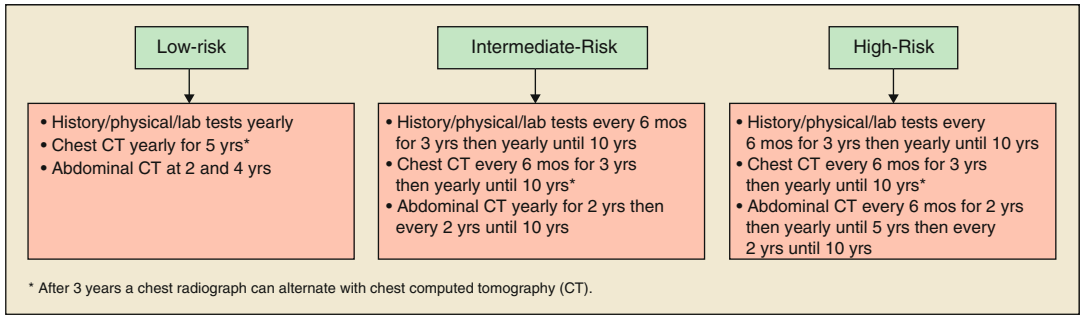

Fig. 17.3 Surveillance protocol following nephrectomy for localized renal cell carcinoma using the University of California Los Angeles Integrated Staging System (Copyright © MedReviews®, LLC. Reprinted with permission of MedReviews®, LLC. Chin AI et al. Surveillance strategies for renal cell carcinoma patients following nephrectomy. Rev Urol. 2006;8(1):1–7. *Reviews in Urology* is a copyrighted publication of MedReviews®, LLC. All rights reserved)

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. 17.3).

In 2005, Chae and colleagues from ASAN Medical Center in Korea retrospectively reviewed 194 patients treated with surgery [37]. 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 CT chest should be done every 6 months during the first 2 years after surgery and then annually for 2 years in patients with a high risk for tumor recurrence [37].

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, 60 months and then continue 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 [60] updated their prior surveillance

Table 17.2 Postoperative surveillance guidelines based on histological subtype – Siddiqui [60]

	Clinical assessment (history, physical exam, laboratory studies)	Chest X-ray	Abdominal CT or US
Clear cell RCC			
Low risk	Yearly	Every 6 months for 2 years, then yearly until 10 years	CT at 18, 24, 30 months then year 5, 7, 10; US at year 3, 4, 6, 8, 9
Intermediate risk	Yearly	Every 3 months for 3 years, then yearly until 10 years	CT at 6, 9, 12, 15, 24, 27, 30, 48 months then yearly until 10 years; US year 3
High risk	Yearly	Every 3 months for 1 years, then at 24 and 30 months	CT every 3 months for 2 years, then every 6 months for 1 years, then yearly until 10 years
Papillary RCC			
Low risk	Yearly	Not recommended	CT at year 1,2; US at 6, 9 months
Intermediate risk	Yearly	At 12, 18, 30, 33, 36 months then yearly until 10 years	CT year 3; US 6, 24 months then every 2 years
High risk	Yearly	At 6, 9, 12, 18, 24 months	CT at 6, 9, 12, 18, 24, months then every 2 years
Chromophobe RCC			
Low risk	Yearly	Not recommended	Not recommended
Intermediate risk	Yearly	Not recommended	CT at year 3, 7; US at year 5, 10
High risk	Yearly	At 6, 9, 15 months	CT at 3, 6 months and at year 7; US at year 3, 5, 10

protocol and included histologic subtype as one of the additional risk factors for recurrence (in addition to the previously reported 1,864 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 17.2), which was not provided in the prior manuscript in 2003 [55].

The recently updated 2012 National Comprehensive Cancer Network guidelines reflect a modified surveillance approach based on panel consensus [61]. The panel has updated the recommendation that the first follow-up should commence at an interval of 2–6 months following nephrectomy rather than 4–6 months as was stated in the 2011 version. Also the specific type of imaging recommended was modified to read "chest and abdominal imaging," leaving the choice of imaging modality at the discretion of the clinician. Follow-up laboratory studies now include the addition of lactate dehydrogenase (LDH) to the comprehensive metabolic panel. In summary, NCCN currently recommends follow-up surveillance every 6 months for 2 years, then annually for 5 years, to include a complete history and physical exam as well as a comprehensive metabolic panel and LDH. At 2–6 months postoperatively, chest and abdominal imaging should be completed and then should be ordered as indicated. Although the NCCN guidelines do not make reference to when these imaging studies are indicated, they do discuss that no single follow-up is appropriate for all patients. 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 [61] (Figs. 17.4 and 17.5).

Surveillance for Hereditary RCC

Patients with familial forms of renal cell carcinoma have a high risk of recurrence and often

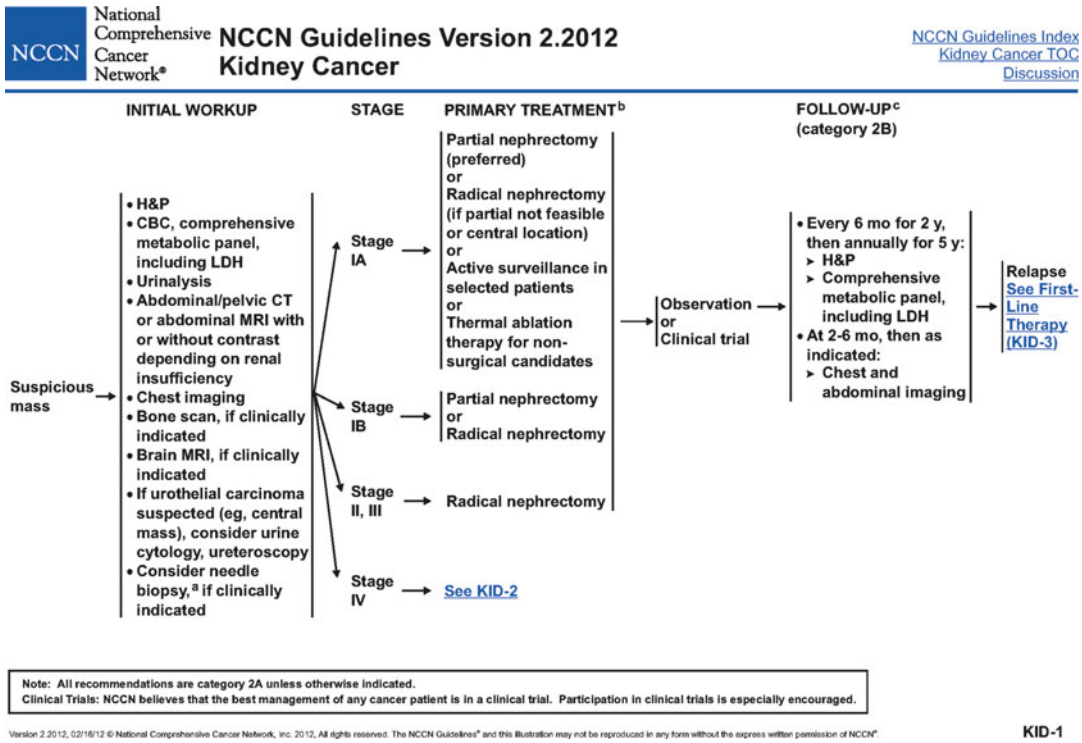

Fig. 17.4 **a** Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies. **b** See Principles of Surgery (KID-A). **c** No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient and tumor characteristics. Alternate follow-up schemes have been proposed

require multiple nephron-sparing surgeries to treat their disease process. Steinbach et al. [62] 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. 51 % 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. [63] 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 [64].

Surveillance Following Ablative Therapies for RCC

As an increasing number of elderly patients with multiple medical comorbidities are diagnosed

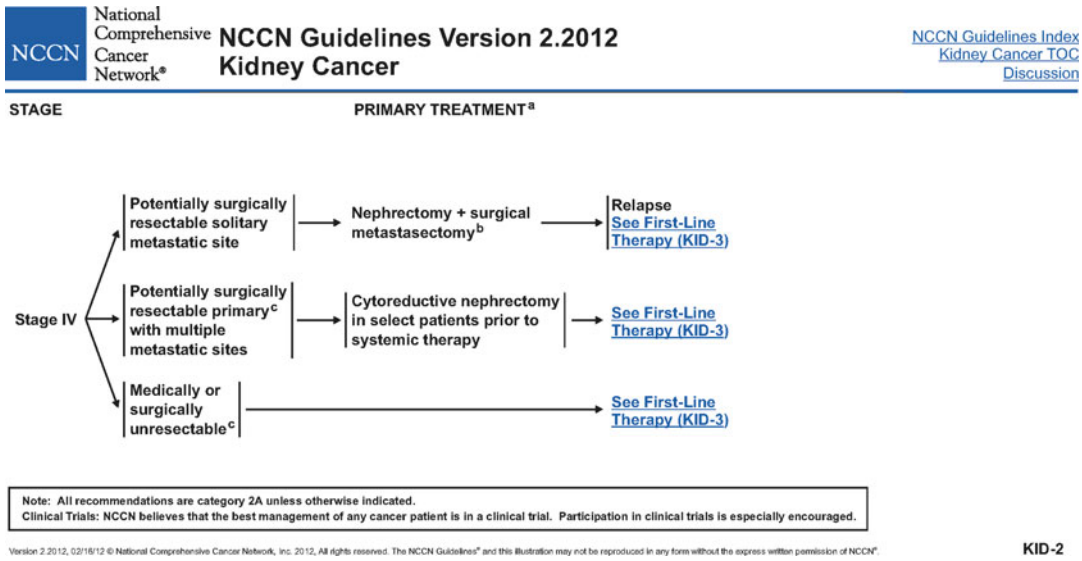

Fig. 17.5 **a** See Principles of Surgery (KID-A). **b** No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient and tumor characteristics. Alternate follow-up schemes have been proposed. **c** Individualize treatment based upon symptoms and extent of metastatic disease

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 [65–68].

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 recent literature reports promising intermediate-term outcomes [31, 69–73]. 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 [74]. Unenhanced areas seen on CT correlate with tissue necrosis, and often, a hyperattenuating halo around the defect can also be seen [75]. 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 [75, 76].

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 ten 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 4 of 5 specimens in the acute group and 3 of 6 specimens in the delayed group [77]. 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 [78]. 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, making it difficult to distinguish treatment effect from viable tumor [79]. 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 [78].

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 [80]. 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 [31].

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 [75]. 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 [81]. Gill et al. reported a 75 % reduction in defect size over 3 years, with no evidence of scar detected in 38 % of patients [82].

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. [78] 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 months follow-up, and of those, only two yielded positive biopsies. There were 11 centrally enhancing lesions identified on imaging at 6 months and positive biopsies were found in four of those patients. The sensitivity of central enhancement on 6-month follow-up to predict a positive biopsy following

Table 17.3 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, then biannually	RFA, 1999	Percutaneous	No
Cleveland Clinic	MRI Day 1, month 1, 3, 6, 12 then yearly	Cryoablation, 1999; RFA, 2002	Percutaneous; laparoscopic	Yes, at 6 months
Fox Chase Cancer Center	CT Month 1, 3, 6, 12, then every 6 months	RFA and cryoablation, 2002	Percutaneous and laparoscopic	No
Massachusetts General Hospital	CT Month 1, 3, 6, and 12, then every 6–12 months	RFA, 1998	Percutaneous	No
M. D. Anderson Cancer Center	CT Month 1, 3, 6, 12, then every 6–12 months	RFA, 2001; cryoablation, 2002	Percutaneous and laparoscopic	No
Southwestern Medical Center	CT Week 6, month 6, 12, then yearly	RFA, 2001	Percutaneous and laparoscopic	No
Wake Forest University	CT Month 2, 8, then every 6 months	RFA, 2000	Percutaneous	No

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cryoablation was 77.8 %, with 95 % specificity, 63.4 % PPV, and 97.7 % NPV [78].

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 [83].

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 [84]. In this retrospective review of data from seven institutions (Table 17.3), 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) [84].

Based on these findings, a minimum schedule of 3–4 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 month 1, 3, 6 (optional), and 12.

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 [85]. 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 on all prognostic molecular markers [86] 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 [87]. 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 [88] and should be further validated in external cohorts. Other studies have evaluated that biomarkers are prognostic factors and 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 [85].

Use of F-18 Fluorodeoxyglucose Positron Emission Tomography in Surveillance and Reducing 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 growing concern over radiation exposure and risk of developing a secondary malignancy [89, 90]. 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 [91]. In 2007, Brenner et al. estimated that as many as 1.5–2 % of cancers could be a result of radiation from CT scans [89]. 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 [91].

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 (PET 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 primary tumor, other groups have demonstrated the sensitivity of PET scans to be inferior [92, 93]. 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 [93, 94]. 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 two 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 versus 83 % for those with negative PET scans [95]. When compared to CT scan alone, the authors concluded that PET scan had little impact on therapeutic decisions. 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 health-care 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 $1,200 for a total cost of $412,800 [14].

Dion et al. performed a cost-analysis comparison of two surveillance strategies in a Canadian cohort [96]. 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 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 [96].

Siddiqui et al. [60] 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.

Conclusion

Patients with renal cell carcinoma are at risk of recurrence, even after definitive surgical therapy, and should be carefully, but rationally, monitored for prolonged duration to detect recurrences early enough to allow meaningful intervention that could lead to prolonged survival. While many current guidelines use loose recommendations for follow-up with much discretion left for individual urologists, it is clear that we need a risk-based approach, driven by evidence, in order to provide optimal postoperative surveillance for patients with renal cell carcinoma. Hopefully,

advances in genomic sciences and molecular markers can help us develop more robust and individualized follow-up schema for our patients in the future.

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Role of Surgery in Locally Recurrent and Metastatic Renal Cancer

18

Paul Russo

The Problem of Renal Cancer and Its Recurrence

An estimated 64,770 new cases and 13,570 from kidney cancer occurred in the United States in 2011. Kidney cancer is increasing at a rate of approximately 3 % per year [1]. Compared with 1971, this represents a fivefold increase in the incidence and twofold increase in the mortality. Associated risk factors include hypertension, smoking, obesity, and diabetes. Epidemiologic evidence suggests an increase in all stages of renal cancer including the advanced and metastatic cases. Approximately 30–40 % of patients with malignant renal cortical tumors will either present with or later develop metastatic disease (mRCC) [2–7].

In a series of 1,618 patients from Memorial Sloan-Kettering Cancer Center (MSKCC) undergoing surgical resection of nonmetastatic tumors between 1989 and 2004, 179 (11 %) patients developed recurrent disease of which 16 were isolated local recurrences (1 %) and 163 (10 %) were metastatic recurrences [8] (Fig. 18.1). Approximately 90 % of metastatic renal cancer patients have the conventional clear cell histological subtype [9]. Although the vast majority of newly mRCC patients will present within the first 2 years following primary tumor resection, unusual sites of metastasis and local tumor recurrences can occur years or even decades after resection of the primary tumor. The local recurrence may be a nodal metastasis after PN or RN (Fig. 18.2), an ipsilateral adrenal metastasis involving the psoas and adjacent organs, or even an intraluminal mass within the inferior vena cava [10–12]. Occasionally, benign conditions such as splenosis, ectopic spleen, and postoperative granulomas in the operative bed or benign neoplasms at distant sites, such as pancreatic islet tumors, can mimic recurrent disease and prompt surgical explorations [13–16]. If a nonmalignant diagnosis is being entertained, it is perfectly reasonable to perform a percutaneous needle biopsy to confirm or refute your suspicion.

Patient Selection Factors Associated with Metastatic Recurrence

A fundamental characteristic of patients with metastatic kidney cancer is a variable clinical spectrum at the time of diagnosis ranging from normal health to profound systemic illness. This variability was first suspected to play an important role in the inconsistent results seen in cytokine-based systemic therapy clinical trials which reported modest benefits to some patients and no benefits to others [17]. A study reported by Motzer et al. of 670 patients with mRCC

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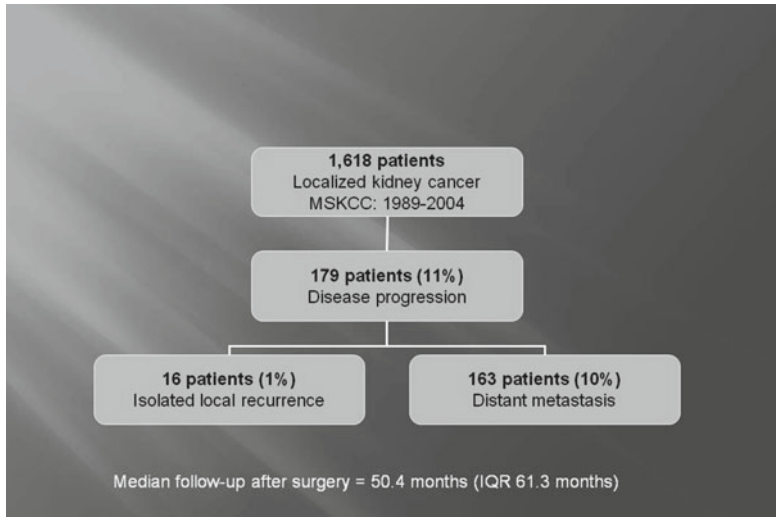

Fig. 18.1 Pattern of local and systemic renal cancer disease progress in 1,618 patients treated for localized, nonmetastatic, renal cancer between 1989 and 2004 [8]

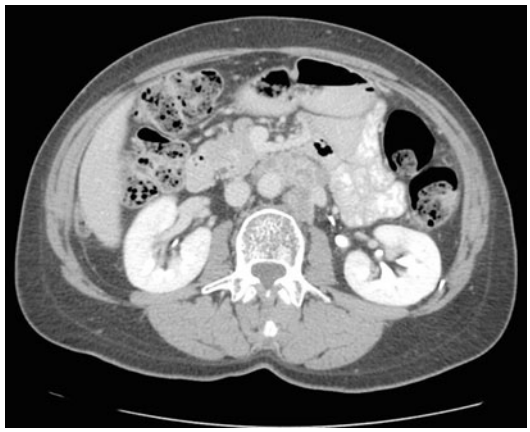

Fig. 18.2 Regional para-aortic local recurrence (adenopathy) 6 years after a partial nephrectomy in a 54-year-old female for high-grade, poorly differentiated, unclassified renal cell carcinoma. Complete resection with retroperitoneal lymph node dissection was performed and the patient is without evidence of disease 9 months later

carcinoma treated at MSKCC identified risk factors associated with a shorter survival. These factors included a low Karnofsky performance status (KPS < 80 %), high serum LDH levels (>1.5 upper limits of normal), low hemoglobin levels: (<13 g/dl males, 11.5 g/dl females), high corrected Ca++ levels, and the absence of nephrectomy. Median survival ranged from 4 to 13 months with the increasing presence of the above risk factors strongly associated with decreased survival [18]. Only 12 patients (1.8 %) in this data set, all assigned to good or intermediate pretreatment risk groups (KPS > 80, prior nephrectomy), were long-term survivors (>5 years). These same risk factors (MSKCC or Motzer factors) also predicted survival in 251 previously treated patients who then entered into second-line clinical trials. For patients without any of the risk factors (favorable group), the median time to death was 22.1 months; for patients with one of the risk factors (intermediate group), the median time to death was 12 months; and for patients with two or three risk factors (poor risk), the median time to death was 5 months [19].

