Diagnosis and Surgical Management of Renal Tumors

Michael A. Gorin
Mohamad E. Allaf
Editors

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Chapter 1
Epidemiology and Risk Factors of Renal Cell Carcinoma

Alexa R. Meyer, Mohamad E. Allaf, and Michael A. Gorin

Introduction

Renal cell carcinoma (RCC) is the most common tumor of the kidney, accounting for 2–3% of all adult malignant neoplasms [1]. Although the majority of cases are clinically localized at the time of initial detection, RCC is considered the deadliest of the common urologic cancers, with the highest ratio of annual deaths to number of incident cases [1, 2]. In this chapter, the epidemiology of RCC will be reviewed. Additionally, risk factors including demographics, lifestyle, comorbidities, and genetics will be discussed.

Incidence and Mortality

Worldwide, RCC is the 9th most common cancer in men and 14th most common in women [3]. The incidence of RCC varies globally, with the highest rates in Northern and Eastern Europe, North America, and Australia and the lowest rates in Africa and Southeast Asia [4]. In the United States, it is estimated that 63,990 new cases of RCC will be diagnosed in 2017 [5]. In 2012, there were approximately 84,000 new cases in the European Union and 338,000 worldwide [6, 7]. While increasing incidence has been reported worldwide, there is evidence of stabilization in most developed countries [4].

Based on data from the Surveillance, Epidemiology, and End Results registry, 65% of patients with renal tumors present with localized disease, 16% with regional

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disease, 16% with metastatic disease, and 3% with an unknown stage [8]. Over time, there has been a decrease in the size of newly diagnosed renal tumors, with the mean diameter of stage I tumors decreasing from 4.1 cm in 1993 to 3.6 in 2003 [9]. This has been attributed to an increasing number of incidentally detected renal tumors found on imaging performed for a wide variety of medical indications [10].

Despite the worldwide rise in the incidence of RCC, mortality rates have been more favorable. Mortality trends are stable in most countries and decreasing in Western Europe, the United States, Australia, and most Northern European countries [3]. It is estimated that the incidence of RCC has risen up to threefold higher than the mortality rate. Just as incidence varies globally, mortality varies as well. The highest mortality rates are in the Czech Republic and the Baltic countries [3]. In 2017, it is estimated that there will be 14,400 deaths from kidney cancer in the United States [5]. In 2008, the estimated kidney cancer-related deaths in the European Union were 39,3000, and globally this number reached 116,000 [6, 7].

Demographics

The incidence of RCC in Europe and the United States increases with age, occurring most commonly in the sixth to eighth decade of life, with a median age at diagnosis of 64 years and a plateau reached around age 70–75 [8, 11]. This lower incidence among the elderly has been attributed to less frequent use of diagnostic imaging [12]. RCC is infrequent in patients under 40 and rare in children [13].

The incidence of RCC is lower among Asians, both in the United States and within Asian countries [3, 11]. Interestingly, the incidence of RCC is low in African countries; however, within the United States, the incidence is highest among African Americans [11]. These racial disparities have been hypothesized to be due to a multitude of factors including access to health care, frequency of imaging, lifestyle or environmental risk factors, and genetics [12].

RCC is 50% more common in males than females worldwide, with 2/3 of new cases of RCC in the United States occurring in males in 2017 [3, 5]. Worldwide, comparison of incidence/mortality ratios revealed a higher case fatality among men, with male mortality rates threefold higher than for females [3].

Lifestyle

Lifestyle plays a significant role in development of RCC. For example, cigarette smoking is a well established risk factor for RCC [12], while the consumption of fruit, vegtables, and alcohol may have protective effects [14–16]. Additionally, the fact that RCC is more common in males than females may be related to lifestyle risk factors. Furthermore, the worldwide variation seen in incidence of RCC suggests that lifestyle plays a critical role in the development of this malignancy.

Smoking

Smoking is a significant risk factor for the development of RCC [12]. Tobacco contains a number of compounds (such as polycyclic aromatic hydrocarbons and aromatic amines) that promote DNA damage by bulky adduct formation, DNA breaks, and base modifications [17]. Furthermore, tobacco promotes the formation of oxygen free radicals further leading to DNA damage and promoting oncogenesis [17].

A 2016 meta-analysis that included 24 studies assessed the association between smoking and RCC [17]. Outcomes were reported for 17,245 patients with RCC and 12,501 controls. The pooled relative risk (RR) for developing RCC was significantly higher for all smokers (RR 1.31, 95% CI 1.22–1.40), current smokers (RR 1.36, 95% CI 1.19–1.56), and former smokers (RR 1.16, 95% CI 1.08–1.25) compared to nonsmokers. Furthermore, disease-specific survival was lower among patients with tobacco exposure. The risk of death from RCC was elevated for all smokers (RR 1.23, 95% CI 1.08–1.40), current smokers (RR 1.37, 95% CI 1.19–1.59), and former smokers (RR 1.02, 95% CI 0.90–1.15). A prior meta-analysis showed similar results, with a strong dose-dependent increase in risk and a higher risk among male smokers than female smokers [18]. Studies have shown that smoking cessation is associated with a decrease in RCC risk compared with current smokers, even after adjusting for confounders such as pack years; however, the benefit may not be seen until >10 years of cessation [18, 19].

Diet

The impact of diet on the development of RCC is the subject of current debate. Several case-control studies suggest that high meat consumption is associated with an increased risk of renal cancer; however results are largely inconsistent [14, 15]. A pooled analysis of prospective studies was performed to examine the association between meat, fat, and protein intake and the risk of RCC [14]. When adjusting for body mass index (BMI), fruit and vegetable intake, and alcohol intake, there was no association between intakes of fat, protein, and their subtypes and risk of RCC. The same group performed another pooled analysis to assess the relationship between fruit and vegetable consumption and the risk of RCC [15]. They found that compared to patients that consumed <200 g of fruits and vegetables a day, the pooled RR for patients that consumed ≥600 g of fruits and vegetables a day was 0.68 (95% CI 0.54–0.87). There have been inconsistent results regarding intake of vitamins and minerals and RCC risk [15].

The inverse relationship between fruit and vegetable intake and RCC risk may be related to carotenoids found in these food groups. Carotenoids protect cells against cancer by inhibiting oxidative damage to DNA, mutagenesis, malignant transformation, and tumor growth [20]. However, as mentioned above, results have been mixed when looking at intake of vitamins and minerals alone and RCC risk.

Alcohol

Alcohol consumption is associated with a decreased risk of development of RCC. A meta-analysis of 20 studies revealed this protective effect of alcohol [16]. Any alcohol drinking was associated with significantly decreased risk of RCC (RR 0.85, 95% CI 0.80–0.92). When assessing the dose-response relationship of alcohol, the RR was 0.90 (95% CI 0.83–0.97) for light drinking, 0.79 (95% CI 0.71–0.88) for moderate drinking, and 0.89 (95% CI 0.58–1.39) for heavy drinking. Results remained consistent when controlling for smoking, BMI, and hypertension.

Potential mechanisms of action that are hypothesized include the interplay between alcohol and insulin sensitivity, or the diuretic effect of alcohol, which increases urine volume and may reduce the time carcinogenic solutes are in contact with renal epithelium [21]. However, studies have shown that total fluid intake is not associated with RCC risk [22].

Medical Comorbidities

Hypertension

Several large prospective studies have shown that hypertension and/or its treatment is associated with RCC. A 2017 meta-analysis of 18 prospective studies revealed that a history of hypertension was associated with a RR of 1.67 (95% CI 1.46–1.90) for the development of RCC [23]. Results were similar after adjusting for BMI, hypertension, and smoking. Furthermore, each 10-mmHg increase in systolic and diastolic blood pressure was associated with 10% and 22% increased risk of kidney cancer, respectively. Given that most studies are based on diagnosis of hypertension, which is inevitably linked to use of antihypertensive medications, the relationship between hypertension, antihypertensives, and RCC is controversial. In a prospective study evaluating the risk of blood pressure, antihypertensives, and RCC, blood pressure was independently associated with RCC, and individuals taking antihypertensive agents were not at a significantly increased risk unless blood pressure was poorly controlled [24]. This supports the hypothesis that hypertension rather than antihypertensives increases RCC risk.

Potential biologic mechanisms underlying the relationship between hypertension and RCC are thought to involve high blood pressure leading to increased levels of lipid peroxidation by-products, which can cause DNA adducts, as well as hypertension leading to renal tubular damage making the kidney more susceptible to circulating carcinogens [25, 26].

Obesity

Several studies have shown that excess body weight is a risk factor for RCC. In a meta-analysis of prospective studies evaluating BMI and cancer incidence, the RR of developing renal cancer was 1.24 (95% CI 1.15–1.34) in men and 1.34 (95% 1.25–1.42) in women [27]. Furthermore, a large prospective cohort study of over 300,000 participants revealed that the risk for RCC increased with baseline BMI [28]. Compared to a reference group with a BMI of 18.5–22.5, the RR for men with a BMI of 25–27.5 was 1.43 (95% CI 1.07–1.92) and 1.57 (1.07–2.29) for women. Additionally, for patients with a BMI ≥35, the RR increased to 2.47 (95% CI 1.72–3.53) for men and 2.59 (95% CI 1.70–3.96) for women. Weight gain in midlife has also been shown to be associated with increased RCC risk [28, 29]. Interestingly, while excess body weight is associated with increased risk of developing RCC, it is also associated with higher overall and disease-specific survival in patients with newly diagnosed RCC, known as the obesity paradox [30]. This paradox may partly be explained by alterations in gene expression by obese patients. For instance, one genome-wide analysis performed in patients with RCC showed downregulation of fatty acid synthase, which may be associated with decreased RCC tumor growth [31].

While the mechanism of BMI leading to increased risk of RCC is not fully understood, it has been proposed that excess BMI can cause damage to the kidneys by a number of mechanisms that may predispose to RCC including oxidative stress (obesity can lead to an increase in lipid peroxidation by-products that can cause DNA adducts), renal atherosclerosis, and hormonal alterations including levels of insulin-like growth factor-1, vascular endothelial growth factor, and estrogen [32, 33].

Acquired renal cystic disease

Acquired renal cystic disease (ARCD) occurs in the setting of prolonged azotemia and therefore develops in patients with end-stage renal disease. ARCD is estimated to be present in 35–50% of patients on chronic dialysis [34]. There is up to 50-fold increased risk of RCC in ARCD than the general population [34]. There are several differences between renal cancers that develop in the setting of ARCD compared to the general population. ARCD patients are younger, predominantly male, and their tumors are often bilateral and multifocal. These tumors are also considered to be of low malignant potential [35]. Furthermore, the International Society of Urological Pathology Vancouver Classification of Renal Neoplasia recognizes ARCD-associated RCC as a distinct epithelial tumor within the classification system [36].

Although transplantation and restoration of renal function are associated with regression of ARCD, the risk of RCC remains [37, 38].

While it is suggested that cysts in ARCD undergo malignant transformation, the mechanism of RCC development in patients with ARCD is largely unknown. Implicated factors include enhanced expression of growth factors and mutations in end-stage kidneys and the uremic milieu leading to immunosuppressive effects [39].

Kidney stones and urinary tract infections

There have been mixed data regarding the association between kidney stones and urinary tract infections and the development of RCC. To elucidate the relationship, a meta-analysis of seven observational studies was performed [40]. The pooled RR for RCC in patients with kidney stones compared to controls was 1.76 (95% CI 1.24–2.49). Interestingly, the association was only significant in males. The study, however, has major limitations including not controlling for confounding factors such as smoking and dietary habits. Furthermore, patients with kidney stones are more likely to undergo additional imaging, increasing detection of RCC. Other studies have shown a potential association between history of urinary tract infection and risk of RCC when confounders such as lifestyle and diet are controlled for; however, results of other studies are largely mixed [41].