When MSKCC surgical investigators applied the Motzer prognostic variables to 118 initially nonmetastatic nephrectomy patients who later developed metastases, survival was again influenced by these same risk factors (Fig. 18.3). Median survival from the time of metastatic recurrence was 21 months and overall survival was strongly associated with risk groups. Median survival for low risk, intermediate risk, and high risk was 76, 25, and 6 months, respectively [20] (Fig. 18.4). In subsequent analysis of 44 patients undergoing metastasectomy involving ten

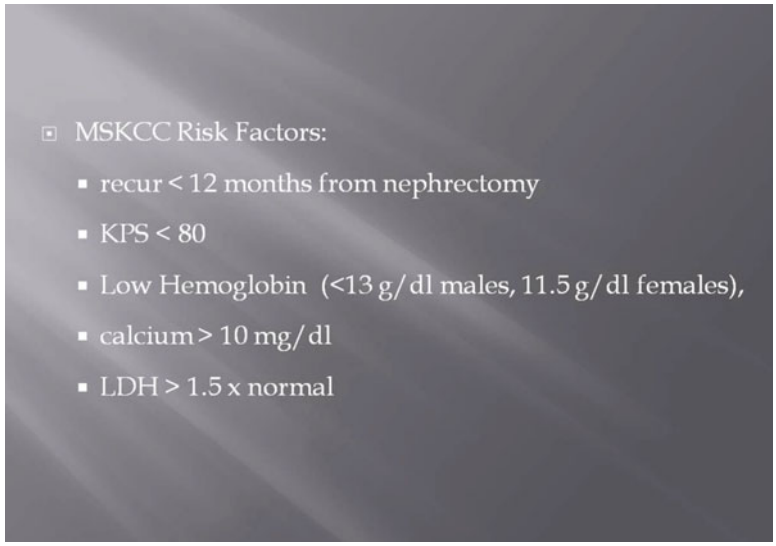

Fig. 18.3 MSKCC patient selection factors applied to previously resected newly metastatic renal cancer patients [20]

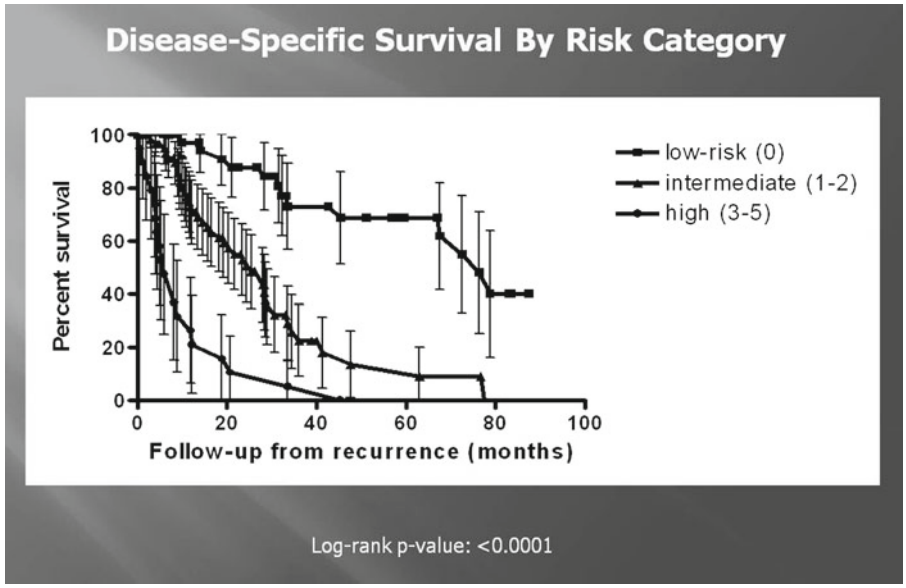

Fig. 18.4 Survival distribution based on MSKCC risk factors from the time previously resected renal cancer patients became metastatic [20]

different organs, patients designated as low risk (51 %) were more likely to undergo surgical resection than intermediate risk (28 %) or high risk (21 %) confirming that surgeons were good at selecting a prognostically favorable group of metastatic patients to operate upon. Among the low-risk patients, metastasectomy was significantly associated with improved survival compared with no surgery (H.R. 2.9, $P=0.03$, median survival not reached vs. 56 months) [21]. When MSKCC investigators looked at 44 surgical patients that developed "late recurrences," defined as metastasis at greater than 5 years from the time of complete surgical resection of the

primary renal cancer and compared them to 256 patients that recurred in less than 5 years, patients with late recurrences tended to have fewer symptoms at presentation, smaller primary tumors (7.0 vs. 8.5 cm), and lower stage disease (pT1 in 39 % vs. 18 %). Five-year actuarial survival from the time of late relapse was 85 % in good risk patients versus14 % in intermediate risk patients [22].

These studies, when taken together, strongly indicate that the condition of the metastatic renal tumor patient at the outset of both medical and surgical care may have as much to do with survival time as the subsequent medical and surgical interventions. Risk stratification factors are likely a reflection of complex interactions between host defenses and the variable malignant potential of renal tumors which directly affect patient survival. Surgical investigators that report an intervention in a locally recurrent or metastatic patient must also consider these important clinical selection factors associated with survival and renal cancer natural history.

Local Tumor Recurrence After Radical Nephrectomy

After curative RN, isolated local tumor recurrence (LR) in the absence of evolving distant metastatic disease is a rare event and may be due to micrometastatic soft tissue disease in the nephrectomy bed, regional adenopathy or adrenal metastasis not addressed at the time of the original radical nephrectomy, or direct tumor involvement of adjacent organs including colon, spleen, pancreas, or stomach [23]. Isolated LR is almost always associated with already present or about to be clinically apparent metastatic disease. Autopsy studies of patients dying of metastatic renal cancer reveal evidence of local tumor, often microscopic and subclinical in nature, in the nephrectomy bed [24]. As would be expected, the evolution of the modern imaging tools of MRI, CT, and CT/PET has enhanced the ability of clinicians to distinguish isolated LR from LR with concomitant metastatic disease. Despite this, reports from centers with large nephrectomy data bases spanning decades such as the Mayo Clinic (30LR/1,737 patients, 1.8 %) [25], MSKCC (34 LR/1,165 patients, 2.9 %) [26], and MD Anderson Cancer Center (54 LR/2,945, 1.8 %) [27] indicate that LR is a rare isolated clinical event. Patients with LR may be detected because of the new onset of local symptoms (60 % Mayo Clinic series, 24 % MSKCC) or by routine postoperative imaging (Fig. 18.5). The clinician, when faced with a clinical LR, must make a difficult decision – does one immediately operate to resect the LR or, in the case of an asymptomatic LR detection, repeat imaging in 3–4 months to rule

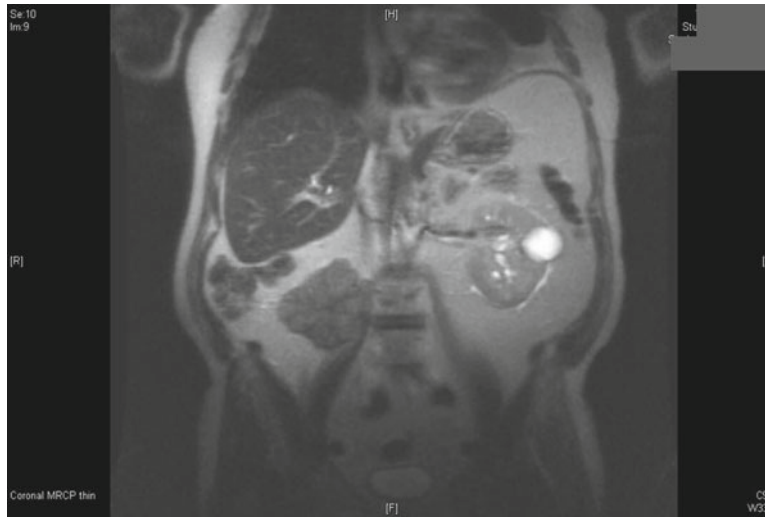

Fig. 18.5 Massive local tumor recurrence along the right psoas muscle in a 73-year-old male with no signs of metastatic disease. Complete surgical resection was performed and associated with an 8-year disease-free survival

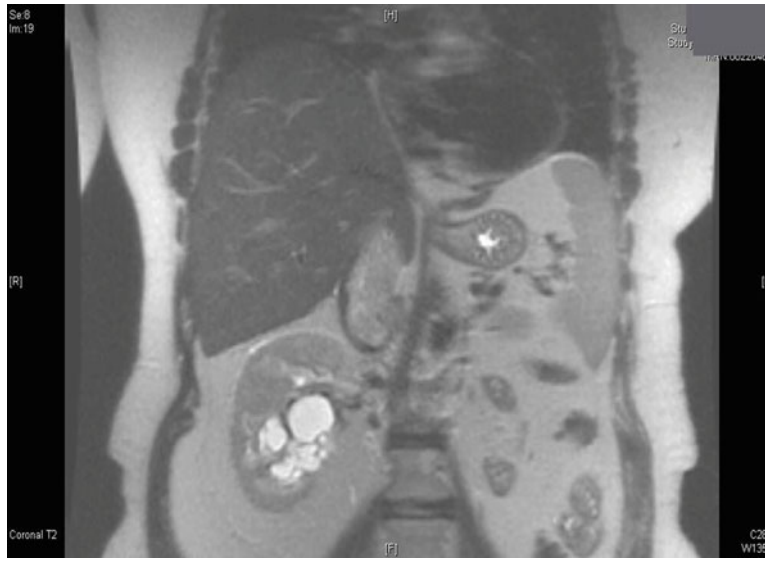

Fig. 18.6 Intracaval (retrohepatic) recurrence of clear cell renal cell carcinoma 9 years after complete resection of left clear cell carcinoma with extension to the right atrium. Repeat caval resection was complete and the patient remains continuously without evidence of disease 6 years later

out the evolution of distant metastatic disease which would render an aggressive local tumor resection irrelevant. Although studies of the above described MSKCC selection factors have not been yet applied to the LR population, MD Anderson investigators reported other adverse prognosticators, including a positive surgical margin of the LR resection specimen, abnormal serum alkaline phosphatase, sarcomatoid features, and increased serum lactate dehydrogenase. Patients with 0, 1, and greater than 1 adverse risk factors demonstrated cancer-specific survival rates of 111, 40, and 8 months, respectively [27].

Despite its rarity, aggressive surgical resections of LR are reported, often combined with adjacent organ resection [28, 29] and adjuvant radiation therapy or intraoperative radiation [30]. Reports from generally small series indicate that limited long-term survival can be achieved in highly selected patients following complete resection of the LR. The impact of additional therapies (chemotherapy, cytokines, and radiation) is difficult to evaluate given the small patient numbers. Five-year survival in the MSKCC series was 18 % [26] and in the Mayo series was 28 % [25].

Particularly challenging late LR can involve the tumor within the inferior vena cava (Fig. 18.6) or heart (right atrium and right ventricle), which can either be free floating or directly attached. Preoperative evaluation with MRI, echocardiography, and transesophageal echocardiography is important for surgical planning. Surgeons may need to replace sections of the vena cava if there is direct invasion of the wall with synthetic or porcine grafts or utilize full cardiac bypass techniques if there is cardiac involvement. Although operations to resect such recurrences can be technically challenging and require coordination with cardiovascular surgeons, operative resection in the absence of metastatic disease is justified [11, 31–34]. Novel approaches to LR, including percutaneous cryoablation [35], laparoscopic resection [36], and percutaneous embolization [37], have also been reported.

The current literature indicates that LR is a difficult clinical problem with a generally poor overall prognosis. Whether the integration of the newly introduced tyrosine kinase and mTOR inhibitors as adjuvant therapies will improve these poor results remains to be seen.

Local Recurrence or New Tumor Formation After Partial Nephrectomy

Over the last 10 years, many well-done clinical studies have provided the oncological and medical rationale for partial nephrectomy in the management of small renal masses. Initially, elective partial nephrectomy was restricted to tumors of 4 cm or less, and then expanded to tumors of 7 cm or less, and now tumors of any size are fair game as long as a complete resection can be obtained. It is now clear that this approach provides equivalent oncological control to RN while at the same time preventing or delaying chronic kidney disease and associated potential cardiovascular morbidity and possible mortality [38–40].

Despite the increasing appeal of PN, a certain percentage of patients, approximately 5 %, undergoing a successful partial nephrectomy will develop a new tumor in the previously operated kidney [41] (Fig. 18.7). Actual recurrences in the PN resection bed are rare, even when there is a positive microscopic surgical margin. MSKCC and Mayo Clinic investigators combined their data and analyzed 1,344 patients undergoing 1,390 PN from 1972 to 2005. Positive surgical margins were documented in 77 cases (5.5 %) and were significantly associated with decreasing tumor size and presence of a solitary kidney. Interestingly, experienced surgeons from both centers describe small endophytic tumors, many of which are not palpable and can be located only by using intraoperative ultrasound, as often difficult to find and resect and commonly associated with close or positive surgical margins. All patients with positive surgical margins were managed expectantly with an overall 10-year probability of freedom from local recurrence and metastatic recurrence of 93 %. There was no significant difference in either local or metastatic recurrence between the patients with positive or negative surgical margins [42]. It is therefore most likely that ipsilateral recurrences represent new tumor formations that were clinically undetected at the time of the initial PN and, over a time period usually measured in years, enlarged to the point of clinical delectability upon routine follow-up imaging. Although multifocal and bilateral tumors are part of hereditary and familial tumor syndromes such as von Hippel-Lindau disease, hereditary papillary renal cancer, and Birt-Hogg-Dube syndrome and may account for 3–5 % of all renal cancers [43], multifocal renal cortical tumors can also occur in sporadic renal tumor patients. MSKCC investigators evaluated 1,071 RN specimens from 1989 to 2002 and found 57 (5.3 %) with pathological evidence of tumor multifocality including six (11 %) that occurred in the bilateral synchronous setting. Preoperative imaging detected multifocality in 19 patients (33 %), and therefore, occult multifocality was detected 38/1,071 RN (3.5 %). Primary tumors in the multifocal group were conventional clear cell (51 %) followed by papillary (37 %), and 74 % had the same tumor histology in all lesions. Multivariate analysis demonstrated that bilaterality, papillary histology, advanced tumor stage, and lymph node metastases were associated with multifocal tumors. After a median follow-up of 40.5 months, disease-free survival was not significantly different between multifocal and unifocal renal tumors [44]. Patients at greatest risk for this type of LR event are those that are young, generally healthy, and have had an early-stage or indolent tumor resected at the time of the first PN. Coupled with

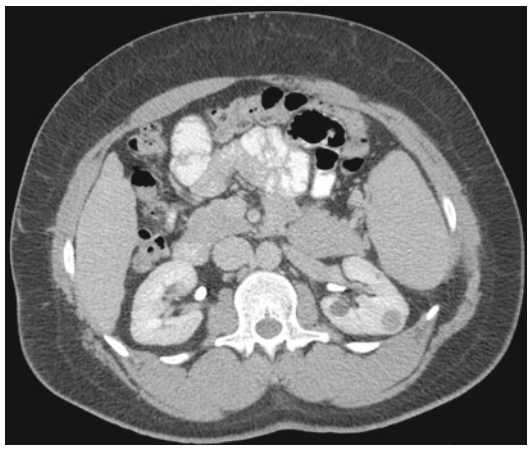

Fig. 18.7 Recurrent left renal mass in a 48-year-old African American male s/p prior partial nephrectomy of type 1 papillary renal cell carcinoma. Despite postoperative scarring, repeat partial nephrectomy was performed

a long life expectancy, the long-term chance of a new tumor formation in these patients may thus be clinically realized.

Bernhard and colleagues reported data from 809 PN performed at eight academic centers in the USA and Europe. After a median follow-up of 27 months, there were 26 ipsilateral recurrences (3.2 %). In this study, factors on multivariate analysis that were significantly associated with LR were tumor stage pT3a, tumor bilaterality, tumor size >4 cm, and positive surgical margins [45]. The identification of an ipsilateral tumor recurrence is a disconcerting finding and can lead to difficult decision making. Important factors to consider include the age and life expectancy of the patient, current renal function, the presence or absence of medical comorbidities, and the tumor histology of the original tumor. The recurrent tumor has the same histology approximately 75 % of the time. Repeat PN can be a difficult operation due to scar tissue from previous renal mobilization and perirenal adhesions often involving the great vessels of the renal hilum. National Cancer Institute surgeons, who commonly perform repeat PN in the management of hereditary and familial cancer syndromes, reported a series of 51 attempted PN in 47 such patients from 1992 to 2006. There were major complications or reoperations in ten patients (19.6 %), one perioperative death, and a significant increase in serum creatinine and decrease in creatinine clearance. Two patients required long-term dialysis. Of the 47 surviving patients, 46 were alive after a median follow-up of 56 months [46]. The same NCI group also reported their experience with repeat partial nephrectomy in a group of 25 patients with a solitary kidney. A median of four tumors were resected with a median estimated blood loss of 2,400 ml and median operating time of 8.5 h. Fifty-two percent of the patients experienced perioperative complications; there were four lost kidneys and one perioperative death. The metastasis-free survival at 57 months was 95 %. The authors describe repeat PN in the solitary kidney as a high-risk surgical alternative to definite dialysis [47] (Fig. 18.8).

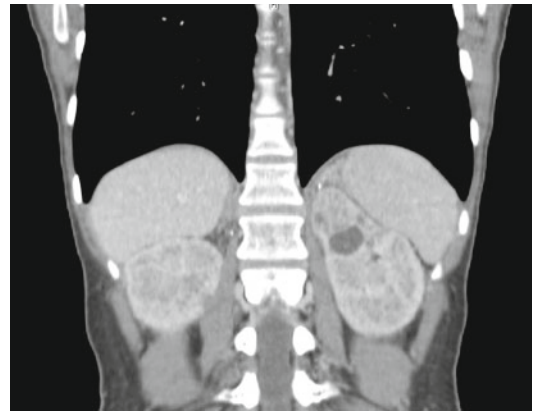

Fig. 18.8 Recurrent left clear cell carcinoma in a 27-year-old female with tuberous sclerosis syndrome. This patient has undergone bilateral primary and repeat partial nephrectomies

Unusual Patterns of Recurrence After Laparoscopic Partial Nephrectomy

It has been more than 20 years since Clayman and colleagues introduced laparoscopic radical nephrectomy (LRN), a technically challenging operation which provided a minimal surgical scar, less analgesic support, and a faster return to normal activities [48, 49] without apparent depreciation of oncological effects [50–54]. As the virtues of PN for the treatment of small renal masses were elucidated [55], skilled minimally invasive surgeons began developing techniques to perform laparoscopic partial nephrectomy (LPN), an operation requiring advanced technical training and expertise [56, 57]. Despite certain technical differences from OPN (i.e., inability to achieve cold ischemia following renal artery cross clamping), higher rates of conversion to RN, and more urological complications, oncological effectiveness did not appear to be diminished by the LPN [58]. However, unusual LR has been recently described in the literature involving intra-abdominal and port sites following minimally invasive PN and RN. A case was reported of LPN for a 4.5 cm type 2 papillary RCC which presented 2 years later with acute GI bleeding and port site with intra-abdominal disease involving the gall

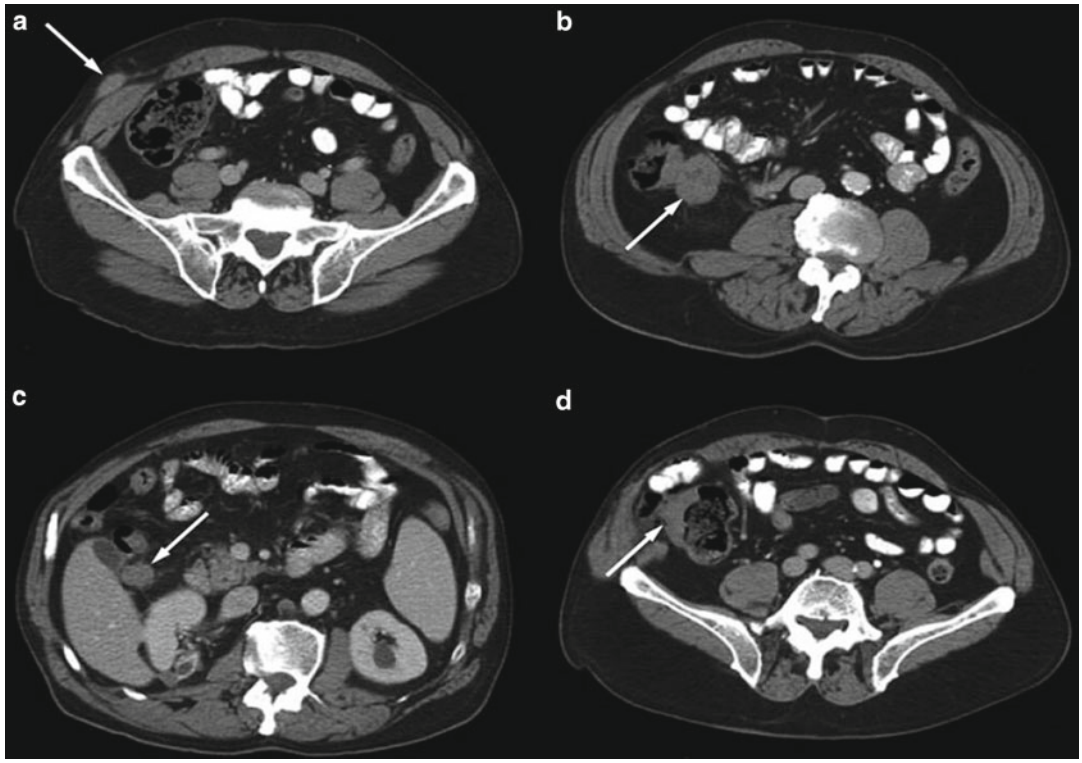

Fig. 18.9 Intra-abdominal, paracolic, and port site recurrences 2 years after hand-assisted laparoscopic partial nephrectomy in a 49-year-old male who presented with gastrointestinal bleeding from erosion of a peritoneal implant into cecum. Despite complete surgical resection of all sites of disease, disseminated metastatic disease developed within 12 months

bladder and right colon. Despite a complete salvage resection of all sites of disease and a 12-month disease-free interval, metastatic disease in liver and peritoneum was later evident [59] (Fig. 18.9). Another case of a 2-year-old girl with Wilms tumor underwent initial LPN and subsequent standard adjunctive chemotherapy only to present with diffuse metastatic intraperitoneal disease 4 months later [60]. Similar reports are now in the current literature which describe the same unusual patterns of RCC intraperitoneal dissemination after LRN and LPN including port site and wound implants, and attempted open surgical salvage with adjunctive systemic therapy. Later metastatic disease and patient mortality are also reported [61–64].

Unlike the LR associated with RN and the resection of massive primary renal tumors, these reports when taken together are disturbing in that it must be presumed that each of the patients initially had a good prognostic tumor amenable to PN. The precise mechanism by which these unusual sites of recurrence occurred can only be speculated, but similar intra-abdominal disease and port site dissemination events have been reported in laparoscopic resection of gynecological tumors and colorectal cancers [65], gallbladder cancer [66], and adrenal cortical cancers [67]. It is not clear what technical or physiological event leads to this form of tumor dissemination. The above described iatrogenic alteration in disease natural history, by whatever mechanism, essentially converts patients with small renal masses with an excellent prognosis to patients requiring surgical salvage, systemic therapy, and now an extremely guarded prognosis. In the absence of a centralized minimally invasive urological tumor surgery registry, it is not known how many other such cases have occurred and are unpublished. At the very least, careful

adherence to surgical principles must apply to both minimally invasive and standard open PN and appropriate warnings presented to patients prior to operative consent.

Local Recurrence Following Thermal Ablation

Renal tumor ablative modalities, including percutaneous and laparoscopic approaches utilizing radiofrequency ablation (RFA) and cryoablation, are offered selectively to some patients with renal tumors that are exophytic and not encroaching upon renal hilar vessels or collecting system elements [68]. Patients considered by many as ideal candidates for ablation are often old or comorbidly ill individuals harboring small renal tumors, the very patients ideally suited for active surveillance [69, 70]. Although the concept of nonsurgical ablation is appealing, the literature has serious deficiencies including up to 40 % of patients not having pre-ablation confirmation of tumor histology due to nondiagnostic or nonexistent biopsy, short overall follow-up, and high rates of tumor recurrence compared to PN ranging from 7.45- to 18.23-fold greater for RFA and cryotherapy, respectively [71, 72]. Additionally, because most studies lacked pathological biopsy confirmation to confirm the completeness of the ablation, it is not known whether changes in radiological images after ablation represent complete or partial tumor destruction or simply a renal tumor inadequately treated and not in active growth. A recent report of RFA reported by Best and colleagues reports recurrence rates of approximately 20 % for tumors of 3 cm or greater [73]. In addition, it would appear that whether the thermal ablation is delivered percutaneously (Fig. 18.10) or laparoscopically (Fig. 18.11), the relative impact on the tumor and the rate of complications are similar [74]. A specific problem relating to thermal ablation is judging the efficacy of the procedure and the lack of "biopsy, ablate, and resect" studies to determine the degree to which a lesion was treated or destroyed (incomplete, complete). Confusion also exists in the literature as to whether a CT enhancing post-ablation lesion is inflammatory or neoplastic in nature. Stein et al. reported five of 30 laparoscopically treated renal lesions with persistent enhancement 3 months following treatment, but only one was still enhancing by 9 months. In this case, a PN was performed which revealed inflammation and no recurrent

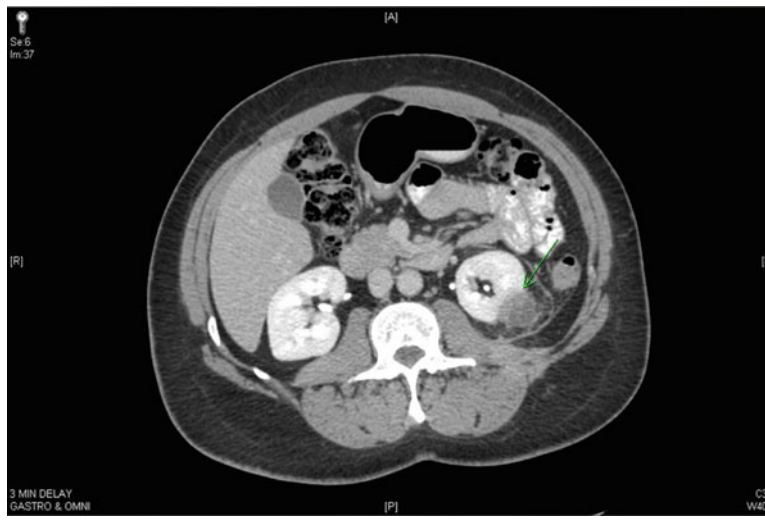

Fig. 18.10 Enhancing left renal mass in a 49-year-old African American female 14 months s/p percutaneous cryoablation of 2.0 cm exophytic clear cell carcinoma (P1aNxM0). Salvage partial nephrectomy was complete and persistent clear cell carcinoma was identified

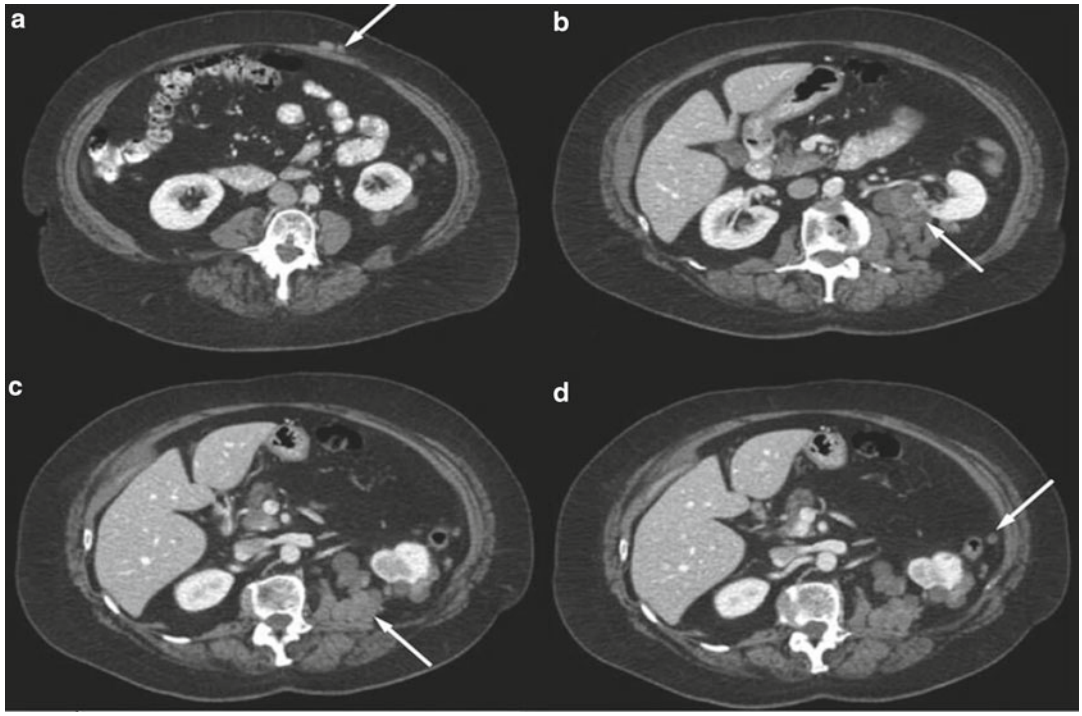

Fig. 18.11 A 74-year-old Russian female 2 years s/p laparoscopically assisted cryoablation of 1.8 cm exophytic renal tumor, histological type unknown. She later presents with port site, perinephric, and intra-abdominal tumor recurrences which were completely resected. Twelve months later, she has documented recurrent intra-abdominal disease and is receiving systemic therapy

cancer [75]. Breda and colleagues scrutinized the literature for insight into how to best manage recurrent (or persistent) lesions after ablation. A period of up to 9 months of surveillance was advocated as an initial step to determine if lesion CT enhancement was inflammatory or neoplastic. A biopsy-proven malignant lesion can undergo repeat ablation, attempted PN, or completion RN if significant post-ablation scarring prevents PN [76]. Increasingly, urological oncologists are being asked to operate on renal masses with imaging evidence of viability following radiofrequency ablation or cryoablation. A Cleveland Clinic report documented recurrence rates for cryoablation of 13/175 cases (7.4 %) and for RFA of 26 of 104 cases (25 %). Mean pre-ablation tumor sizes were 3.0 and 2.8 cm, respectively. Repeat ablations were performed in 26 patients but 12 patients were not candidates for repeat ablation due to large tumor size, disease progression, or repeat ablation failure. Of these, ten patients underwent attempted resection and only two patients were able to undergo a PN (open) with seven patients requiring RN. One operation was aborted [77]. NCI investigators recently reported their experience with 13 patients previously treated with RFA at a median time of 2.75 years prior using salvage PN. No tumors were converted to RN but the salvage operations were very difficult due to extensive fibrosis and scarring. Median operative time was 7.8 h (range 5–10.7 h) and median blood loss was 1,500 ml (range 500–3,500 ml) [78]. This data indicates that a failed ablation in a patient originally eligible for a PN or active surveillance makes for a difficult surgical salvage with a low likelihood of PN. Awareness of the difficulties of accurate radiological assessment of thermal ablation effectiveness, challenging operations required for attempted surgical salvage, and complications induced by such procedures should be a fundamental part of the informed consent for all such procedures [79].

Renal Cancer Metastasectomy

In 1939, Barney and Churchill first reported a patient that underwent nephrectomy and a resection of an isolated pulmonary metastasis for a renal cancer only to die 23 years later of coronary artery disease [80]. Over the last 60 years, the surgical resection of limited metastatic disease (metastasectomy) was offered to patients and selectively performed due to the absence of effective systemic therapies. The reported selection criteria for this aggressive surgical approach varied from study to study and significant prognostic factors included the site and number of metastatic deposits, completeness of resection, patient performance status, and the disease-free interval from treatment of the primary tumor to the diagnosis of metastatic disease. Complete resection of isolated metastases was associated with 5-year survival rates between 35 % and 60 %. Despite successful resection of metastatic disease and associated patient survival, definitive proof from these studies was lacking that the surgical intervention itself, as opposed to patient selection factors [21], and the natural history of renal cancer lead to the observed outcomes [5, 6, 81–87]. Pogrebniak and colleagues reported 23 patients who underwent resection of pulmonary metastases from RCC, 15 of whom had previously been treated with IL-2-based immunotherapy. Patients with resectable lesions had a longer survival (mean 49 months) than those patients with unresectable lesions (mean 16 months). Furthermore in this study, survival was not dependent upon the number of nodules removed [88]. The authors concluded that patients with metastatic RCC should be offered an operation if the likelihood that complete resection of all sites of disease was high. Favorable subgroups include those patients with a solitary site of metastases and disease-free interval to the development of metastases of greater than 1 year. It should be noted that, occasionally, sites of disease presumed to be metastatic RCC are instead secondary tumors (i.e., pancreatic islet cell tumor) of either benign or malignant histology. This diagnostic dilemma may be addressed in the future with the further development of conventional clear cell-specific immunoPET scanning with 124-I cG250 scanning [89].

Several major centers have reported their experience with metastasectomy. In a report from Memorial Sloan-Kettering Cancer Center (MSKCC), prognostic factors associated with enhanced survival in 278 patients who underwent surgical metastasectomy included a disease-free interval of greater than 12 months (55 % vs. 9 % 5-year overall survival), solitary versus multiple sites of metastases (54 % vs. 29 % 5-year overall survival), and age younger than 60 years (49 % vs. 35 % 5-year survival). Patient survival was longer when the solitary site of resection was lung (54 % 5-year survival) compared to brain (18 % 5-year survival). Twenty-nine percent of patients with completely resected multiple sites of metastases within a given organ survived 5 years, again suggesting that complete resection of all metastatic deposits was more important than the number of metastatic deposits within a given site [90]. MSKCC investigators reported a later experience with 61 patients who underwent nephrectomy followed by complete metastasectomy from 1989 to 2003. Of these patients, 59 % had a Karnofsky performance status (KPS) > 90, 90 % had conventional clear cell histology, and 62 % had renal tumors that were greater than stage T2. Median survival was 30 months which is considerably better than the 12 months for patients undergoing cytoreductive nephrectomy alone [91] (Fig. 18.12). Ultimately, a prospective and randomized clinical trial comparing metastasectomy to best standard systemic therapy could more clearly define the exact role of this approach.

Van der Poel and colleagues reported a multi-institutional Dutch study of 101 patients who underwent metastasectomy including 35 who underwent 2 and 6 who underwent 3 resections, respectively. Median survival was 28 months with better survival observed for lung when compared to other locations. In this study too, an interval of greater than 2 years from nephrectomy to metastasectomy was associated with a better prognosis. Survival of greater than 5 years was achieved in 7 % of patients and 14 % were alive

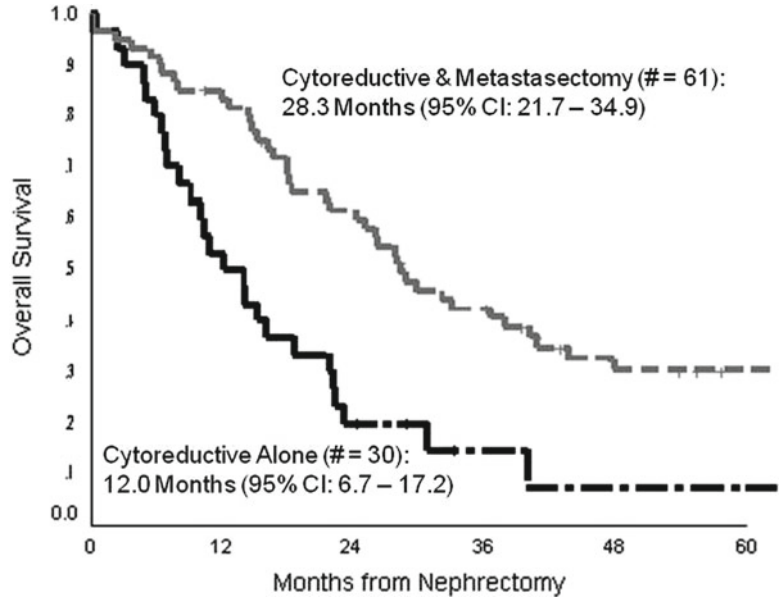

Fig. 18.12 Survival distributions of MSKCC patients undergoing metastasectomy and cytoreductive radical nephrectomy [102]

without evidence of disease after a minimal follow-up of 45 months. Resection of solitary metastasis versus multiple metastases did not offer a survival advantage [92]. Mayo Clinic investigators reported their experience with 125 patients who underwent metastasectomy for renal cancer. A cancer-specific survival advantage was associated with complete metastasectomy versus incomplete (4.8 years vs. 1.3 years). Complete resection remained predictive for improved cancer-specific survival for patients with greater than three metastatic lesions as well as patients with synchronous and asynchronous multiple metastases [93]. Cleveland Clinic investigators identified 92/417 patients with pulmonary metastases who underwent resection. In 50 % of patients, one or two lesions were resected and 37 % had five or more resected. In 63 patients (68 %), complete resection was achieved. Five-year survival was 45 % for patients undergoing a complete resection. For completely resected patients, a shorter disease-free interval was an adverse prognostic indicator for worse overall survival. Fewer pulmonary nodules predicted a higher probability of complete resection [94].