The theorized mechanism for the potential increased risk of RCC in patients with kidney stones and urinary tract infections is related to the inflammatory response, which can promote the growth of neoplastic cells [42, 43].

Diabetes It is debated whether diabetes is an independent risk factor for development of RCC. A large retrospective study showed a significantly increased risk of RCC in diabetics in both men (RR 1.3, 95% CI 1.1–1.6) and women (RR 1.7, 95% CI 1.4–2.0), as well as higher risk of cancer mortality [44]. Another large retrospective cohort study also showed elevated risk of RCC in diabetic patients; however, this elevated risk declined after controlling for obesity [45]. Other studies have shown no significantly increased risk of RCC in patients with a history of diabetes [46]. Overall, the increased risk of RCC in patients with a history of diabetes appears to be linked to associated risk factors such as obesity and hypertension.

Hepatitis C A large cohort study of over 67,000 patients in a cancer registry tested for hepatitis C virus (HCV) showed that RCC was diagnosed in 0.6% of HCV-positive patients versus 0.3% of HCV-negative patients, with a RR of 1.77 (95% CI 1.05–2.98) in HCV-positive patients [47]. Additionally, HCV-positive patients were diagnosed at a younger age than HCV-negative patients ($p < 0.001$). In contrast, other large retrospective studies have shown no association between HCV and RCC [48]. However, in a recent prospective study, adults with RCC or newly diagnosed colon cancer were screened for HCV antibody, and RCC patients had a higher rate of HCV antibody positivity (8%) than colon cancer patients (1%) ($p < 0.01$) [49].

The mechanism for the potential association between HCV and RCC is not known. In HCV-mediated chronic kidney disease, HCV RNA and core protein have been isolated in kidney glomerulus and tubules [50]. Whether there is an oncogenic potential associated with these proteins is under exploration.

Exposures

Occupational exposure

Exposure to toxic compounds has been linked to the development of RCC. An international multicenter population case-control study evaluated the relationship between occupational exposures and RCC [51]. A number of exposures were significantly associated with RCC including employment in the blast furnace, coke oven, and iron and steel industries. Additionally exposure to asbestos, cadmium, dry cleaning solvents, gasoline, and other petroleum products was found to be associated with RCC. These analyses were adjusted for age, center, BMI, and cigarette use. Interestingly, for the majority of exposures, there was no clear dose-dependent increase in risk, except for other petroleum products. Overall, the literature on occupational exposures and RCC risk is conflicting with difficult to parse out confounding variables. Regardless, it is recommended to prevent exposure to carcinogens such as asbestos and cadmium, which are known to cause DNA damage [12].

Analgesic exposure

Evidence regarding the association between analgesic use and RCC is largely mixed. Two large prospective studies investigated the relationship with conflicting results [52, 53]. One study included data from the Nurses' Health Study and the Health Professionals Follow-up Study, which included 77,525 women and 49,403 men, respectively, with long-term follow-up [52]. This study found that aspirin and acetaminophen use were not associated with RCC risk; however, regular use of nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with increased RCC risk with a RR of 1.51 (95% CI 1.12–2.04), with a dose-response relationship between duration of nonaspirin NSAID use and RCC risk. This was consistent in both cohorts analyzed in the study. A multivariable model was used which adjusted for BMI, smoking, hypertension, physical activity, fruit and vegetable intake, alcohol use, and parity in women. Of note, the authors did not control for history of chronic kidney disease. The second study to evaluate the association of analgesic use and RCC included data from two large patient cohorts: the US Kidney Cancer Study and the Prostate Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [53]. The US Kidney Cancer Study included 1,217 RCC cases and 1,235 controls, and PLCO consisted of 98,807 participants. In this study,

acetaminophen use was associated with significantly increased RCC risk (OR 1.35, CI 1.01–1.83 in the US Kidney Cancer Study, and HR 1.68, 95% CI 1.19–2.39 in PLCO). This was further supported by a meta-analysis performed by the authors. Interestingly, in the US Kidney Cancer Study cohort, RCC risk was not associated with prescription acetaminophen use, and in the PLCO cohort elevated risk was absent among long-term users. Neither aspirin nor NSAIDs were associated with RCC risk in this study.

Overall, it is unclear if aspirin, NSAIDs, or acetaminophens are associated with an increased risk of RCC, particularly outside of development of chronic kidney disease. Potential biologic mechanisms for association do exist for each class. NSAIDs inhibit cyclooxygenases 1 and 2, which are important regulators of homeostasis. Renal damage with poor maintenance of homeostasis may contribute to carcinogenesis [54]. In the case of acetaminophen, the drug is converted to N-acetyl-p-benzoquinoneimine in the liver and kidney, which in excess levels can form protein adducts, bind to liver and kidney DNA, and disrupt homeostasis [55].

Genetics

The majority of cases of RCC are sporadic, with hereditary syndromes accounting for <5% incident cases [12, 56]. Hereditary syndromes include von Hippel-Lindau syndrome, hereditary papillary renal cell carcinoma, hereditary leiomyomatosis renal cell carcinoma, and Birt-Hogg-Dube syndrome [57, 58]. Outside of hereditary syndromes, there is evidence that genetic factors impact susceptibility to RCC. For instance, the risk of RCC for a first-degree relative of a patient with RCC is increased twofold [12]. Furthermore, genome-wide association studies of RCC revealed that genetic variants increase the risk of sporadic RCC, including variants of genes encoding for hypoxia-inducible factor 2 alpha and telomere length [59, 60]. In patients with RCC, factors that favor hereditary contribution to RCC include patients with first-degree relatives with a renal tumor, early onset of disease (prior to age 40), and multifocal or bilateral disease [61].

Conclusions

RCC incidence has been increasing worldwide, with recent stabilization in developing countries. Despite this rise in incidence, mortality rates have largely been stable. RCC incidence varies globally, by sex and race. At least part of these trends can be attributed to exposure to risk factors in certain parts of the world. Lifestyle, medical comorbidities, and chemical exposures all appear to be linked to RCC development. While part of the growing incidence of RCC may be linked to the increased use of medical imaging, efforts such as smoking reduction may be contributing to declining mortality rates. With continued identification of risk factors for the development of RCC, progress can be made in disease prevention.