For patients with non-solitary metastatic disease, some advocate systemic therapy first prior to consideration of surgical metastasectomy in hopes of improving the chance of a subsequent complete metastasectomy [95]. With the advent of the highly effective tyrosine kinase and mTOR inhibitors, investigators have increasing enthusiasm for this neoadjuvant approach. Firek and colleagues from Germany reported 11 patients who underwent metastasectomy after 3 or more months of stable partial remission and subsequent complete resection of all metastatic disease. After sizeable operations, including a liver resection and vena caval resection, and a median follow-up of 12 months, five patients were without evidence of disease whereas six others developed distant disease [96]. Cleveland Clinic and MD Anderson investigators reported a "consolidative" metastasectomy after neoadjuvant targeted therapy. Fifty percent of patients experienced recurrent disease at a median of 42 weeks and 50 % of patients were without evidence of disease at 43 weeks [97]. These data are limited by small numbers, likely selection biases, and short follow-up, and hence, it remains unclear whether neoadjuvant

targeted therapy will enhance the effectiveness of metastasectomy.

Although the curative impact of metastasectomy remains uncertain, operative intervention can also provide effective palliation for symptomatic metastatic disease to sites such as bone, brain, and adrenal gland [98, 99]. In addition, improvements in hepatobiliary surgical techniques and perioperative care have allowed surgeons to perform metastasectomy of liver and pancreatic metastases [100, 101].

Conclusions

It is now known that renal cell carcinoma represents a family of neoplasms possessing unique molecular and cytogenetic defects with 90 % of the metastases emanating from the conventional clear cell carcinoma subtype which is associated with mutations and dysfunction of the VHL gene. For patients with metastatic renal cancer, prognostic factors defined in systemic therapy clinical trials effectively stratify patients into good, intermediate, and poor risk groups (MSKCC, Motzer factors) with median survival varying between 4 and 13 months. These same factors also stratify patients whose renal cancers that were initially resected completely and then developed subsequent metastatic disease. Careful case selection in the medical and surgical management of mRCC can often make it difficult to distinguish between disease natural history and subsequent therapeutic effects. Isolated LR following RN is a rare occurrence and can appear in the nephrectomy bed or within the vena cava. Resection of isolated LR can be a formidable operation requiring adjacent organ resection and can be associated in a minority of cases with prolonged survival. Similarly, LR after partial nephrectomy is an uncommon event and more commonly represents a new tumor formation rather than an LR. In recent years, new forms of LR have been encountered including persistent disease after thermal ablation and port site and intra-abdominal disease after laparoscopic RN and PN. These forms of LR represent alterations in disease natural history and carry a generally poor prognosis despite salvage resection. Metastasectomy in carefully selected patients can be associated with prolonged disease-free survival. Distinguishing the therapeutic impact of metastasectomy from prolonged disease natural history and patient selection factors can be difficult. The impact of the newly introduced tyrosine kinase and mTOR inhibitors on the management of LR and isolated metastases remains to be determined.

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Outcomes: Prognostic Factors, Models, and Algorithms

19

Brandon K. Isariyawongse and Michael W. Kattan

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 minimally invasive surgical techniques and targeted therapy for systemic disease – 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 nearly 65,000 new cases of renal cancer are diagnosed yearly, and more than 13,000 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 the advent of targeted therapy for renal cancer – most specifically, inhibitors of the vascular endothelial growth factor (VEGF) receptor – 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. 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

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 [5]. The subsequent Robson staging system – a modification of the earlier staging model – was

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Table 19.1 2010 American Joint Committee on Cancer TNM staging for renal cancer with expected 10-year cancer-specific survival rates

TNM stage		10-year cancer-specific survival rate[a]
TX	Primary tumor cannot be assessed	
*T*0	No evidence of primary tumor	
*T*1	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 %
*T*2	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 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 %
*T*4	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. [9])

employed primarily through the early 1990s but has since been supplanted by the more prognostically accurate TNM (tumor, node, metastasis) staging system [6]. 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, and, most recently, 2010 [7, 8]. 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 19.1). Additionally, tumors that 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. 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 equalling 0.85 (Table 19.1) [9].

Nuclear Grade

In addition to tumor stage, tumor nuclear grade for renal cell carcinoma (RCC) has demonstrated significant correlation with both pathologic

stage and survival outcomes. The Fuhrman classification system remains the most widely applied criteria by genitourinary pathologists and is based on nuclear size, irregularity, and nucleolar prominence [10]. The utility of the Fuhrman grading system was evaluated by Bretheau et al. in a retrospective review of 190 patients with RCC, which demonstrated that nuclear grade was significantly associated with synchronous metastases, lymph node involvement, renal vein involvement, tumor size, and perirenal fat involvement [11]. Furthermore, 5-year survival outcomes for patients with Fuhrman grades I, II, III, and IV were found to be 76 %, 72 %, 51 %, and 35 %, respectively. However, despite the evidence that nuclear grade is a significant prognostic factor for RCC, there has been widespread criticism that the reproducibility of nuclear grading between different pathologists is marginal, at best, and some authors have argued for a simplification of the Fuhrman system into a two-tiered schemata [12]. In spite of the noted inter-observer variability, multivariate analyses have consistently demonstrated that tumor nuclear grade is an independent predictive factor of staging and survival outcomes in RCC [13].

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 19.2) [14]. 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 [15]. 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) [16, 17]. 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 [18, 19]. Sarcomatoid differentiation of the primary tumor is another extremely poor prognostic factor with median survival less than 1 year in most series [20].

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 discrepancies 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 [21, 22]. 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 [23, 24]. Yet another study demonstrated no significant prognostic effect for low levels of CA-IX [25]. 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 19.2. 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 [26].

Table 19.2 Prognostic factors by category in renal cell carcinoma (Data from Lane et al. [14])

Prognostic factors in renal cell carcinoma	
Anatomic factors	Clinical factors
Tumor size	Performance status
Extension into perinephric or renal sinus fat	Cachexia
Venous involvement	Platelet count
Extension into ipsilateral adrenal gland	Blood count
Lymph node metastasis	Calcium
Distant metastasis	Alkaline phosphatase
	C-reactive protein
	Erythrocyte sedimentation rate
Histologic factors	Molecular factors
Nuclear grade	*Hypoxia-inducible factors*: CA-IX, CA-XII, CXCR3, CXCR4, HIF, IGF-1, VEGF, VEGFRs
Histologic subtype	*Co-stimulatory molecules*: B7-H1, B7-H3, B7-H4, PD-1
Presence of sarcomatoid features	*Cell cycle regulators*: p53, Bcl-2, PTEN, Cyclin A, p27, Skp2
Presence of necrosis	*Adhesion molecules*: EpCAM/KSA, EMA, E-Cad, alpha-catenin, Cad-6
Vascular invasion	*Other factors*: Ki-67, XIAP, Survivin, EphA2, Vimenin, CA-125, Annexin II
Invasion of collecting system	

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 [27] and patients in general would actually prefer to receive even more information than is presented to them [28]. Furthermore, it is clear that patients who are better-informed experience improved psychosocial outcomes following therapy [29].

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. 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 [30]. Moreover, approximately 20 % of clinical stage I renal masses will ultimately prove to be benign, and only around one fourth of cases will exhibit potentially aggressive pathologic features [31–34]. 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.

Our group had previously constructed a nomogram predicting the risk of malignancy in T1 renal masses based on patient sex, size of mass, presence of symptoms, and history of smoking [35]. The model was based on a cohort of 862 patients from the Cleveland Clinic in which 20 % of the tumors were benign and 80 % were malignant, and the most powerful predictors based on the visual scale were age and size of the renal mass. The predictive accuracy of the model for differentiating between benign and malignant disease was reasonably good, as measured by the boot-strap corrected concordance index (0.644).

Kutikov et al. more recently composed a preoperative nomogram that incorporated RENAL nephrometry score as a variable in predicting malignant and high-grade pathology for renal tumors (Fig. 19.1) [36]. The RENAL nephrometry score is a system that has been devised to more

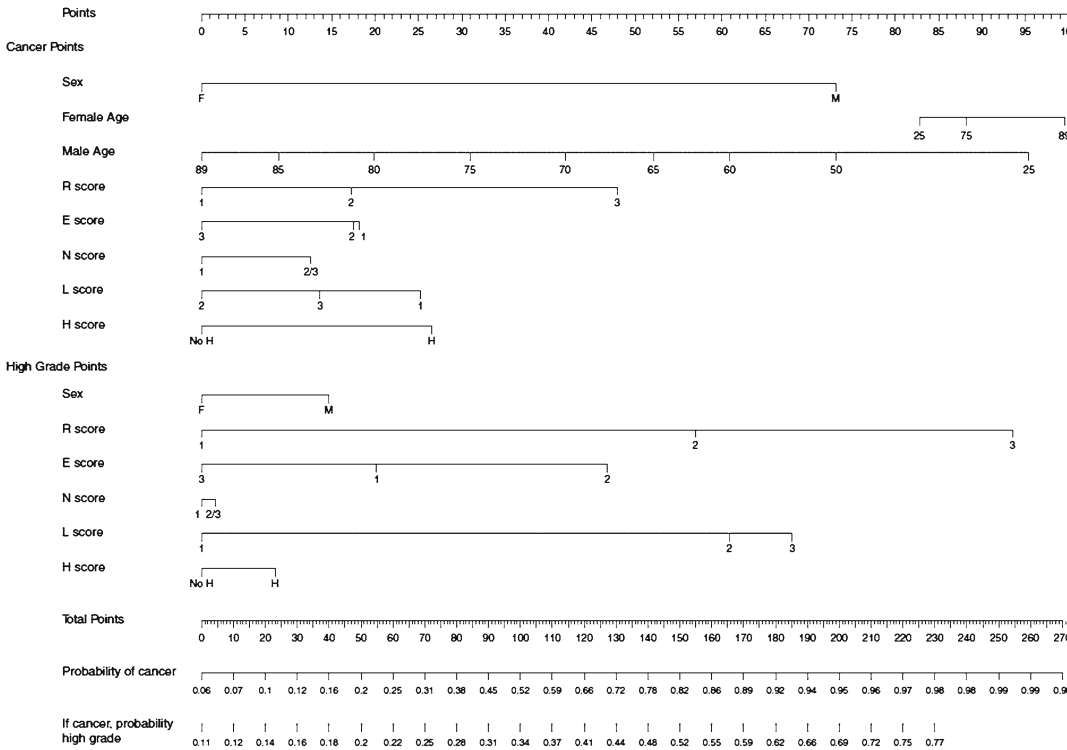

Fig. 19.1 Preoperative nomogram that incorporates RENAL nephrometry score to predict the risk of malignancy and high-grade pathology in renal tumors (Reproduced with permission from Kutikov et al. [36])

explicitly characterize the anatomic features of renal masses; RENAL serves as an acronym for its individual components: radius (maximum diameter of mass), endophytic/exophytic properties, nearness of mass to the collecting system, anterior/posterior, and location relative to the polar lines [37]. Additionally, an H designation is assigned if the mass abuts the renal hilar vasculature. Although not initially devised as a prognostic tool, RENAL nephrometry score was shown to be predictive of malignancy during the creation of this nomogram. Other predictive variables included patient age and sex, and the overall model performed well: the measured area under the curve (AUC) was 0.76 and 0.73 for histology and grade, respectively. The model and its discrimination were subsequently validated in an external cohort with an AUC equal to that of the original study [38].

It is apparent from these models that the combination of several prognostic factors for RCC can be especially helpful to patients deciding between definitive therapy and active tumor surveillance. The recognition that treatment-related harm may exceed therapeutic benefit represents a shift towards 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.

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 [39]. The predictive factors included tumor size, pathologic T stage, Fuhrman nuclear grade, presence of necrosis, presence of vascular invasion, and clinical presentation (Fig. 19.2). 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.

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 19.3) [40]. 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 [41]. Indeed, in a multicenter European study, the UISS fared worse in terms of discriminating accuracy when compared to other models including a postoperative nomogram [42].

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 19.4 and 19.5) [43]. The model was based on more than 1,800 patients who underwent nephrectomy between 1970 and

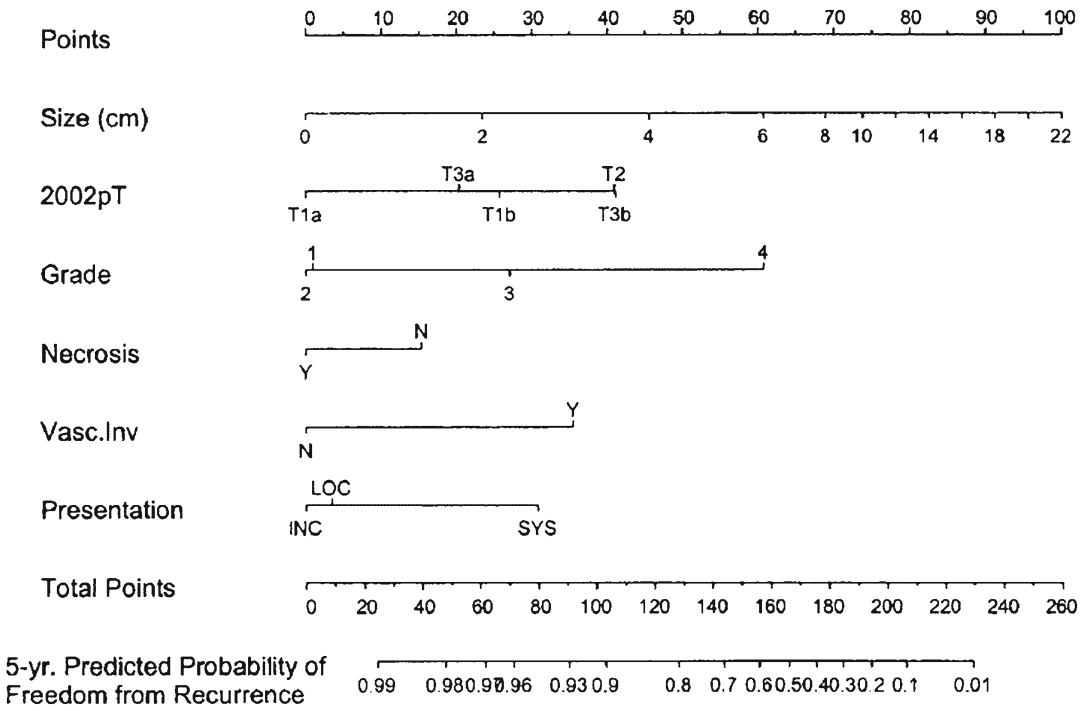

Fig. 19.2 Postoperative nomogram predicting the probability of freedom from recurrence following nephrectomy for conventional renal cell carcinoma (From: Sorbellini et al. [39])

Table 19.3 University of California, Los Angeles Integrated Staging System (UISS) for patients with renal cell carcinoma (Data from Zisman et al. [40])

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	

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 European cohort, SSIGN demonstrated a superior AUC, particularly in the nonmetastatic setting [44–47].

Table 19.4 Tumor stage, size, grade, and necrosis (SSIGN) score for prognosis in patients undergoing radical nephrectomy for clear cell renal cell carcinoma (Data from Frank et al. [43])

	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

Table 19.5 Prognostic outcome predictions for 1-year, 5-year, and 10-year cancer-specific survival rates based on the SSIGN score (Data from Frank et al. [43])

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

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 [48–51]. 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, 10, 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 versus 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 has 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 [52]. The utility of these criteria lies primarily in their ability to stratify patients for the purposes of clinical trials, 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.

Motzer and colleagues did embrace the movement towards 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 [53]. The model was internally validated, and the calculated concordance index was 0.63.

More recently, Karakiewicz et al. utilized data from a randomized phase III study of bevacizumab plus interferon-alpha versus interferon-alpha alone to construct a nomogram that predicts

progression-free survival [54]. The model allows calculation of survival at four 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. However, the model has yet to be externally validated.

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 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 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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20 Adjuvant Systemic Therapy, Immunotherapy, and Targeted Treatment

Linda Cerbone and Cora N. Sternberg

Systemic Therapy for Metastatic Disease

Introduction

For many years the standard treatment for metastatic renal cell carcinoma (mRCC) was based on the cytokines interleukin-2 (IL-2) and interferon-α (IFN-α), because the immune system was thought to play a key role in the natural history of this disease. Unfortunately, with these treatments only some patients benefitted in terms of overall survival (OS), and many suffered their toxicities [1]. Currently, their use is limited to a very small selected category of patients. In the past few years, seven new molecular targeted agents have been approved by the US Food and Drug Administration (FDA) and in Europe by the European Medicines Agency (EMA) for the treatment of mRCC.

The key to the development of these new therapies has been discovery of the von Hippel-Lindau tumor suppressor protein (pVHL) and its relation to factors inducible by hypoxia (HIF) 1 and 2. Through loss of pVHL, transcription factors HIF 1 and 2 accumulate and activate the transcription of various genes including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). VEGF and PDGF are critical mediators of tumor angiogenesis in RCC and other cancers [2].

These targeted drugs, tyrosine kinase inhibitors (TKIs) and VEGF-inhibitors, are sunitinib, pazopanib, sorafenib, axitinib, and bevacizumab plus interferon. In addition, inhibition of the rapamycin complex in mammals (mTOR) represents an important therapeutic target in mRCC. Two drugs, everolimus and temsirolimus, have demonstrated improved outcomes [3].

European and US guidelines are based upon the clinical trials in which the drugs were developed. Risk classification for these studies has been based on MSKCC prognostic criteria which includes Karnofsky performance status (<80 %), time from diagnosis to treatment with IFN-α (<12 months), hemoglobin (<normal), lactate dehydrogenase (>1.5 upper normal limit), and corrected serum calcium (> normal). These criteria identify three categories: low risk with 0 risk factors, intermediate risk with 1–2 risk factors, and high risk with ≥ 3 risk factors [4]. The current treatment algorithm in 2012, based on risk stratification, is shown in Table 20.1. The risk factors are currently debated because MSKCC criteria were validated in patients who received interferon in the "cytokines era." Retrospective studies have tried to understand their value in the "targeted era" and have added other variables such as neutrophilia and thrombocytosis [5]. This issue is still unsolved.

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Immunotherapy

Interferon

Interferon's antitumor activity has been extensively documented in numerous preclinical and clinical studies. There are three classes of interferon: IFN-α (alpha), IFN-β (beta), and IFN-γ (gamma). Of these, IFN-α has been most evaluated in RCC for its antiproliferative and antiangiogenic properties. Although the mechanism of antitumor activity remains unclear, many phase II studies have been conducted in mRCC to investigate IFN-α as monotherapy in different dosages. An objective response rate of 3–31 % has been achieved with a median PFS ranging from 3 to 22 months and response duration from 7 to 17 months. A small percentage of patients have achieved complete remission. There is no clear dose-response relationship, even if a higher-dosage schedule appears associated with greater activity. The highest efficacy has been achieved using doses between 5 and 18 MU s.c. three times per week. In all the studies the most common toxicities have been flu-like syndrome, fever, myalgia, anorexia, and fatigue. A median of 31 % of patients have required dose reductions. Anti-IFN antibodies are found in 14–63 % in the serum of treated patients. Predictors of response to IFN are good performance status, limited tumor mass, and the presence of lung lesions as the sole site of metastatic disease [1, 6].

IFN-α has been compared in only two randomized trials to non-cytokine therapy. In the REO1 study 350 patients with mRCC were randomized to IFN-α 10 MU s.c. TIW or to medroxyprogesterone acetate (MPA) 300 mg daily for 12 weeks. The IFN arm demonstrated a higher reduction in the risk of death (28 %, HR = 0.72; $p = 0.017$) and an improvement in median survival (8.5 months vs. 6 months) [7]. In another phase III trial comparing IFN-α 18 MU s.c. TIW plus vinblastine 0.1 mg/kg I.V. every 21 days versus vinblastine alone, the combination arm was superior in terms of response rate (RR) (16.5 % vs. 2.5 %, $p = 0.0025$) and median overall survival (OS) (15.8 vs. 8.8 months; $p < 0.01$) (Table 20.2) [8].

Interleukin-2

IL-2 demonstrates antitumor activity through proliferation of natural killer cells (NK), lymphokine-activated killer cells (LAK), and other cytotoxic cells involved in host-immune activity. Its efficacy has been evaluated in mRCC using different schedules of administration. In 1992 the FDA approved the use of high-dose IL-2 for the treatment of patients with mRCC because a small number of patients achieved durable responses. High-dose IL-2, administered in bolus I.V., was evaluated in seven phase II trials, involving 255 patients [9]. Doses of I.V. IL-2 ranging from 600,000 U/kg to 2.6 MU/kg were administered by I.V. bolus every 8 h for 14 consecutive doses over

Table 20.1 Treatment algorithm of mRCC based on MSKCC criteria

Regimen	Setting	Therapy	Options
Treatment-naïve patient	MSKCC risk: good or intermediate	Sunitinib	High-dose IL-2
		Bevacizumab + IFNα	Sorafenib
		Pazopanib	Clinical trials
			Observation
	MSKCC risk: poor	Temsirolimus	Sunitinib
			Clinical trials
Treatment-refractory patient (≥second line)	Prior Cytokine	Sorafenib	Sunitinib
		Pazopanib	
		Axitinib	
	Prior VEGF-TKI	Everolimus	Clinical trials
		Axitinib	
	Prior mTOR inhibitor	Clinical trials	

Table 20.2 Selected trials of IFNα and IL-2 in mRCC

Treatment	No. of patients	Response rate (%)	Median PFS (months)	Median OS (months)
IFNα (10 MIU sc TIW) versus medroxyprogesterone acetate (MPA) (300 mg daily) [7]	350	13 7	4	8.5 6 ($p<0.01$)
IFNα (18 MIU sc TIW) + vinblastine (0.1 mg/kg iv q3W) versus vinblastine (0.1 mg/kg iv q3W) [8]	160	16.5 2.5 ($p=0.0025$)		15.8 8.8 ($p<0.01$)
IL-2	400			
720,000 U/kg every 8 h iv versus 72,000 U/kg every 8 h iv 250,000 U/kg to 125,000 U/kg sc 5 days on 7 [10]		21 14 11		No difference in OS

5 days and repeated after a 1 week interval. Response was assessed after 12 weeks. An overall objective RR of 15 % was reported, with 7 % complete responses and a median duration of 20 months. Median survival was 16 months. High-dose IL-2 therapy is extremely toxic and 4 % treatment-related deaths were reported. For this reason, many investigators have tried to evaluate the response of lower doses of IL-2 [10]. A randomized phase III trial compared three schedules of administration: high-dose I.V., low-dose I.V. (72,000 U/kg every 8 h), and s.c. (5 days on seven days starting with 250,000 U/kg then 125,000 U/kg). Toxicity was less in the low-dose arm but RR was higher in the high-dose treated arm (21 % with high dose vs. 13 % with low dose; $p=0.048$). No difference in OS between the three arms was observed, but the survival of patients who obtained complete remissions in the high-dose arm was longer than in the low-dose arm ($p=0.04$). IL-2, however, has not become a mainstay of treatment because of the expense and toxicity associated with this therapy (Table 20.2).

High-dose IL-2 may be considered a therapeutic option for selected good and intermediate MSKCC-risk criteria patients especially in experienced centers able to manage the adverse events. For better patient selection, surrogate markers predictive of response have been investigated [11].

The SELECT trial (NCT00554515) evaluated the relationship between response to high-dose IL-2 and tumor expression of carbonic anhydrase IX (CAIX). Data presented at ASCO in 2010 showed a higher RR with high-dose IL-2 compared to the historical experience (29 % vs. 21 %, $p=0.0009$), although two treatment-related deaths were observed. CAIX overexpression was not predictive of response [12].

Targeted Therapy

Anti-VEGF

Several TKIs have shown efficacy in mRCC with improvement in PFS as both first- and second-line treatments of mRCC [13–18] (Table 20.3).

Sunitinib

Sunitinib (Sutent®) is an oral TKI that inhibits tyrosine kinases VEGFR-1,2,3, platelet-derived growth factor receptor (PGFR-α,β), c-kit, and FTL-3. On February 2, 2007, the FDA approved sunitinib from accelerated approval to full regular approval for advanced kidney cancer following confirmation of improvement in PFS in a randomized trial.

In a phase III first-line study of 750 patients comparing sunitinib 50 mg orally daily,4 weeks on and 2 weeks off with IFN-α 9 MIU×3 s.c. weekly, sunitinib achieved a longer PFS (11 months vs. 5 months, $p<0.000001$) and a better RR (31 % vs. 6 %, $p<0.001$). No difference in OS was observed between the two arms (26.4 vs. 21.8 months; $p=0.051$). An expanded access

Table 20.3 Clinical trials of approved VEGF e mTOR-targeted therapies

Treatment	No. of patients	Objective response (%)	Median PFS (months)	Median OS (months)
Sunitinib versus IFNα [13]	750	31 versus 6 ($p<0.001$)	11 versus 5 ($p<0.000001$)	26.4 versus 21.8 ($p=0.051$)
Pazopanib versus placebo [14, 19]	435	30 versus 3	9.2 versus 4.2 ($p<0.0001$)	22.9 versus 20.5 ($p=0.224$)
Bevacizumab + INFα versus INFα (AVOREN trial) [17]	649	25.5	10.2 versus 5.4	23.3 versus 21.3 ($p=0.33$)
(CALGB 90206 trial) [16]	732	31	TTP: 8.5 versus 5.2	18.3 versus 17.4 ($p=0.097$)
Sorafenib versus placebo [18]	903	10	5.5 versus 2.8 ($p<0.001$)	19.3 versus 15.9 ($p=0.02$)
Temsirolimus versus IFNα versus temsirolimus+ IFNα [24]	626	8.6 4.8 8.1	5.5 ($p<0.001$) 3.1 4.7	10.9 ($p=0.008$) 7.3 8.4
Everolimus versus placebo [25]	416		4.9 versus 1.9 ($p<0.001$)	14.8 versus 14.4 ($p=0.162$)
Axitinib versus sorafenib [20]	732	19.4 versus 9.4 ($p=0.0001$)	6.7 versus 4.7 ($p<0.0001$)	

study permitted patients in the IFN arm to cross over to sunitinib after the first PFS analysis.

Adverse events occurring more commonly on sunitinib included gastrointestinal events (diarrhea, nausea, mucositis, vomiting, dyspepsia, abdominal pain, gastroesophageal reflux, oral pain, glossodynia, and flatulence), bleeding, hypertension, dermatologic events (rash, skin discoloration, dry skin, and hair color changes), hand-foot syndrome, limb pain, decreases in cardiac ejection fraction, and peripheral edema. Treatment-emergent hypothyroidism was also more common in patients receiving sunitinib.

Grade 3/4 adverse events more common on sunitinib included hypertension, diarrhea, hand-foot syndrome, nausea, vomiting, mucositis, and bleeding. Grade 3/4 laboratory abnormalities more common in sunitinib-treated patients included hematologic abnormalities (neutropenia, thrombocytopenia, and leucopenia), increased lipase and amylase, hyponatremia, hyperuricemia, and hyperbilirubinemia [13].

Pazopanib

Pazopanib (Votrient®) is an oral tyrosine kinase inhibitor of VEGFR 1,2,3, PDGFR-α,β, and c-kit. On October 19, 2009, the FDA granted approval for the treatment of patients with advanced RCC. A multinational phase III trial randomized 435 patients (ratio 2:1) to Pazopanib (800 mg daily) or placebo. Fifty-four percent of the patients were treatment naïve and 46 % had received prior cytokine therapy. More than half of the population (54 %) randomized to placebo, crossed over to the active treatment arm, many as early as 6 weeks. Pazopanib significantly improved PFS compared to placebo (9.2 months vs. 4.2 months, $p<0.0001$; HR 0.46). This benefit was confirmed in both groups and was most noticeable in patients who were treatment-naïve. In patients who had no prior therapy PFS was 11.1 months versus 2.8 months, $p<0.0001$; HR 0.40 and in patients who had received prior cytokine therapy, it was 7.4 months versus 4.2 months, $p<0.001$; HR 0.54. Overall objective responses were, respectively, 30 % versus 3 % ($p<0.001$) in the entire population, 32 % versus 4 % ($p<0.001$) in treatment-naïve patients, and 29 % versus 3 % ($p<0.001$) in cytokine pretreated patients. The median duration of response in Pazopanib arm was 58.7 weeks. Median OS in the Pazopanib arm was 22.9 months compared to 20.5 months for placebo (HR = 0.91, $p=0.224$) [14]. These results are heavily influenced by the high crossover rate.

The most common adverse reactions, reported in 20 % of patients, were diarrhea, hypertension, hair color changes, nausea, anorexia, and vomiting. Grade 3/4 adverse reactions were abnormal liver aminotransferases (ALT/AST), diarrhea, hypertension, and proteinuria. A low incidence of Grade 3/4 hematological events was reported [19].

Pazopanib is under investigation as first-line therapy in two other studies, COMPARZ (NCT00720941) and PISCES (NCT01064310), that have both been closed to accrual [15]. PISCES is a randomized double-blind trial investigating patient preferences between pazopanib and sunitinib and will be reported at ASCO 2012. The COMPARZ trial is a non-inferiority study comparing pazopanib versus sunitinib. The primary endpoint is PFS and secondary endpoints are OS, objective RR, safety, and quality of life.

Bevacizumab + IFNα

Bevacizumab (Avastin®) is a humanized monoclonal antibody that binds and neutralizes VEGF-A, which blocks angiogenesis and reduces tumor vascularization. On July 31, 2009, the FDA granted approval for bevacizumab in combination with IFN-α for mRCC. The approval was based on results from the CALGB trial which demonstrated a 5-month improvement in median PFS in patients treated with bevacizumab and IFN-α as compared to IFN-α [16].

Two randomized phase III studies of bevacizumab and IFN-α have been conducted: the US CALGB 90206 [16] and the European AVOREN trials [17]. Both studies have investigated bevacizumab 10 mg/kg I.V. every 2 weeks plus IFN-α 9 MIU×3 s.c. weekly versus IFN-α alone. The benefit in PFS for the combination arm was statistically significant: 8.5 versus 5.2 months in the CALGB trial (HR=0.71; $p<0.0001$) and 10.2 versus 5.4 months (HR=0.6; $p=0.0001$) in the AVOREN trial. Bevacizumab+IFN-α showed superiority in ORR and OS. In the CALGB trial ORR was 31 % versus 13 % ($p<0.0001$) and OS was 18.3 versus 17.4 months ($p=0.097$). In the AVOREN trial ORR was 25.5 % versus 13.1 % and OS was 23.3 versus 21.3 months ($p=0.33$). At the time of progression, the majority of patients in both studies received multiple subsequent treatments that impacted on survival rendering no statistically significant differences between the arms.

The most common side effects of bevacizumab were epistaxis, hypertension, and proteinuria. Serious adverse events reported were gastrointestinal perforation, wound healing complications, and arterial thrombotic events.

Sorafenib

Sorafenib (Nexavar®) is a multi-targeted receptor TKI that inhibits VEGFR 2,3, PDGFR-β, raf kinase, and FTL-3. On December 20, 2005, the FDA approved sorafenib for advanced RCC. This indication is based on the demonstration of improved PFS in a large, multinational, randomized double-blind, placebo-controlled phase III study.

The TARGET study evaluated pretreated patients (primarily cytokines) and showed an improvement in PFS in patients randomized to sorafenib 400 mg BID orally daily versus placebo (5.5 vs. 2.8 months, $p<0.001$) [18]. This trial failed to demonstrate a statistically significant difference in OS (19.3 vs. 15.9 months, $p=0.02$) most likely due to the number of patients who were allowed to cross over to this active treatment after progression on placebo. The most common side effects reported were fatigue, hand-foot syndrome, diarrhea, and hypertension.

Axitinib

Axitinib (Inlyta®) is a multi-targeted kinase that inhibits VEGFR 1,2,3, PDGFR α,β, and c-kit. On January 27, 2012, the FDA approved axitinib treatment of advanced RCC after failure of one prior systemic therapy. The phase III AXIS trial enrolled 723 patients and compared axitinib 5 mg BID orally daily versus sorafenib 400 mg BID orally daily as second-line treatment after failure of any approved first-line therapy. Median PFS, the primary endpoint, was higher in the axitinib arm (6.7 vs. 4.7 months, $p<0.0001$). The benefit

with axitinib was most remarkable post-cytokine therapy with PFS of 12.1 months as compared to post-sunitinib with PFS of 4.8 months. Data on OS are not yet available.

The most common (at least 20 %) adverse reactions in patients treated with axitinib were diarrhea, hypertension, fatigue, decreased appetite, nausea, dysphonia, hand-foot syndrome, decrease in weight, vomiting, asthenia, and constipation. Other severe reactions reported in patients treated with axitinib included hypertensive crisis, arterial and venous thrombotic events, hemorrhage, gastrointestinal perforation and fistula formation, and reversible posterior leukoencephalopathy syndrome [20].

Tivozanib

Tivozanib (AV951) is an oral tyrosine kinase inhibitor of VEGFR 1,2,3 and PDGFR for the treatment of mRCC. Promising data were obtained in a randomized phase II discontinuation trial (NCT00502307). This study included 272 patients with advanced or mRCC. The median PFS of 11.7 months was even better, 14.8 months, in those patients with clear cell RCC who had undergone nephrectomy [21]. These promising results led to the phase III TIVO-1 trial (NCT01030783). This study randomized 517 patients with mRCC, who were treatment naïve or had one prior non-VEGF-targeted therapy, to tivozanib 1.5 mg orally daily 3 weeks on/1 week off versus sorafenib 400 mg BID continuously allowing crossover to tivozanib in patients who progressed on sorafenib. Tivozanib demonstrated a statistically significant improvement in PFS compared to sorafenib (11.9 vs. 9.1 months). This result was even better in the subgroup of patients who were treatment naïve with PFS of 12.7 versus 9.1 months [22]. The full data will be presented at ASCO 2012.

Dovitinib

Dovitinib (TKI258) is a tyrosine kinase inhibitor targeting FGFR 1,2,3 and also VEGFR 1,2,3, and PDGFR. FGF and activation of its receptor FGFR may be a mechanism in which tumors overcome resistance to VEGF inhibition. A phase I/II trial (NCT00715182) in 59 mRCC patients previously treated with VEGFR and/or mTOR inhibitors showed promising results with PFS of 6.1 months and OS of 16 months [23]. A phase III randomized trial (NCT01223027) is comparing dovitinib 500 mg orally daily 5 days on/2 days off scheduled in 28 day cycles to sorafenib 400 mg BID in patients who have failed one VEGF and one mTOR inhibitor. The primary endpoint is PFS and secondary endpoints are OS, RR, safety, patient-reported outcomes, and pharmacokinetics [15].

mTOR Inhibitors

Mammalian target of rapamycin (mTOR) inhibitors, which affect the mTOR pathway, show significant efficacy in mRCC in the second-line setting and as first-line therapy in poor-risk patients [24, 25] (Table 20.3).

Temsirolimus

Temsirolimus (Torisel®) is a specific inhibitor of the mammalian target of rapamycin. mTOR is a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. mTOR integrates the input from upstream pathways, including insulin growth factors (such as IGF-1 and IGF-2), and amino acids. A phase III trial (NCT00065468) including 626 untreated, poor-risk patients with mRCC, randomized to single agent temsirolimus 25 mg I.V. weekly, IFN-α 3 MIU × 3 s.c. weekly, with an increase to 18 MIU or the combination 15 mg I.V. of temsirolimus weekly plus 6 MIU of IFN-α three times weekly. This trial demonstrated a 49 % improvement in OS in favor of single agent temsirolimus.

Common adverse reactions reported in patients receiving temsirolimus were rash, asthenia, and mucositis. Common laboratory abnormalities were anemia, hyperglycemia, hyperlipidemia, and hypertriglyceridemia. Serious but rare cases of interstitial lung disease, bowel perforation, and acute renal failure were observed.

Temsirolimus demonstrated superiority in terms of OS and PFS over IFN-α and provides an additional treatment option for patients with advanced RCC [24].

Everolimus

Everolimus (Afinitor®) is an oral mTOR inhibitor. On March 30, 2009, the FDA approved everolimus for advanced RCC after failure of treatment with sunitinib or sorafenib. The RECORD-1 (NCT00410124) phase III study enrolled 416 patients with mRCC who had failed previous anti-VEGFR treatment and were randomized 2:1 to everolimus 10 mg orally daily or placebo. PFS was higher in the treatment arm (4.9 vs. 1.9 months; HR 0.33, $p<0.001$). The median OS was 14.8 months for everolimus versus 14.4 months for placebo (HR 0.87, $p=0.162$), because 80 % of the patients in the placebo arm crossed over to receive everolimus.

The most common adverse reactions (incidence ≥30 %) were stomatitis, infections, asthenia, fatigue, cough, and diarrhea. The most common grade 3/4 adverse reactions (incidence ≥3 %) were infections, dyspnea, fatigue, stomatitis, dehydration, pneumonitis, abdominal pain, and asthenia. The most common laboratory abnormalities were anemia, hypercholesterolemia, hypertriglyceridemia, hyperglycemia, lymphopenia, and increased creatinine (incidence ≥50 %). The most common grade 3/4 laboratory abnormalities (incidence ≥3 %) were hyperglycemia, anemia, hypophosphatemia, and hypercholesterolemia. Deaths due to acute respiratory failure (0.7 %), infection (0.7 %), and acute renal failure (0.4 %) occurred on the everolimus arm but not on the placebo arm. Not common but important to recognize is the possibility of developing noninfectious pneumonitis [25].