References

1. Campbell SC, Lane BR. Malignant renal tumors. In: Wein AJ, Kavoussi LR, Partin AW, Peters CA, editors. Campbell-Walsh urology. 11th ed. Philadelphia: Elsevier; 2016. p. 1314–64.
2. Cairns P. Renal cell carcinoma. Cancer Biomark. 2011;9:461–73.
3. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. Eur Urol. 2015;67(3):519–30.
4. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nat Rev Urol. 2010;7(5):245–57. PMCID: 3012455.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
6. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374–403.
7. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.
8. SEER stat fact sheets: kidney and renal pelvis. 2014 [updated 2014; cited]; Available from: https://seer.cancer.gov/statfacts/html/kidrp.html.
9. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. Cancer. 2008;113(1):78–83.
10. Decastro GJ, McKiernan JM. Epidemiology, clinical staging, and presentation of renal cell carcinoma. Urol Clin North Am. 2008;35(4):581–92; vi.
11. Chow WH, Devesa SS. Contemporary epidemiology of renal cell cancer. Cancer J. 2008;14(5):288–301. PMCID: 3077538.
12. Ljungberg B, Campbell SC, Choi HY, Jacqmin D, Lee JE, Weikert S, et al. The epidemiology of renal cell carcinoma. Eur Urol. 2011;60(4):615–21.
13. Thompson RH, Ordonez MA, Iasonos A, Secin FP, Guillonneau B, Russo P, et al. Renal cell carcinoma in young and old patients--is there a difference? J Urol. 2008;180(4):1262–6; discussion 6. PMCID: 2615196.
14. Armstrong B, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. Int J Cancer. 1975;15(4):617–31.
15. Food N. Physical activity, and the prevention of cancer: a global perspective. Washington, DC: American Institute for Cancer Research; 2007. Contract no.: document number|.
16. Bellocco R, Pasquali E, Rota M, Bagnardi V, Tramacere I, Scotti L, et al. Alcohol drinking and risk of renal cell carcinoma: results of a meta-analysis. Ann Oncol Off J Eur Soc Med Oncol. 2012;23(9):2235–44.
17. Cumberbatch MG, Rota M, Catto JW, La Vecchia C. The role of tobacco smoke in bladder and kidney carcinogenesis: a comparison of exposures and meta-analysis of incidence and mortality risks. Eur Urol. 2016;70(3):458–66.
18. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. Int J Cancer. 2005;114(1):101–8.
19. Parker AS, Cerhan JR, Janney CA, Lynch CF, Cantor KP. Smoking cessation and renal cell carcinoma. Ann Epidemiol. 2003;13(4):245–51.
20. Lee JE, Mannisto S, Spiegelman D, Hunter DJ, Bernstein L, van den Brandt PA, et al. Intakes of fruit, vegetables, and carotenoids and renal cell cancer risk: a pooled analysis of 13 prospective studies. Cancer Epidemiol Biomark Prev. 2009;18(6):1730–9. PMCID: 2883186.
21. Lee JE, Hunter DJ, Spiegelman D, Adami HO, Albanes D, Bernstein L, et al. Alcohol intake and renal cell cancer in a pooled analysis of 12 prospective studies. J Natl Cancer Inst. 2007;99(10):801–10.
22. Lee JE, Giovannucci E, Smith-Warner SA, Spiegelman D, Willett WC, Curhan GC. Total fluid intake and use of individual beverages and risk of renal cell cancer in two large cohorts. Cancer Epidemiol Biomark Prev. 2006;15(6):1204–11.
23. Hidayat K, Du X, Zou SY, Shi BM. Blood pressure and kidney cancer risk: meta-analysis of prospective studies. J Hypertens. 2017;35(7):1333–44.

24. Weikert S, Boeing H, Pischon T, Weikert C, Olsen A, Tjonneland A, et al. Blood pressure and risk of renal cell carcinoma in the European prospective investigation into cancer and nutrition. Am J Epidemiol. 2008;167(4):438–46.
25. Purdue MP, Moore LE, Merino MJ, Boffetta P, Colt JS, Schwartz KL, et al. An investigation of risk factors for renal cell carcinoma by histologic subtype in two case-control studies. Int J Cancer. 2013;132(11):2640–7. PMCID: 3717609.
26. McLaughlin JK, Lipworth L, Tarone RE. Epidemiologic aspects of renal cell carcinoma. Semin Oncol. 2006;33(5):527–33.
27. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569–78.
28. Adams KF, Leitzmann MF, Albanes D, Kipnis V, Moore SC, Schatzkin A, et al. Body size and renal cell cancer incidence in a large US cohort study. Am J Epidemiol. 2008;168(3):268–77. PMCID: 2727262.
29. Chow WH, Gridley G, Fraumeni JF Jr, Jarvholm B. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med. 2000;343(18):1305–11.
30. Choi Y, Park B, Jeong BC, Seo SI, Jeon SS, Choi HY, et al. Body mass index and survival in patients with renal cell carcinoma: a clinical-based cohort and meta-analysis. Int J Cancer. 2013;132(3):625–34.
31. Hakimi AA, Furberg H, Zabor EC, Jacobsen A, Schultz N, Ciriello G, et al. An epidemiologic and genomic investigation into the obesity paradox in renal cell carcinoma. J Natl Cancer Inst. 2013;105(24):1862–70. PMCID: 3866155.
32. Chade AR, Lerman A, Lerman LO. Kidney in early atherosclerosis. Hypertension. 2005;45(6):1042–9.
33. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004;4(8):579–91.
34. Truong LD, Krishnan B, Cao JT, Barrios R, Suki WN. Renal neoplasm in acquired cystic kidney disease. Am J Kidney Dis. 1995;26(1):1–12.
35. Marple JT, MacDougall M, Chonko AM. Renal cancer complicating acquired cystic kidney disease. J Am Soc Nephrol. 1994;4(12):1951–6.
36. Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. The International Society of Urological Pathology (ISUP) Vancouver classification of renal neoplasia. Am J Surg Pathol. 2013;37(10):1469–89.
37. Ishikawa I, Yuri T, Kitada H, Shinoda A. Regression of acquired cystic disease of the kidney after successful renal transplantation. Am J Nephrol. 1983;3(6):310–4.
38. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. Am J Transplant. 2004;4(6):905–13.
39. Denton MD, Magee CC, Ovuworie C, Mauiyyedi S, Pascual M, Colvin RB, et al. Prevalence of renal cell carcinoma in patients with ESRD pre-transplantation: a pathologic analysis. Kidney Int. 2002;61(6):2201–9.
40. Cheungpasitporn W, Thongprayoon C, O'Corragain OA, Edmonds PJ, Ungprasert P, Kittanamongkolchai W, et al. The risk of kidney cancer in patients with kidney stones: a systematic review and meta-analysis. QJM. 2015;108(3):205–12.
41. Parker AS, Cerhan JR, Lynch CF, Leibovich BC, Cantor KP. History of urinary tract infection and risk of renal cell carcinoma. Am J Epidemiol. 2004;159(1):42–8.
42. Chow WH, Lindblad P, Gridley G, Nyren O, McLaughlin JK, Linet MS, et al. Risk of urinary tract cancers following kidney or ureter stones. J Natl Cancer Inst. 1997;89(19):1453–7.
43. Federico A, Morgillo F, Tuccillo C, Ciardiello F, Loguercio C. Chronic inflammation and oxidative stress in human carcinogenesis. Int J Cancer. 2007;121(11):2381–6.
44. Lindblad P, Chow WH, Chan J, Bergstrom A, Wolk A, Gridley G, et al. The role of diabetes mellitus in the aetiology of renal cell cancer. Diabetologia. 1999;42(1):107–12.
45. Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, et al. Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. J Natl Cancer Inst. 1997;89(18):1360–5.

46. Zucchetto A, Dal Maso L, Tavani A, Montella M, Ramazzotti V, Talamini R, et al. History of treated hypertension and diabetes mellitus and risk of renal cell cancer. Ann Oncol: Off J Eur Soc Med Oncol. 2007;18(3):596–600.
47. Gordon SC, Moonka D, Brown KA, Rogers C, Huang MA, Bhatt N, et al. Risk for renal cell carcinoma in chronic hepatitis C infection. Cancer Epidemiol Biomark Prev. 2010;19(4):1066–73.
48. Hofmann JN, Torner A, Chow WH, Ye W, Purdue MP, Duberg AS. Risk of kidney cancer and chronic kidney disease in relation to hepatitis C virus infection: a nationwide register-based cohort study in Sweden. Eur J Cancer Prev. 2011;20(4):326–30. PMCID: 3104067.
49. Gonzalez HC, Lamerato L, Rogers CG, Gordon SC. Chronic hepatitis C infection as a risk factor for renal cell carcinoma. Dig Dis Sci. 2015;60(6):1820–4.
50. Wiwanitkit V. Renal cell carcinoma and hepatitis C virus infection: is there any cause-outcome relationship? J Cancer Res Ther. 2011;7(2):226–7.
51. Mandel JS, McLaughlin JK, Schlehofer B, Mellemgaard A, Helmert U, Lindblad P, et al. International renal-cell cancer study. IV. Occupation. Int J Cancer. 1995;61(5):601–5.
52. Cho E, Curhan G, Hankinson SE, Kantoff P, Atkins MB, Stampfer M, et al. Prospective evaluation of analgesic use and risk of renal cell cancer. Arch Intern Med. 2011;171(16):1487–93. PMCID: 3691864.
53. Karami S, Daughtery SE, Schwartz K, Davis FG, Ruterbusch JJ, Wacholder S, et al. Analgesic use and risk of renal cell carcinoma: a case-control, cohort and meta-analytic assessment. Int J Cancer. 2016;139(3):584–92.
54. Ruffin MT, Krishnan K, Rock CL, Normolle D, Vaerten MA, Peters-Golden M, et al. Suppression of human colorectal mucosal prostaglandins: determining the lowest effective aspirin dose. J Natl Cancer Inst. 1997;89(15):1152–60.
55. Bessems JG, Vermeulen NP. Paracetamol (acetaminophen)-induced toxicity: molecular and biochemical mechanisms, analogues and protective approaches. Crit Rev Toxicol. 2001;31(1):55–138.
56. Zbar B, Glenn G, Merino M, Middelton L, Peterson J, Toro J, et al. Familial renal carcinoma: clinical evaluation, clinical subtypes and risk of renal carcinoma development. J Urol. 2007;177(2):461–5; discussion 5.
57. Coleman JA. Familial and hereditary renal cancer syndromes. Urol Clin North Am. 2008;35(4):563–72; v.
58. Adeniran AJ, Shuch B, Humphrey PA. Hereditary renal cell carcinoma syndromes: clinical, pathologic, and genetic features. Am J Surg Pathol. 2015;39(12):e1–e18.
59. Purdue MP, Johansson M, Zelenika D, Toro JR, Scelo G, Moore LE, et al. Genome-wide association study of renal cell carcinoma identifies two susceptibility loci on 2p21 and 11q13.3. Nat Genet. 2011;43(1):60–5. PMCID: 3049257.
60. Machiela MJ, Hofmann JN, Carreras-Torres R, Brown KM, Johansson M, Wang Z, et al. Genetic variants related to longer telomere length are associated with increased risk of renal cell carcinoma. Eur Urol. 2017;72:747.
61. Gnarra JR, Glenn GM, Latif F, Anglard P, Lerman MI, Zbar B, et al. Molecular genetic studies of sporadic and familial renal cell carcinoma. Urol Clin North Am. 1993;20(2):207–16.