Sequencing and Combination of Targeted Therapy

There is evidence that targeted agents given sequentially improve PFS of patients with mRCC. The rationale of this approach is related to the different and numerous pathways involved in the development, progression, and drug resistance of this disease. Sequential therapy is considered as a way to overcome resistance. Until recently only retrospective data were available about VEGF-VEGF sequencing. Prospective data supporting both VEGF-mTOR and VEGF-VEGF sequencing have emerged with the results of RECORD-1 and the AXIS trials. Ongoing trials are, however, trying to assess the optimal sequence of treatment. SWITCH (NCT00732914) is a phase III trial comparing sunitinib followed by sorafenib or the opposite sequence. RECORD-3 (NCT00903175) is a phase II studying everolimus followed by sunitinib versus sunitinib followed by everolimus. Meanwhile, START (NCT01217931) is a phase II trial performed at the M. D. Anderson Cancer Center in which 240 patients will be assigned to compare six different two-drug "sequence" of everolimus, bevacizumab, or pazopanib [26].

Another approach used to overcome resistance is the simultaneous inhibition of pathways using combinations of targeted agents. Data, available from phase I/II trials conducted, provided preliminary indications of the efficacy of the combination despite a heavy toxicity of the combination of anti-VEGF therapy. More studies are needed to validate the outcome of this approach [26, 27].

Predictive Markers

Several tumor biomarkers of efficacy and safety have been retrospectively identified as predictors of response. The most interesting findings are related to the correlation between single nucleotide polymorphism (SNPs) and efficacy and tolerability of targeted agents. Efficacy of sunitinib may be affected by the identification of two polymorphism in VEGFR3, while a higher toxicity is related to CYP3A5*1 polymorphism [28]. Efficacy of pazopanib seems to be related to presence of polymorphisms in IL-8, HIF1A, NR1I2, and VEGFA [29].

Regarding the potential role of clinical side effects as predictive factors of response, it has

been retrospectively demonstrated for sunitinib and axitinib in patients who developed hypertension during therapy [30, 31], for sunitinib and sorafenib in patients who developed hypothyroidism [32], and recently for temsirolimus in patients who developed an increase in cholesterol levels [33].

Novel Therapeutic Strategies

One of the most challenging questions in the "targeted era" is whether or not immunotherapy still has a role in the treatment of mRCC. Many patients do not respond to VEGF and mTOR inhibition and other pathways should be considered. Recently, novel immunotherapeutic and angiogenesis inhibition strategies have been evaluated. Vaccine therapy, cytotoxic T-lymphocyte antigen 4 (CTLA-4) blockade, and programmed death-1 inhibition belong to the first group, while inhibition of Ang/Tie-2 to the second. Among the novel compounds in development in mRCC are IMA901 and AGS-003 (both vaccines), ipilimumab (monoclonal antibody against CTLA-4), and MDX-1106 (a fully human IgG_4 antibody blocking PD-1). PD-1 is a member of the extended CD28/CTLA-4 family of T cell regulators. Overexpression of PD-L1 by RCC tumors has been shown to be associated with adverse clinical/pathologic features. Targeting programmed death PD-1 and the PD-L1 pathway is under intensive investigation [34]. AMG-386, also under investigation, is a peptibody preventing the interaction of Ang-1 and 2 with Tie-2 [35].

Adjuvant Systemic Therapy

Although 70 % of localized or locally advanced RCCs can be cured by radical surgery, recurrence rates range from 35 % to 65 %. During the past years, several strategies have been investigated to reduce this recurrence rate. In the adjuvant setting, all studies conducted with cytokines (interleukin or interferon) and most with vaccines have not shown benefit in terms of PFS or OS [36]. In addition, trials evaluating therapies such as thalidomide, UFT, 5-fluorouracil associated with interferon alpha and interleukin-2 (IFN-α/IL-2) and medroxyprogesterone have failed to demonstrate improvement in OS [37] (Table 20.4).

Current studies are attempting to evaluate TKIs (sorafenib, sunitinib, and pazopanib), the monoclonal antibody (WX-G250), and everolimus in this setting [16]. Outside the setting of controlled clinical trials, there is currently no indication for adjuvant therapy following radical surgery.

Immunotherapy

IFN-α has been evaluated in a phase III trial randomizing 247 patients to 6 MIU intramuscularly (I.M.) TIW for 6 months or observation. At 5 years, there were no significant differences in disease-free survival (DFS) (56.7 % treated arm vs. 61.1 %, $p=0.107$) or OS (66 % vs. 66.5 %, $p=0.861$). There was a trend in benefit in the subgroup of patients treated with INF-a with pN2 nodal status [38].

The same lack of efficacy in DFS and OS was seen in another randomized trial of 283 patients. The treatment arm was IFN-α-NL (lymphoblastoid interferon) daily for 5 days every 3 weeks 3 MIU/m^2 day 1; 5 MIU/m^2 day 2; 20 MIU/m^2 days 3, 4, and 5 by I.M. versus placebo. At a median follow-up of 10.4 years, median survival was 7.4 years in the observation arm and 5.1 years in the treatment arm ($p=0.09$). Median recurrence-free survival was 3.0 years in the observation arm and 2.2 years in the interferon arm ($p=0.33$) [39]. These data clearly show that adjuvant immunotherapy is not necessary and may even be detrimental.

High-dose IL-2 has also been investigated as adjuvant therapy in a small randomized trial [40]. Sixty-nine patients with locally advanced or metastatic resected RCC were enrolled. Twenty-one patients with locally advanced resected tumor were treated with a single course of IL-2 600,000 U/kg every 8 h on days 1–5 and days 15–19; 23 patients were observed. Differences in DFS (32 % treatment arm vs. 45 %, $p=0.431$) and OS (80 % vs. 86 %, $p=0.906$) were not significant between the two arms.

Table 20.4 Adjuvant immunotherapy, vaccines, and other therapies

Clinical trials	No. of patients	Outcome
IFNα versus observation [38]	247	PFS: 56.7 % versus 61.1 %, $p=0.107$ OS: 66 % versus 66.5 %, $p=0.861$ Negative (positive trend in pN2 status)
IFNα NL versus observation [39]	283	OS: 5.1 year versus 7.4 year, $p=0.09$ Negative
HD IL-2 versus observation [40]	69	PFS: 32 % versus 45 %, $p=0.431$ OS: 80 % versus 86 %, $p=0.906$ Negative
IL-2 + IFNα versus observation [41]	310	DFS: 0.73 versus 0.60, $p=0.47$ Negative
IL-2 + IFNα + 5FU versus observation [37]	203	OS: 81 % versus 91 %, $p=0.0278$ Negative
Autologous vaccine +/− BCG versus observation [43]	120	DFS: 63 % versus 72 % Negative
Autologous renal tumor cell vaccine (Reniale) [42]	553	Positive in term of PFS: 77 % versus 68 %, $p=0.02$
HSPPC-96 (vitespen) versus observation [45]	918	Relapse: 37.7 % versus 39.8 %, $p=0.506$ Negative
MPA versus observation [37]	136	Relapse: 33 % versus 34 % Negative
UFT versus observation [37]	71	RFS: 80.5 % versus 77.1 % Negative
Thalidomide versus observation [37]	46	RFS: 47.8 % versus 69.3 %, $p=0.022$ Negative

Combination therapy with IL-2 and IFN has likewise not proven efficacious. One hundred and fifty-seven patients were randomized to a 4-week cycle of s.c. IL-2 1 million UI/sqm BID days 1–2 and 1 million UI/sqm on days 3,4,5 + IFN 1.8 million UI/sqm days 3 and 5 of each week. Cycles were repeated every 4 months for the first 2 years and every 6 months for the remaining 3 years. The control arm enrolled 153 patients. DFS at 5 and 10 years was 0.73 and 0.73 in arm A versus 0.73 and 0.60 in arm B (HR 0.84; 95 % CI: 0.54-1.33 $p=0.47$). No difference was found in OS [41].

Vaccine Therapy

Reniale is an autologous renal tumor cell vaccine. A randomized phase III trial demonstrated some benefit with Reniale adjuvant therapy after radical nephrectomy. In a multicenter phase III study with a follow-up period of more than 10 years, OS was in favor of the vaccine. The postoperative progression-free survival of the patients after 70 months was 72 % in the vaccine group, while it was only 59.3 % in the control group. OS was not statistically different between the two arms. Although this study was published in 2004, it has been heavily subjected to criticism [42].

The major issues identified were related to the methodology. One hundred and seventy-nine patients, enrolled before surgery, were excluded because of a histologic diagnosis negative for carcinoma or due to the lack of survival data. In addition the use of an independent radiological review was not considered.

In another prospective randomized trial, 120 patients were evaluated after radical nephrectomy and randomized 1:1 to a vaccine consisting of three intradermal injections of $10^{(7)}$ autologous irradiated tumor cells mixed with $10^{(7)}$ Bacillus Calmette-Guèrin in the first two vaccinations or alone or control. After 5 years disease-free survival (DFS) was 63 % in the treatment

Table 20.5 Adjuvant RCC phase III trials [15]

Trial	No. of patients	Population/design	Primary endpoint	Study start
S-TRAC (NCT00375674)	720	Placebo versus sunitinib, 1 year	DFS	2007
ASSURE (NCT00326898)	1,923	Placebo versus sunitinib versus sorafenib, 1 year	DFS	2006
SORCE (NCT00492258)	1,656	Placebo versus sorafenib 1 year versus sorafenib 3 years	DFS	2007
PROTECT (NCT01235962)	1,500	Placebo versus pazopanib 1 year	DFS	2010
EVEREST (NCT01120249)	1,218	Placebo versus everolimus 1 year	DFS	2011
ARISER (NCT00087022)	864	Placebo versus WX-G250 (Rencarex) 24 weeks	DFS	2004

group versus 72 % and OS, respectively, 69 % versus 78 % [43].

HSPPC-96 is a protein peptide complex consisting of a 96 kDa heat shock protein (Hsp), gp96, and an array of gp96-associated cellular peptides. Immunization with HSPPC-96 induces T cell-specific immunity against these peptides [44]. HSPPC-96 is an immunotherapeutic agent made from an individual patient's own tumor, collected at the time of surgery. A multicenter, open-label, randomized (1:1), phase III trial of adjuvant HSPPC-96 (vitespen) versus observation in high-risk patients after surgery was performed (NCT00033904). Tumor tissue was sent to Antigenics manufacturing facility where it underwent a process to create a vaccine. Patients in the treatment arm received the vaccine intradermally weekly for 4 weeks and then every 2 weeks until vaccine depletion or disease recurrence. Recurrence was reported in 37.7 % of 361 patients treated with vitespen and in 39.8 % of patients in the control group ($p=0.506$, HR 0.923, 95 % CI: 0.729-1.169). Median DFS was not significantly improved by vaccine, although a positive trend was shown in stages I and II (recurrence of 15.2 % vs. 27 %, $p=0.056$, HR 0.576). No difference in recurrence-free survival (RFS) was seen between patients given vitespen and those who received no treatment. Thus far, this agent has only been approved in Russia and patients are still followed for OS [45].

Other Therapies

Thalidomide, MPA, UFT, and 5-FU as adjuvant treatment have been investigated in randomized trials versus observation and none of them showed improvement in recurrence rates (Table 20.4) [37].

Targeted Therapies

With the advent of targeted therapies for patients with advanced or mRCC, there has been an interest in evaluating these therapies in the adjuvant setting (Table 20.5). S-TRAC is a randomized, double-blind, phase III trial evaluating 1 year of adjuvant sunitinib 50 mg daily 4/6 weeks versus placebo in high risk after nephrectomy (NCT00375674). The primary endpoint is DFS. Secondary endpoints are RFS, OS, and safety [15]. Seven hundred and twenty patients will be recruited between 2007 and 2017. The entry criteria have been slightly modified due to difficulties in accrual.

The ASSURE trial (NCT00326898) was initiated in 2006. This is an ECOG cooperative group trial (E2805) of approximately 1,923 patients. ASSURE is a three-arm randomized, double-blind, phase III trial comparing 1 year of adjuvant sunitinib 50 mg daily 4/6 weeks for 9 cycles versus 1 year of sorafenib 400 mg BID daily for 6 weeks for 9 cycles versus placebo. The primary endpoint is DFS; secondary endpoints are OS and toxicity. Difficulties in delivering full doses of therapy in the adjuvant setting have been raised. A translational research side study will evaluate angiogenic markers, frequency of oncogene or tumor suppressor gene mutations, and tumor and genetic polymorphism as predictive factors [15].

The SORCE trial was initiated in 2007. It is a phase III, double-blinded study comparing

sorafenib with placebo in the adjuvant setting (NCT00492258). It is of major interest because it asks a relevant question: if 1 versus 3 years of adjuvant therapy is beneficial. Approximately 1,656 patients will be randomized in three different arms (ratio 2:3:3). In arm A patients are treated for 3 years with placebo, in arm B with sorafenib 400 mg BID daily for 1 year followed by 2 years of placebo, and in arm C patients will receive sorafenib 400 mg BID daily for 3 years. The primary endpoint is DFS. Secondary endpoints include OS, RCC-specific survival time, and toxicity. Translational studies will attempt to define if biologic parameters can be considered as predictive factors [15]. Enrollment should be complete in August 2012.

The PROTECT trial is an international randomized phase III study with an estimated enrollment of 1,500 patients to evaluate whether 1 year of adjuvant pazopanib 600–800 mg daily compared with placebo can prevent or delay recurrence in patients at moderately high or high risk of developing recurrence after nephrectomy or partial nephrectomy (NCT01235962). The primary endpoint is DFS and secondary endpoints include OS, disease-free survival rates at yearly time points, safety, and health outcomes [15].

Everolimus is also under investigation in the adjuvant setting post-nephrectomy in a SWOG trial. The EVEREST trial (NCT01120249) is a randomized phase III trial of 10 mg p.o. everolimus versus placebo. Enrollment was initiated in April 2011 and 1,218 patients are planned. Everolimus and placebo will be administered orally for 9 cycles; 1 cycle corresponds to 6 weeks of treatment. The primary endpoint is RFS; secondary endpoints are OS and toxicity [15].

WX-G250 (Rencarex®) is a chimeric monoclonal antibody that binds to carbonic anhydrase IX (G250/MN), which is present on greater than 95 % of clear cell RCCs. The suggested working mechanism of WX-G250 is via ADCC. Following initial promising results in metastatic disease, a randomized, double-blind, phase III trial called ARISER was initiated to evaluate adjuvant cG250 treatment versus placebo in patients with clear cell RCC at high risk of recurrence (NCT00087022). The trial is still ongoing, but no longer recruiting participants. Patients have received monoclonal chimeric antibody cG250 (WX-G250) I.V. over 15 min weekly for 24 weeks. Primary endpoints of this trial are DFS and OS. Secondary endpoints are safety, quality of life, and pharmacokinetics [15]. The study was initiated in 2004 and 864 patients were to have been recruited. Due to few recurrences, in November 2011, the IDMC recommended cancelling the interim analysis and performing the final DFS analysis of the trial. In addition, preliminary results with 124I-labeled antibody (cG250) positron emission tomography (PET) imaging are of interest.

Current Scenario

Immunotherapy has been largely unsuccessful in the adjuvant setting for patients with high-risk RCC. The introduction of novel agents for the treatment of mRCC has radically changed the natural history of this disease. The main focus of current research has concentrated on managing the side effects of these therapies and evaluating their possible use in the adjuvant setting. Results in the adjuvant setting must be extremely promising, or patients and physicians will be reluctant to employ these agents in otherwise "healthy" patients. Important topics in which to focus research include better understanding of the genetic differences among populations in order to understand their ability to respond to individual drugs and their individual possibilities of suffering from toxicity. Novel immunotherapeutic agents targeting the PD-1/PD-L1 pathway on the near horizon hold future promise.

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Role for Radiation Therapy in Renal Cancer

21

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 [9] 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 [30, 48]. Over this same period, technological advances have provided the ability to deliver larger doses of radiation with far greater precision. Nonetheless, surgical resection justifiably remains the gold standard in the treatment of RCC [2, 26, 32], and the overall role of radiation therapy in the definitive treatment of RCC still remains minimal (with several important exceptions). In this chapter we will review the literature with an emphasis on adjuvant and palliative interventions.

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Definitive Radiation

The current data do not support a definitive role for radiation therapy. Elsewhere in the chapter we will discuss several atypical instances in which radiation was employed in the absence of surgical intervention [4].

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

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(300 rads) was administered either to the whole body or left lung alone. IL-2 (5,000 Cetus units) was given intraperitoneally twice daily for five 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 (non-irradiated) 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 [10]. 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 [44]. 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.

Clinical studies are needed to assess the role of a combination of immune modulators and RT in patients with cancers such as RCC, in which the immune system seems to play an important antitumor role.

Preoperative Neoadjuvant Radiation

Irradiation of human RCC before its transplantation into NMRI nu/nu mice yielded significantly lower acceptance rates than those for non-irradiated tumors (1/7 as compared to 13/13) [34]. These findings suggested a potential role for preoperative adjuvant radiation as it conceivably stands to lower the risk of intraoperative seeding of tumor cells [31]. A number of anecdotal accounts also suggested easier resectability as a result of tumor shrinkage and vessel sclerosis following radiation [39, 40]. Correspondingly, several retrospective series conducted prior to modern staging, surgery, and radiation therapy techniques reported positive outcomes following preoperative external beam radiation [12, 38].

Disappointingly, the two prospective randomized trials undertaken as a result of this prior research found little benefit. The Rotterdam Trial [46] 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 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 [47]. 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 [30].

The Swedish Trial [21] 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, despite the fact that 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.

Postoperative Adjuvant Radiation

Early retrospective data from the 1950s to 1960s reported improved survival at both 5 and 10 years following postoperative external beam radiation (EBRT) [5, 12, 38]. In a larger retrospective cohort [37]. found significantly improved survival and local control among those receiving postoperative radiation. 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 [11]. Most discouraging was the Copenhagen Renal Cancer Study [24] 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 % [36]. 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 non conformal radiation plan and the resulting toxicity superimposed upon 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 [16, 22, 28, 43]. 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 [45] 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 [13, 25]. The site of primary origin was the kidney in the majority [28] 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 delivering 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 (five patients), IV (three patients), or lumbar fossa recurrence (three patients) of renal cancer were treated with IOERT and surgical resection [25]. Histological confirmation of clear cell adenocarcinoma was available in ten 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, three patients were reported with a distant relapse. One of the three 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.

At the University of Heidelberg, another series of 11 patients with RCC (locally advanced primary – three, locally recurrent – eight) 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 IORT were detected [25].