Chapter 2
Pathology of Renal Tumors

Tiffany M. Graham, Todd M. Stevens, and Jennifer B. Gordetsky

Introduction

In this chapter we provide a brief overview of renal cortical neoplasms, including benign and malignant tumors. In the last several years, the International Society of Urological Pathology (ISUP) and the World Health Organization (WHO) have standardized the nomenclature and categorization of renal tumors (Table 2.1). In addition, the original classification of renal tumors has been revised to add several newly recognized morphologically and immunophenotypically distinct entities. Standardized reporting of histologic findings is performed according to the College of American Pathologists (CAP) Cancer Protocol Templates [1]. Renal cell carcinoma (RCC) is staged using the 8th edition of the American Joint Committee on Cancer Staging Manual [2].

Malignant Renal Tumors

Clear Cell (Conventional) Renal Cell Carcinoma

Clear cell RCC is the most common malignant renal tumor, accounting for approximately 70% of all renal cancers [3–5]. Although most of these tumors occur sporadically, some cases are hereditary [6]. The majority of clear cell RCCs are

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Table 2.1 World Health Organization (WHO) 2016 classification of kidney tumors

Renal cell tumors
Previously established tumors
Clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Collecting duct carcinoma
Renal medullary carcinoma
Mucinous tubular and spindle cell carcinoma
Unclassified renal cell carcinoma
Papillary adenoma
Oncocytoma
Newly accepted tumors
Multilocular cystic renal neoplasm of low malignant potential
Hybrid oncocytic/chromophobe tumor
MiT family translocation renal cell carcinomas
Xp11 translocation renal cell carcinoma
t(6;11) renal cell carcinoma
Tubulocystic renal cell carcinoma
Acquired cystic disease-associated renal cell carcinoma
Succinate dehydrogenase-deficient renal cell carcinoma
Clear cell papillary renal cell carcinoma
Hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma
Metanephric tumors
Metanephric adenoma
Metanephric adenofibroma
Metanephric stromal tumor
Nephroblastic tumors
Nephrogenic rests
Nephroblastoma
Cystic partially differentiated nephroblastoma
Pediatric cystic nephroma
Mesenchymal tumors
Pediatric
Clear cell sarcoma
Rhabdoid tumor
Congenital mesoblastic nephroma
Ossifying renal tumor of infancy
Adult
Leiomyosarcoma
Angiosarcoma
Rhabdomyosarcoma
Osteosarcoma
Synovial sarcoma
Ewing sarcoma

Angiomyolipoma
Epithelioid angiomyolipoma
Leiomyoma
Hemangioma
Lymphangioma
Juxtaglomerular cell tumor
Renomedullary interstitial cell tumor
Schwannoma
Solitary fibrous tumor
Mixed mesenchymal and epithelial tumors
Adult cystic nephroma/mixed epithelial stromal tumor
Neuroendocrine tumors
Well-differentiated neuroendocrine tumor
Large cell neuroendocrine carcinoma
Small cell neuroendocrine carcinoma
Paraganglioma
Renal hematopoietic neoplasms
Lymphoma
Leukemia
Plasmacytoma
Germ cell tumors
Teratoma
Choriocarcinoma
Mixed germ cell tumors
Metastatic tumors

From Moch et al. [5], p 13, European Urology, with permission from Elsevier

discovered incidentally on imaging [7, 8]. However, larger tumors may be symptomatic, causing flank pain and hematuria [7, 8]. Metastatic spread is typically via a hematogenous route, with a general predilection for the renal sinus veins, renal vein, and vena cava [9, 10]. The 5-year survival ranges from 43% to 89%, depending on the stage at presentation [11, 12]. Clear cell RCCs can have a large variability in size and typically occur as a solitary mass. Multifocal or bilateral disease presents in less than 5% of cases and can be associated with hereditary syndromes [13].

Clear cell RCC has a golden-yellow appearance due to the abundance of lipids within the cells. These tumors generally form a well-circumscribed mass with a pseudocapsule (Fig. 2.1). Areas of necrosis, hemorrhage, and/or cystic change are not uncommon. Clear cell RCC arises within the renal cortex and often has a pushing border. Sometimes gross involvement of the renal sinus or renal vein is apparent. Microscopic examination shows diverse morphology. Tumor cells can appear in sheets, alveolar or acinar patterns (Fig. 2.2). Clear cell RCC has a characteristic network of thin vessels which creates a “lace-like” pattern. As the name suggests, tumor cells have clear cytoplasm due to the presence of lipids and glycogen that are dissolved during tissue processing. Higher-grade tumors may have more eosino-

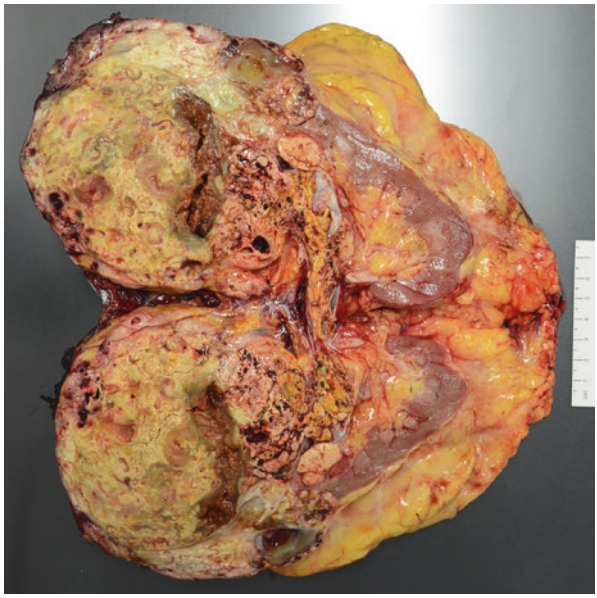

Fig. 2.1 Gross image of a large clear cell renal cell carcinoma with extension of tumor into the perinephric fat

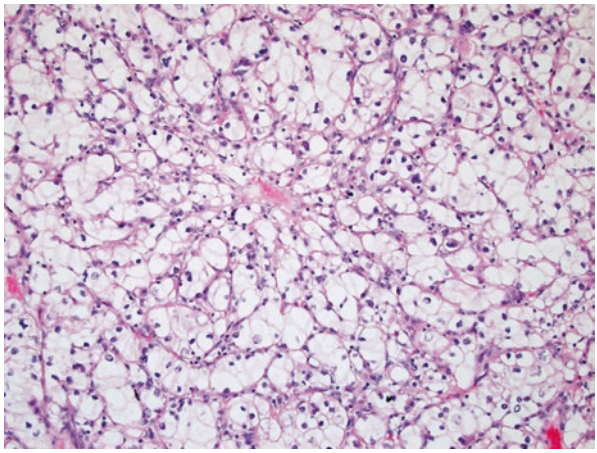

Fig. 2.2 H&E, high magnification, clear cell renal cell carcinoma

philic cytoplasm. Nucleoli range from absent to strikingly prominent, which determines the grade of the tumor per the ISUP nucleolar grading system [5]. Sarcomatoid or rhabdoid features may be present, which conveys a poor prognosis.

The majority of clear cell RCCs demonstrate mutations involving the tumor suppressor gene von Hippel-Lindau (*VHL*) on the short arm of chromosome 3 (3p25-26) [14]. This mutation can arise in both sporadic clear cell RCC as well as in patients with the VHL syndrome [6]. The *VHL* gene produces a protein that interacts with an E3 ubiquitin ligase complex, which targets hypoxia-inducible factors (HIFs) for polyubiquitination and proteasomal degradation. HIFs are transcription factors that

activate genes such as vascular endothelial growth factor (*VEGF*), a promoter of angiogenesis. The absence of functional VHL allows HIFs to escape degradation and thereby contribute to tumorigenesis. Promoter region methylation is a common mechanism by which the *VHL* gene is silenced [14]. Allelic losses on chromosome 14q, loss of 4p, and loss of 9p have been associated with a poor prognosis [14]. In addition, genes involved in chromatin remodeling such as *PBRM1*, *SETD2*, and *BAP1* have been shown to predict survival [14]. The tumor's immunophenotype shows nuclear expression for PAX8, which is seen in nearly all renal epithelial tumors [15–17]. CAIX, vimentin, CD10, and pan-cytokeratin will also be positive in the majority of cases [16, 17].

Papillary Renal Cell Carcinoma

Papillary RCC is the second most common malignant renal tumor, comprising approximately 15% of RCCs in adults [3, 4, 13]. The 5-year survival of papillary RCC is generally considered better than clear cell RCC, ranging from 57% to 85% [11, 12]. Multifocality is more common in papillary RCC compared to clear cell RCC [13]. The majority of papillary RCCs occur sporadically; however, these tumors can be seen in some hereditary syndromes, such as familial papillary RCC syndrome [6, 13]. Papillary RCC has several known predisposing factors including end-stage renal disease with scarring and acquired cystic kidney disease [18].

Papillary RCC usually appears well-circumscribed and friable on gross examination. These tumors range in color from tan to brown and may show areas of hemorrhage, necrosis, or cysts. Microscopically, papillary RCC is composed of numerous fibrovascular cores lined by malignant cells. Foamy macrophages and psammomatous calcifications may be present. Spontaneous hemorrhage has been reported as a presenting feature in 8% of cases [3, 4]. In some cases with previous hemorrhage, hemosiderin can be found entrapped within the cytoplasm of tumor cells, which can be a helpful feature distinguishing these tumors on needle biopsy. The ISUP nucleolar grading system has been validated for papillary RCC [19].

Classically, papillary RCC has been divided into two categories (type 1 and type 2) based on specific morphologic features [18, 20]. Type 1 papillary RCC is defined by fibrovascular cores lined by a single layer of nuclei with scant cytoplasm (Fig. 2.3). These tumors tend to have a more basophilic appearance at low power due to the high nuclear/cytoplasmic (N:C) ratio. Type 2 papillary RCC is defined by fibrovascular cores lined by more than one cell layer with pseudostratified nuclei and abundant eosinophilic cytoplasm (Fig. 2.4). Due to the lower N:C ratio, these tumors tend to look more eosinophilic at low power. Type 2 RCC tends to be of higher grade than the type 1 tumors. It was thought in the past that type 1 papillary RCC had a better prognosis compared to type 2 tumors. However, this concept has been challenged in recent studies [21, 22]. In addition, several new molecularly distinct tumors with papillary features have been recognized since the original subtype classification of papillary RCCs [3, 4]. Assigning a particular subtype can also be challenging to