At the University of California, San Francisco, 14 patients with local recurrence of RCC underwent subsequent surgical resection with ten of the 14 also receiving IOERT [25, 29]. 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)" [25].

Stereotactic Body Radiotherapy (SBRT)

Renal cancer cells have been historically classified as radioresistant to fractionated conventional radiation therapy and molecular mechanisms to explain this was recently published [19]. 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). Molecular and the biological mechanisms to explain these excellent results have recently been proposed. Studies by Fuks [14] 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 [9] 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 [27]. 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 [49] reported quite recently that nude mice transfected with A498 human renal cell carcinoma cells exhibited sustained decrease in tumor volume

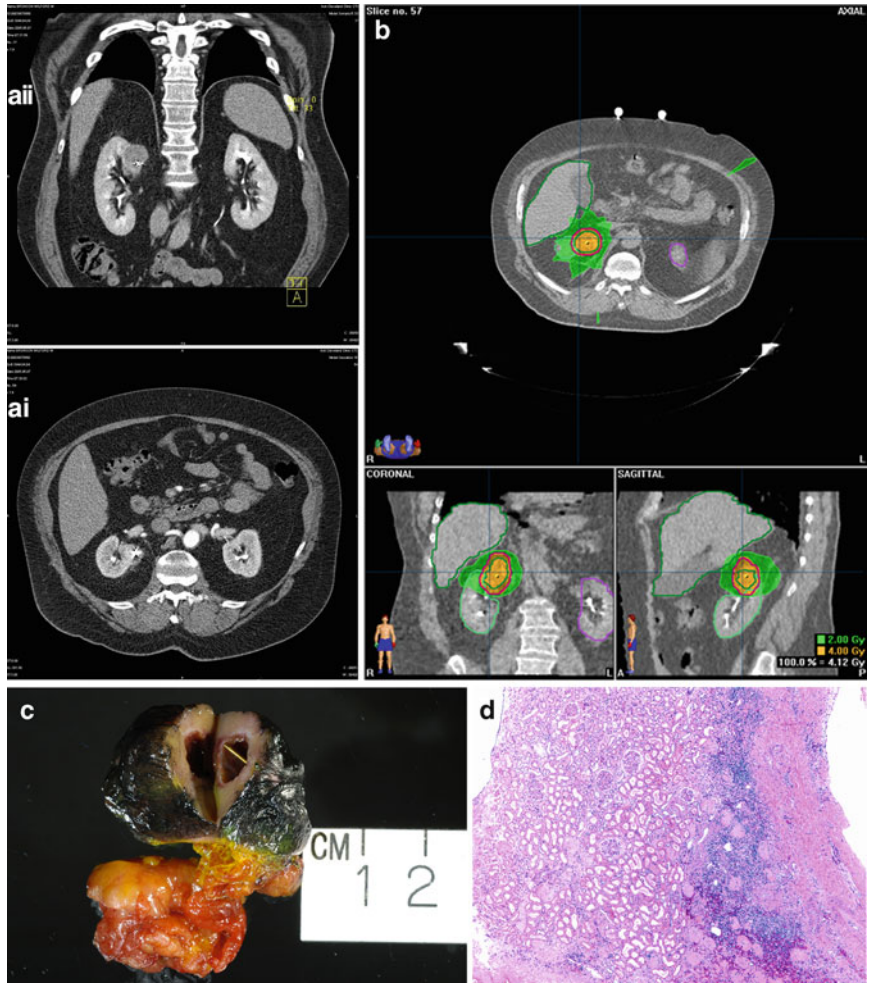

Fig. 21.1 (**ai**) R kidney lesion (clear cell type) with fiducial for SBRT – axial and (**aii**) coronal. (**b**) SBRT isodose plan (600 cGy × 4 fractions in 2 days – twice daily). (**c**) Laparoscopic partial nephrectomy specimen with fiducial. (**d**) Pathology showing complete necrosis at the site of tumor (*right*) with normal surrounding renal parenchyma (*left*)

following high-dose-per-fraction radiation (three fractions for total dose of 48 Gy). In an attempt to examine the efficacy of definitive radiation treatment, Beitler [4] reported a series of nine patients with non-metastatic renal cell carcinoma who refused definitive surgery. Patients received 40 Gy in five 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 [50] 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 five 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. These studies suggest that stereotactic treatment offers an appealing alternative for inoperable patients with primary tumor, recurrent disease, or, as we will discuss in the greater detail, metastases. Figure 21.1 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.

Palliative Radiotherapy

Brain metastases are diagnosed in approximately 10 % of patients with metastatic renal cell carcinoma [51, 52]. In a survey of patients treated at Massachusetts General Hospital for CNS metastases from renal cell carcinoma, Halperin [18] 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 [52]. 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 [17]. 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 non-neurologic causes. A number of similar studies confirming efficacy and providing reassurance in regard to side effects emerged shortly thereafter [20, 35]. In 2003, Sheehan [41] 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 [23]. 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 a 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 [42] 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 [15]. In 1983, Halperin [18] 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 [33]. 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 [15] 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, 53]. 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 five 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

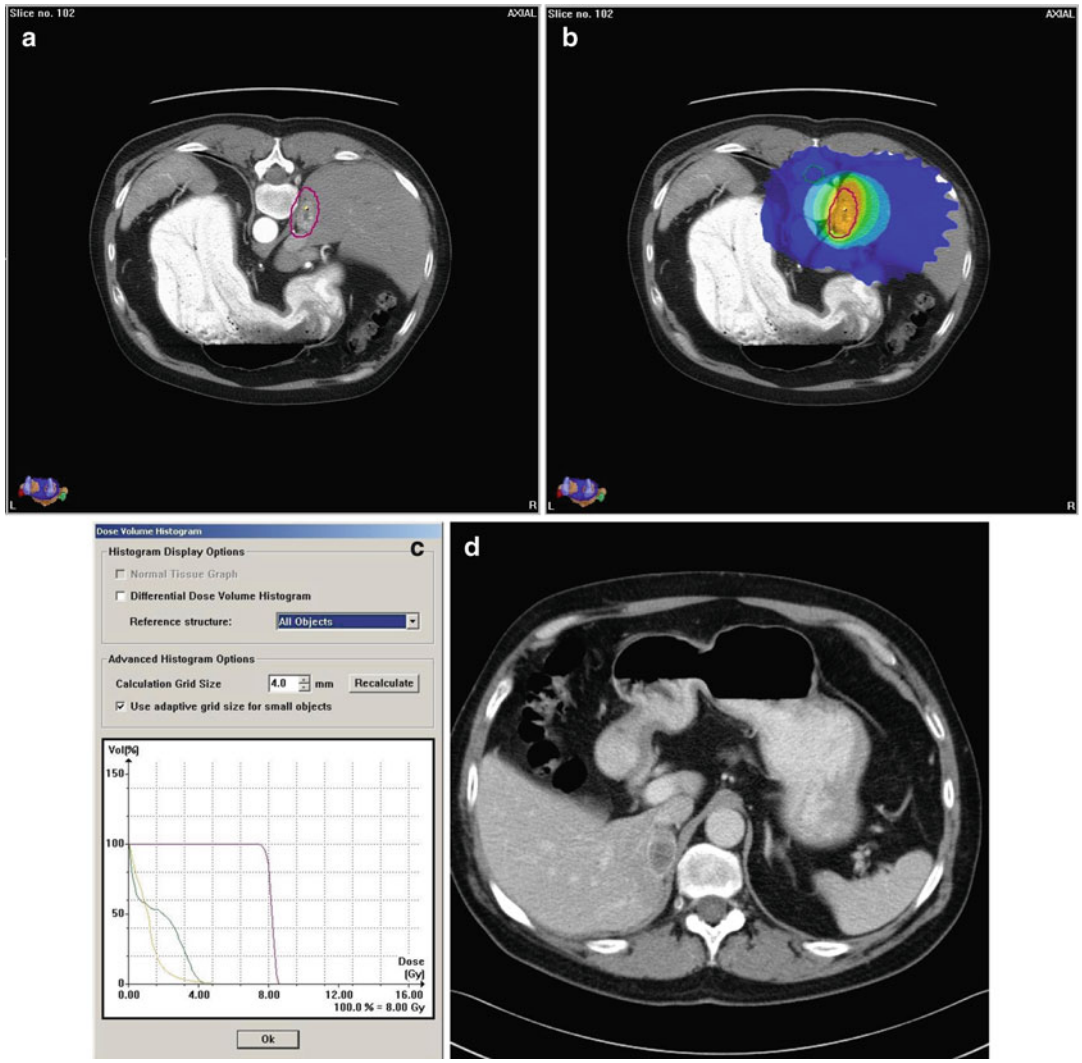

Fig. 21.2 (**a**) 55-year-old male with history RCC s/p radical nephrectomy in 2002, s/p right lower and middle lobectomy for 1.5 cm RCC lung oligometastasis in 2004, presented in 2006 with local recurrence in right nephrectomy bed. Target delineated with 4D CT scan and treatment planning allowing for 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**) Post-treatment CT with increased conspicuity of treated lesion due to central hypoattenuation seen at 4 months post treatment. Patient is now 6 years post SBRT and NED

hypofractionated regimens [54]. Multivariate analysis revealed that 24 Gy versus a lower dose ($p = 0.009$) and a single dose versus hypofractionation ($p = 0.008$) were significant predictors of improved local progression-free survival.

It seems reasonable to believe that the palliative role of radiation therapy especially stereotactic and hypofractionated RT will continue to develop in coming years. Figures 21.2 and 21.3 are representative examples of current radiation therapy techniques including stereotactic body radiation therapy for recurrent renal fossa mass (Fig. 21.2) and spinal radiosurgery for spinal metastasis (Fig. 21.3).

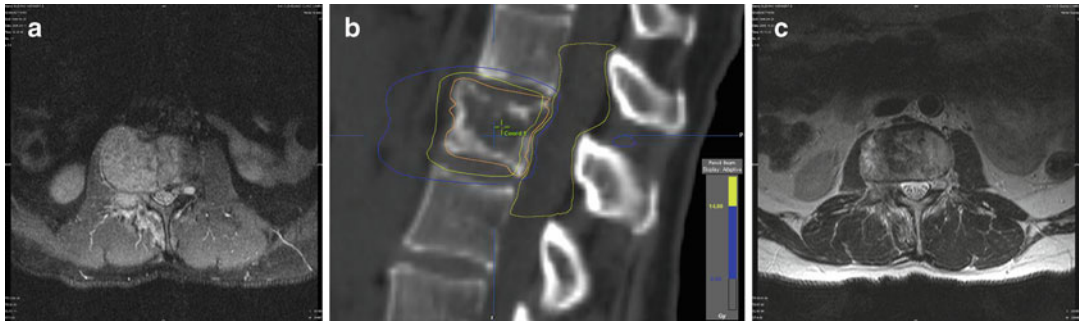

Fig. 21.3 (**a**) A 61-year-old male with severe back pain. MRI revealed spinal metastasis with paraspinal mass and mild thecal compression – biopsy metastatic RCC. (**b**) Isodose plan sagittal view. (**c**) Six months post SRS – regression of paraspinal mass and thecal compression. Patient pain-free at this site

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 determine the role radiation may play as an adjuvant therapy. There is no established definitive role for radiation therapy at this time.

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22 Surgical Management for Transitional Cell Carcinoma of the Upper Tract

Jason R. Gee

Epidemiology

Upper tract malignancies are relatively uncommon, with an estimated annual incidence of 1–4 per 100,000 [1]. Renal pelvic tumors account for 15 % of all renal tumors, and ureteral cancers account for 1–2 % of urologic cancers [2, 3]. The vast majority of these cancers are urothelial in origin, whereas up to 10 % may feature squamous histology [4]. Relatively rare histologic variants include adenocarcinoma, small cell carcinoma, and micropapillary urothelial carcinoma [5–7], and benign pathology such as fibroepithelial polyps and glomus tumors may also be encountered [8, 9]. Upper tract urothelial carcinoma is more prevalent in Caucasians and males [10, 11]. 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 [12].

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 % [13]. Likewise, patients who are diagnosed with upper tract tumors are at high risk for developing bladder cancer. As justification for regular cystoscopic surveillance, an estimated 25–75 % of these patients can develop bladder cancer [14–16]. Fortunately, synchronous and metachronous involvement of the upper tracts occurs uncommonly in only 5 % of patients with this disease [17].

Biology

In general, the prognosis associated with upper tract urothelial malignancies tends to be worse than that of bladder cancers. This may be due to differences in biology of these cancers. For instance, evidence exists 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 [18]. 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 [19]. 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 [20]. 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

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Table 22.1 TNM staging

TNM staging of upper urinary tract transitional cell carcinoma [28]	
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

in tumor biology which have been reported based on location [21–24]. In these studies, ureteral tumor location was found to be associated with a worse prognosis. The hypothesis associated with this finding was that the ureteral adventitia was relatively thin and had a more extensive network of blood vessels and lymphatic drainage which contributed to the potential for invasion and metastasis. Another hypothesis is that the renal parenchyma can act as a protective barrier to tumor spread in some instances. However, this remains controversial in that other investigators have reported no difference in tumor biology between ureteral and renal pelvic tumors [25, 26].

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 [27]. The most recent TNM staging criteria for these tumors is shown in Table 22.1 [28]. Multiple series have validated pathologic stage as an indicator of metastatic potential and prognosis [29–31]. Accordingly, investigators have also identified tumor grade and architecture as prognostic factors [32]. Lymphovascular invasion, tumor necrosis, and the presence of hydronephrosis have also been identified as indicators of worse prognosis in patients with these tumors [31, 33–35].

Carcinogenesis/Risk Factors

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 [36]. Aromatic amines in industrial dyes have also been implicated [37]. 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 [38]. Region-specific susceptibility has also been identified with Balkan endemic nephropathy. Multiple theories exist ranging from exposure-related events to infectious etiology [39, 40]. Interestingly, the regular consumption of Chinese herbs containing aristolochic acid both in this region and China has been associated with

specific mutations of upper tract cancer and may prove as a common factor in the development of this disease in individuals who consume these herbs [41–43].

Diagnosis

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 [44–46]. 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 [47, 48]. 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 [46]. Following radical cystectomy, the majority of early recurrences can be detected through routine oncologic surveillance [49]. However, long-term recurrences may only be detected following development of symptoms [50].

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. 22.1. 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 [51]. An example of a stipple pattern by CT scan for a papillary calyceal tumor is shown in Fig. 22.2.

With the advent of CT urography, excretory urography is being utilized less frequently.

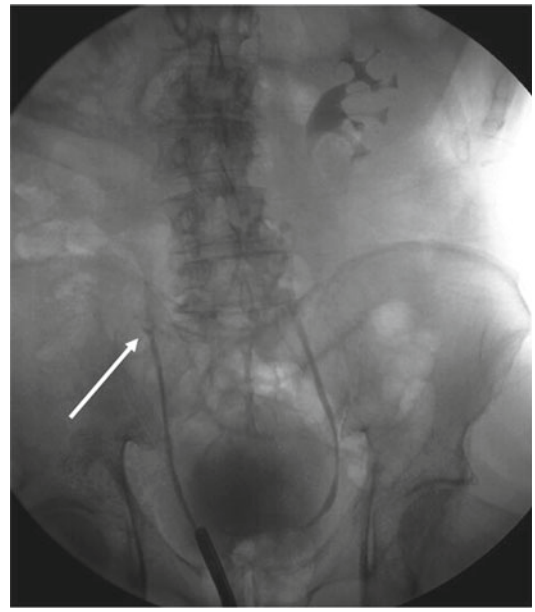

Fig. 22.1 Patient with a right mid-ureteral tumor exhibiting a "goblet sign" by retrograde pyelography

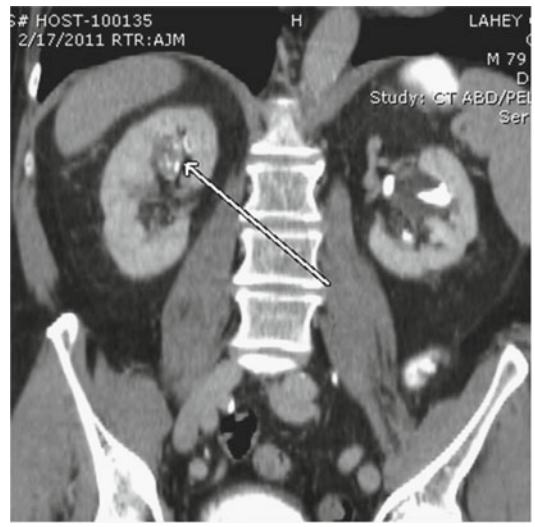

Fig. 22.2 Upper calyx papillary tumor with a stippled contrast pattern

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 % [52], with newer helical CT and multidetector computed tomography (MDCT) technology, a recent meta-analysis revealed a sensitivity and specificity of 96–99 %, respectively [53]. This compares much more favorably to the reported sensitivity of excretory urography of 50 % [54].

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 [51].

Endoscopic Approaches to Treatment

Upper tract TCC features multifocality and recurrence of these cancers tend to be ipsilateral, with only 1–5.8 % developing tumors in the contralateral kidney [55]. Given this natural history, nephroureterectomy has been traditionally considered the gold standard in treating upper tract TCC for over 60 years [56]. 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 [57–59]. 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 [60], tumor grading by cytology is accurate with 90 % correlation with that of final pathology of the tumor specimen [61]. 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 [61, 62].

Table 22.2 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

Endoscopic management of upper tract TCC has traditionally been reserved for patients with a solitary kidney, bilateral involvement, or renal insufficiency. The currently accepted indications for endoscopic management of upper tract TCC are listed and include renal insufficiency, solitary kidney, bilateral disease, severe medical comorbidities, palliation, and low-grade, papillary tumors (Table 22.2) [63].

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. [64], 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.

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 forcep (Cook) has been designed for the purpose of obtaining larger tissue samples [65].

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 [66]. 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 [67].

Complications associated with ureteroscopic management of upper tract tumors tend to be less significant than that of percutaneous resection [68]. These include ureteral perforation (0–10 %) and ureteral stricture (5–14 %) [69]. 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 [67].

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 [70]. 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 [71]. The entire tumor should be ablated and flexible nephroscopy can be subsequently performed to inspect the tumor bed and remaining renal pelvis [72].

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 [73]. 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 [74].

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 has 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 [75]. 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 one third to one tenth 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 [76]. In their experience, a 70 % response rate was achieved, with the greatest response occurring in patients with carcinoma in situ [77]. Also utilizing this approach, Katz et al. report 80 % complete response to BCG-interferon retrograde instillation [78]. 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 [79]. However, Studer et al. [80] 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 [81].

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 [82]. 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 [64]. 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 [83–86]. 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 [87]. 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 [81]. Percutaneous tract seeding remains a concern, although only two cases to date have been reported [88, 89]. Furthermore, many other clinical series have reported no tract seeding with this technique [81, 85, 90–93].

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 [94]. 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 [95, 96]. 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 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 [97]. Earlier studies have also revealed a direct correlation between prognosis and tumor stage [98, 99].

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

1. Open technique
   Following the nephroureterectomy portion of the operation, the ureter is mobilized to the level of the pelvic brim. Dissection of the distal ureteral 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. [100], 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 [101].

2. 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 [102]. 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 [103].

   Oncologic outcomes were similar in a comparison of patients undergoing bladder cuff removal versus intussusception in a retrospective study by Hara et al. [103]. 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) [103].
3. 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 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 [104–106].
4. 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 [107].
5. 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 one 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 [108, 109].

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 [110, 111].

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. In these instances, pyelovesicostomy has been described [112], 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 [113]. However, it is difficult to know whether these outcomes were due to biology of their disease as opposed to this technique which should be based on more robust data. Furthermore, autotransplantation as described by Wotkowicz and Libertino has been utilized primarily for renovascular and reconstructive indications [114], and there is consensus that this technique should be considered only in select cases of upper tract TCC in which endoscopic management is not feasible [115].

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 [116, 117]. Indeed, the 5-year cancer-specific survival of these patients ranges from 0 % to 39 %, and therefore, these high-risk patients should be identified as they may benefit from adjuvant therapies [118]. 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 [118–120].

While it is postulated that selected patients with limited nodal involvement (pN1/pN2) are potentially cured by lymphadenectomy [120, 121], a clear survival advantage for patients undergoing lymphadenectomy has not been demonstrated [122, 123]. 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 [124, 125].

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, $p=0.007$) [126]. 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 [127]. However, most other studies have not measured a survival advantage [128], 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, $p = 0.9$) [129]. 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 [130]. Adjuvant chemotherapy has also been found to be effective in this disease [131]. 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 [132, 133]. Furthermore, a recent multi-institutional study revealed no significant survival benefit for adjuvant chemotherapy [134]. 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 four 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 [135]. Another encouraging study of cisplatin-based neoadjuvant chemotherapy has revealed significant downstaging with an overall response rate of 53 % and complete remission in two of 15 (13 %) patients [136]. 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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Management of Non-clear Cell Renal Cell Carcinoma

23

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Management of Non-clear Cell Histology

Introduction

In 2013, over 65,000 Americans are expected to be diagnosed with cancer of the kidney and renal pelvis, and over 13,500 will die of their disease [1]. Over the last 35 years, there has been an increasing trend in years of life lost due to renal cancer [2], but the mortality trend may have recently leveled off [3]. This translates to a lifetime cumulative mortality risk of 0.5 % and 0.2 % for men and women, respectively, in the developed world [4].

Surgical resection remains the primary treatment modality in early-stage renal cell carcinoma (RCC), irrespective of histologic 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 [5–7]. 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 [8, 9].

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 [10]. Spontaneous responses of metastatic RCC can occur, but are seen in less than 2 % of patients treated with cytoreductive surgery [11, 12]. Comparatively, at experienced centers, the mortality of cytoreductive surgery may be lower than 0.1 % [13]. 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 [14], but without 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), nephrectomy may only delay systemic therapy [15]. Conversely, in more indolent RCC, cytoreductive surgery or metastasectomy may offer clinical benefit.

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Renal cell cancers have historically been considered radioresistant [16]. A dose-response 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, renal cancer 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 %), and medullary renal cell 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]. Though the presence of sarcomatoid features seems to portend a poorer prognosis independent of Tumor Node Metastasis (TMN) staging [22], the effect of histologic subtype of RCC on prognosis remains unclear. In univariate analysis, histologic subtype seems to be a prognostic indicator, but may or may not be preserved in multivariate analysis [23, 24]. chRCC, however, is significantly associated with a better prognosis than other RCC subtypes. Non-clear cell histologies of RCC may have diminished metastatic potential compared to ccRCC, but once metastatic, prognosis between the two groups becomes similar [25, 26]. Histologic subtype may be predictive of response to immunotherapy, with non-clear cell histologies resistant [27, 28]. Such differences in outcome may be mitigated with the use of anti-vascular endothelial growth factor (VEGF) agents and mammalian target of rapamycin (mTOR) inhibitors, but the number of patients with non-clear cell histologies included in most clinical trials has been relatively small, and so, this remains controversial [23, 29]. Potential treatment options for non-clear cell renal cancers are subtype specific (Table 23.1).

Table 23.1 Reported clinical trials of therapy in non-clear cell RCC

RCC subtype	Agent	Reference
pRCC	Sorafenib	[41, 42]
	Sunitinib	[43–46]
	Temsirolimus	[29]
	Erlotinib	[53]
	Foretinib	[55]
	Capecitabine	[57]
chRCC	Sorafenib	[42]
	Sunitinib	[45]
	Temsirolimus	[29]
	Capecitabine and docetaxel	[68]
	Capecitabine	[57]
Translocation renal cancer	Sunitinib, sorafenib, or bevacizumab	[80, 81]
RMC/CDC	Gemcitabine and platinum (cis- or carbo-)	[95]
	Bortezomib	[101]

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 increasing concentrations of hypoxia-inducible factor (HIF) within the affected cells [30, 31]. The overexpression 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 1 may be characterized by dysregulation of MET pathway [32, 33]. MET expression can be influenced by mutation, constitutive kinase activation, and genetic amplification [34]. Activation of the MET pathway can result in upregulation of hepatocyte growth factor receptor, which in turn can effect cell survival, cell adhesion, and invasion. MET mutation can be found in most patients

with hereditary pRCC type 1 and 13 % of sporadic cases [33]. Moreover, increased MET expression has been found in over 80 % of sporadic pRCC type 1, with a trend to worse prognosis in those tumors that do have increased MET expression [35]. pRCC type 2 may represent an entirely different molecular entity. 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 [36]. pRCC type 2 has been associated with fumarate hydratase (FH) tumor suppressor gene loss [37, 38] and MYC pathway activation [39]. These pathways seem to upregulate HIF proteins, with a similar end result as VHL mutations. These differences between ccRCC and pRCC highlight the need for further study into the pathobiology of RCC subtypes.

Gene expression profiling may also play a greater role in classifying subtypes of pRCC. Survival of patients with pRCC type 1, low-grade pRCC type 2, and mixed tumors was found to have a superior prognosis than 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 [40].

The optimal treatment strategy for metastatic pRCC is debatable. Although the pivotal phase III clinical trial of sorafenib included only ccRCC [41], an expanded access trial of sorafenib included non-clear cell histologies [42]. 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 (PFS) was 8.5 months (95 % CI, 8–11 months), and the median overall survival (OS) 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 [43, 44]. The subsequent expanded access trial was made up of 14 % non-clear cell subtypes [45]. The overall response rate in the intention-to-treat population was 17 % with a median PFS of 10.9 months (95 % CI, 10.3–11.2) and OS of 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) [46]. Median PFS for 55 evaluable patients was 2.7 months (95 % CI, 1.4–5.4). Median PFS for patients with pRCC was 1.6 months (95 % CI, 1.4–5.4). Median OS 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 PFS of 6.4 months [47]. 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 unclassified. 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 [29]. 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 PFS of 7.0 months versus 1.8 months and median OS of 11.6 months versus 4.3 months, respectively [48]. Quality of life, as measured by the EuroQol-5Dimension index and EuroQol-Visual Analogue Scale, was also improved significantly in this patient population ($p=0.0279$ and $p=0.0095$, respectively) [49]. 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 [50]. 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 [51]. 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 downregulate the HIF-dependent pathways and reduce tumor growth in these tumors [52]. To date, one phase II single-arm clinical trial with erlotinib has been completed in patients with metastatic pRCC [53]. The overall response rate was 11 % (95 % CI, 3–24 %), with a disease control rate, which includes patients with stable disease, of 64 %. The actuarial median OS of this cohort was 27 months (95 % CI, 13–36 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 prespecified 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 II setting [54]. Further study of anti-EGFR therapy, either alone or in combination with other treatments, is being undertaken (Table 23.2).

Most treatments common to ccRCC have not been studied in non-clear cell renal cancers. Although it may be reasonable to extrapolate the success seen with sunitinib and sorafenib to other VEGFR inhibitors, such as pazopanib, axitinib, or tivozanib, this approach should not be considered standard of care and should only be used in the context of a clinical trial. Similarly, everolimus, an oral mTOR inhibitor, has not been studied in pRCC. However, clinical trials are ongoing.

If MET mutations or activation plays a role in pRCC proliferation, inhibition of this pathway may prove a useful therapeutic target. 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 1-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, nonfatal pulmonary embolism was observed in 11 % of patients treated with foretinib [55]. 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 [56]. Additional study of this agent appears justified.

Capecitabine, an oral fluoropyrimidine analogue 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 [57]. Over 75 % of the included patients had pRCC histology. The median PFS was 10.1 months (95 % CI, 8.7–11.5), and median OS 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 [58].

Table 23.2 Ongoing trials/trials not yet reported

Agent	Subtype	Trial type	Trial number
Sunitinib or sorafenib versus placebo	ccRCC/pRCC in postoperative limited stage	Randomized phase III	NCT00326898
Everolimus versus placebo	ccRCC/pRCC in postoperative limited stage	Randomized phase III	NCT01120249
Temsirolimus versus sunitinib	Non-ccRCC	Randomized phase II	NCT00979966
Everolimus versus sunitinib	Non-ccRCC	Randomized phase II	NCT01108445
Everolimus versus sunitinib	Non-ccRCC	Randomized phase II	NCT01185366
MK2206 versus everolimus	ccRCC/pRCC	Randomized phase II	NCT01239342
Everolimus + bevacizumab	Non-ccRCC	Single-arm phase II	NCT01399918
Everolimus	Non-ccRCC	Single-arm phase II	NCT00830895
Sunitinib	Non-ccRCC	Single-arm phase II	NCT00465179
Sunitinib	Non-ccRCC	Single-arm phase II	NCT01219751
Sunitinib	Non-ccRCC	Single-arm phase II	NCT01034878
Sunitinib	pRCC	Single-arm phase II	NCT00541008
Pazopanib	Non-ccRCC	Single-arm phase II	NCT01538238
Everolimus	pRCC	Single-arm phase II	NCT00688753
Foretinib	pRCC	Single-arm phase II	NCT00726323
Tivozanib biomarker study	ccRCC/non-ccRCC	Single-arm phase II	NCT01297244
Bevacizumab	pRCC	Single-arm phase II	NCT00601926
Erlotinib	pRCC	Single-arm phase II	NCT00060307
Bortezomib	Non-ccRCC	Single-arm phase II	NCT00276614
EPO906	Non-ccRCC	Single-arm phase II	NCT00035243
Capecitabine	Non-ccRCC	Single-arm phase II	NCT01182142
Pemetrexed + gemcitabine	Non-ccRCC	Single-arm phase II	NCT00491075
Gemcitabine + irinotecan	ccRCC/non-ccRCC	Single-arm phase II	NCT00401128
Paclitaxel + carboplatin	CDC	Single-arm phase II	NCT00077129
Crizotinib	Multi-tumor/pRCC type1	Single-arm phase II	NCT01524926
Hematopoietic stem cell transplantation	Multi-tumor/pRCC	Phase I/phase II	NCT00027820

Chromophobe Renal Cell Carcinoma

chRCC, in addition to its distinct morphologic appearance, has other unique features with potential management implications. Unlike other RCC subtypes, chRCC stains readily for c-KIT due to c-KIT proto-oncogene amplification [59]. chRCC can also be defined by its hypodiploidy of multiple chromosomes including 1, 2, 6, 10, 13, 17, or 21 [60, 61]. Since chRCC can often be found in patients exhibiting the Birt-Hogg-Dube (BHD) syndrome of follicle tumors, lung cysts, and renal tumors, the Birt-Hogg-Dube tumor suppressor gene may play a role in chRCC development [62]. Mutations in the BHD gene lead to altered folliculin, a protein that interacts with the mTOR pathway, which may result in unregulated cellular hyperproliferation [63]. However, patients can also develop ccRCC or pRCC in conjunction with BHD mutations, so the role of this gene in the pathogenesis of chRCC specifically is unclear [64]. BHD inactivation in sporadic renal cancers also appears to be infrequent, even in chRCC [65]. The restriction pattern alteration in the mitochondrial DNA of chRCC has also been observed [66].

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 [29, 42, 45]. In the sorafenib expanded access trial, the observed response rate

was only 5 %, but 90 % of patients had stable disease. In the single-arm phase II trial with sunitinib conducted at MDACC in advanced non-clear cell RCC, two patients with chRCC achieved a partial response; median PFS for this small cohort of five patients with chRCC was 12.7 months (95 % CI, 8.5-NA). The differential response of chRCC to sunitinib, unlike pRCC, suggests a therapeutically relevant biological heterogeneity exists within non-clear cell RCC subtypes. In a single case report of chRCC with sarcomatoid dedifferentiation, pazopanib also resulted in a partial response [67].

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 [68]. Single-agent capecitabine has also been studied in non-clear cell RCC in the phase II setting [57]. 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. No statistical differences in outcomes were found across the histologic subtypes.

Translocation Renal Cancer

Translocation carcinomas share histologic 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 % when systematically examining pathology specimens for the presence of a defined translocation [69]. Only recently recognized as a distinct entity, up to one third of pediatric and adolescent RCC may, in fact, be translocation RCC [70]. Although this renal cancer subtype may demonstrate various chromosomal abnormalities, they all involve a break at Xp11 resulting in altered TFE3 transcription-factor gene expression [71–73]. The Xp11 translocation can be uncovered by molecular genetic analysis, but alternatively, immunohistochemistry can also be performed utilizing nuclear antibodies to TFE3 and TFEB proteins to diagnose translocation RCC [74, 75]. Translocations involving t(6;11) have also been described, causing altered TFEB function: a related protein of TFE3, with similar function [76, 77]. Based on data from tumor microarrays, the mTOR pathway seems upregulated in translocation RCC [71]. 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 then females [78]. However, as a group, translocation RCC may be a more indolent tumor type than ccRCC or pRCC in children and adolescents, but more aggressive than chRCC [79].

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 [80]. Median PFS was 7.1 months, while median OS was 14.3 months. In the first-line setting, targeted therapy appears to improve PFS over cytokines [81]. 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 PFS 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 [81].

Medullary/Collecting Duct Renal Cell Carcinoma

In contrast to most RCCs, RMC has a clear clinical association: sickle cell trait [82–84]. The typical RMC patient is a male of African descent, young, and has sickle cell trait and presents with local and/or systemic symptoms. The median age at diagnosis of is 30 years. RMC affects males

over females in a 2:1 ratio, although it may have an even greater propensity for males in the pediatric population. RMC tends to be highly aggressive, with distant metastases often present at the time of diagnosis. For unknown reasons, the right kidney is involved in over 75 % of cases. The genetic signature of RMC by gene expression profiling clusters more closely with urothelial carcinoma of the renal pelvis rather than ccRCC, suggesting that RMC should be treated differently from other RCC subtypes [85]. A specific genetic mutation, ALK mutation with t(2;10)(p23;q22) translocation, has been reported in RMC [86]. The loss of the ATP-dependent chromatin-modifying complex, INI1, has also been found in RMC and is associated with a more aggressive clinical course [87]. The role of VEGF and mTOR are unknown in this tumor type. Immunoexpression and gene copy analysis has provided additional information with the potential to guide management of RMC: it appears as though topoisomerase II may be overexpressed in up to 85 % of RMC [88]. Of 95 cases of RMC identified at Illinois Masonic Medical Center, three cases of ABL gene amplification were identified, but no evidence of BCR-ABL translocation was detected [89].

CDC and RMC may be difficult to distinguish by light microscopy. From a histologic perspective, CDC resembles transitional carcinoma of the bladder and stains readily for cytokeratin 20, unlike other kidney cancers [90]. RMC may also express OCT3/4, an immunohistochemical marker also expressed by germ-cell tumor [91]. Similarly to RMC, CDC tends to occur in the young and behave aggressively [92, 93].

Even in the era of targeted therapy for most patients with RCC, traditional cytotoxic therapy remains the standard for RMC and CDC. For example, in a series of 22 patients with RMC from four major institutions, targeted therapy had low efficacy when given as monotherapy [94]. To date, the best studied regimen for CDC consists of gemcitabine in combination with either cisplatin or carboplatin [95]. 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 PFS of 7.1 months (95 % CI, 3–11.3) and OS of 10.5 months (95 % CI, 3.8–17.1). Medullary RCC may also respond to cytotoxic chemotherapy. The three-drug combination of either cisplatin or carboplatin, combined with paclitaxel and gemcitabine, has also been reported to produce responses [96] as has the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) [97, 98], among others. 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 widespread metastatic RMC post-gemcitabine/paclitaxel chemotherapy produced a significant response and PFS for 9 months. Gene expression analysis confirmed that this patient's tumor overexpressed topoisomerase II [99].

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 and mitosis, increasing cell susceptibility to apoptosis [100]. 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) [101]. A patient with RMC enrolled in this trial achieved a partial response. Since then, this single patient continued to respond, achieving a complete response after 7 months of therapy and remained without demonstrable disease for 27 months [102]. 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 [103]. Sunitinib has also been reported to have activity [104], 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 PFS was only 3.1 months [46].

Miscellaneous Renal Cancers

Other tumor subtypes of RCC are beginning to emerge from the previously unclassified category or from reclassification 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 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 [105]. Immunohistochemical analysis for MTSCC resembles the staining pattern of papillary RCC and may represent an unusual variant of pRCC [106, 107]. Cytogenetic examination may reveal a host of abnormalities including loss or gains of chromosomes 1, 4, 6, 8, 11, 13, 14, 15, 18, 22, and Y. Trisomies of chromosomes 7 and 17 have also been reported [108]. In general MTSCC is considered an indolent tumor type, but it has been reported to metastasize to lymph nodes and distant organs [109]. Sarcomatoid dedifferentiation may also occur in conjunction with MTSCC, leading to a worse prognosis [110, 111]. tcRCC is also closely related to pRCC, with similar IHC and chromosomal abnormalities as pRCC and MTSCC [112]. It is identified by the presence of packed tubules and cysts [113]. tcRCC may also metastasize.

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 [114–116]. Gene expression profiling has shown multiple abnormalities including underexpression and overexpression 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 [117]. This patient was treated with sunitinib for 1 year followed by cytoreductive nephrectomy and retroperitoneal lymph node dissection. She has stable disease now 4 years since 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 [118]. 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), worse performance status (HR = 2.1), and sarcomatoid features (HR = 2.8) 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 [119]. 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 yes, how to time it with the administration of targeted therapy.

Conclusion

Non-clear cell renal 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 and mTOR inhibitors, have been shown to have activity in many types of non-clear cell RCC, but definitive evidence for the optimal agents and sequencing is 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 (Table 23.2). Further basic, translational, and clinical research is required to further improve patient outcomes.

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