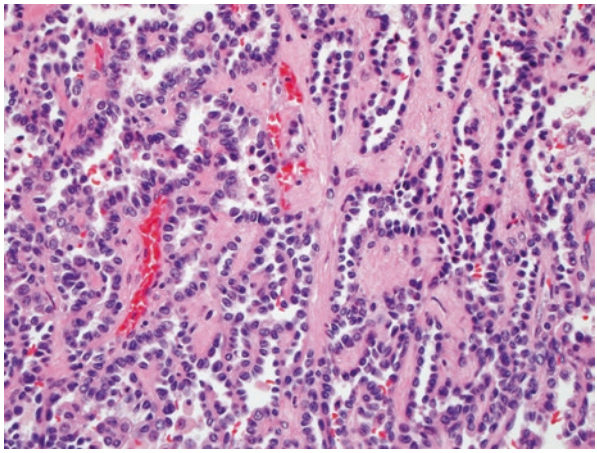

Fig. 2.3 H&E, high magnification, papillary renal cell carcinoma, type 1

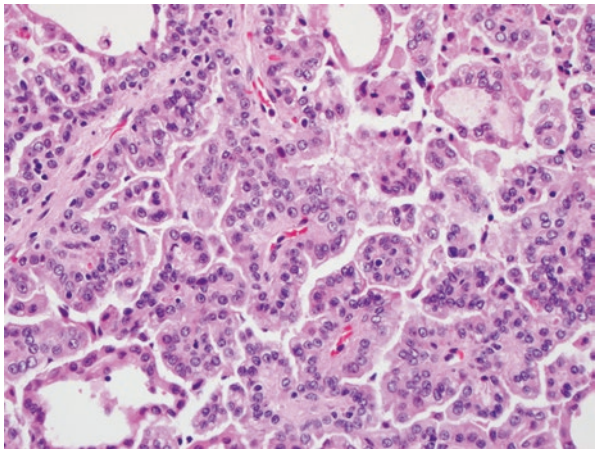

Fig. 2.4 H&E, high magnification, papillary renal cell carcinoma, type 2

pathologists in that many tumors have features of both type 1 and type 2 morphologies. A recent analysis showed distinct molecular differences between type 1 and type 2 tumors; however, type 2 tumors were discovered to be heterogeneous [23]. This raises the question of whether there truly is a distinct type 2 tumor. As such, subtyping papillary RCC remains controversial. Regardless of subtype, it is recommended that papillary RCC be given an ISUP nucleolar grade [3–5]. Oncocytic papillary RCC should no longer be identified as a specific subtype.

Several mutations have been associated with papillary RCC including MET, SETD2, NF2, and BAP1 [23–25]. Gains of chromosomes 7 and 17 are common, especially in type 1 tumors [24, 25]. Type 2 tumors frequently have loss of chromosome 9p and alterations in CDKN2A [25]. Loss of the Y chromosome has also been frequently reported in papillary RCC [14]. Immunohistochemistry will typically show positivity in tumor cells for CK7, AE1/AE3, CAM5.2, EMA, AMACR, vimentin, and CD10 [15, 17].

Chromophobe Renal Cell Carcinoma

Chromophobe RCC accounts for approximately 5% of all cases of RCC [3, 26–28]. Chromophobe RCC has a better prognosis than both clear cell RCC and papillary RCC. The 5-year cancer-specific survival has been reported from 78% to 100% [26–28]. Poor prognostic features include high pathologic stage, sarcomatoid features, lymphovascular invasion, and necrosis [28]. Chromophobe RCC should not be graded, as the innate nuclear atypia does not portend to a worse prognosis. Patients with Birt-Hogg-Dubé syndrome have high incidence of chromophobe RCC as well as hybrid oncocytic/chromophobe tumors (HOCTs) [29]. Birt-Hogg-Dubé syndrome is associated with mutations in the folliculin (*FLCN*) gene and is inherited in an autosomal dominant manner. This syndrome is also associated with fibrofolliculomas, pulmonary cysts, and spontaneous pneumothorax.

Chromophobe RCCs are well-circumscribed, unencapsulated tumors that are classically tan-brown and homogenous. Chromophobe RCCs tend to be large at presentation, with one study reporting an average size of 8 cm [26]. Tumor cells grow in solid sheets with variable oncocytic cytoplasm and classic perinuclear halos (Fig. 2.5). Cells have thick plant-like cell membranes, irregular "raisinoid" nuclei, and binucleation, which create a resemblance to koilocytes. Chromophobe RCCs show strong, diffuse positivity for CK7 and diffuse cytoplasmic staining for Hale colloidal iron, which can help distinguish them from oncocytomas [15, 30]. The genetic profile of chromophobe RCC is variable. Studies have reported losses of chromosomes Y, 1, 2, 6, 10, 13, 17, and 21. Mutations of TP53 and *PTEN* and rearrangements in the *TERT* promoter region have also been identified [31].

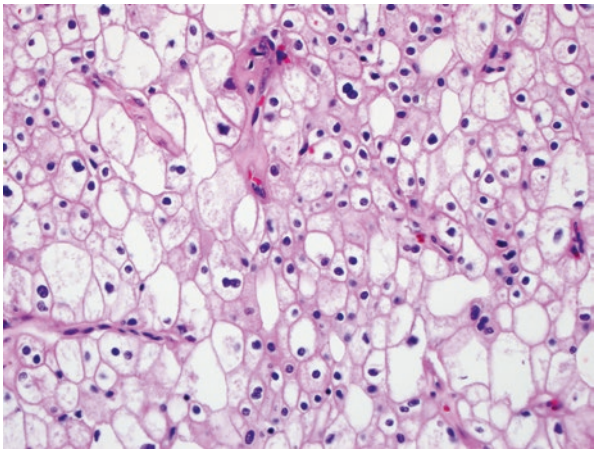

Fig. 2.5 H&E, high magnification, chromophobe renal cell carcinoma

Clear Cell Papillary Renal Cell Carcinoma

Clear cell papillary RCC is a low-grade renal tumor recently recognized by the World Health Organization [4, 32–40]. Previously this tumor was mistaken for conventional clear cell RCC and is more common than once thought, with two studies finding it to be the fourth most common variant of RCC [38, 40]. Although clear cell papillary RCC has an indolent biologic behavior, some cases occur with other synchronous malignant RCCs [32–35]. Clear cell papillary RCC is found in association with end-stage renal disease, and one study showed an association with African American race [37, 38].

Most tumors are small, encapsulated, and variably solid and cystic. Almost all cases are organ confined at presentation. As its name suggests, clear cell papillary RCC contains cells with clear cytoplasm as well as papillary and tubular structures. Clear cell papillary RCC has low-grade nuclei that show reverse polarity, with nuclei arranged in a linear fashion at the luminal surface (Fig. 2.6).

Tumor cells will show strong diffuse staining for PAX8 and CK7 and lack of staining for AMACR [41]. CAIX shows diffuse positivity with an absence of membranous staining along the luminal surface of cells, creating a "cup-shaped" appearance [36]. *VHL* gene mutations and trisomy of chromosomes 7 and 17 are not seen in clear cell papillary RCC [39].

Hybrid Oncocytic/Chromophobe Tumor

HOCTs are indolent renal tumors that have features of both chromophobe RCC and benign oncocytomas [29, 42–45]. It is thought that HOCTs are a distinct entity, rather than a malignant progression of oncocytoma to chromophobe RCC [42, 43, 45]. These tumors are seen in adult patients and can arise sporadically or be seen in

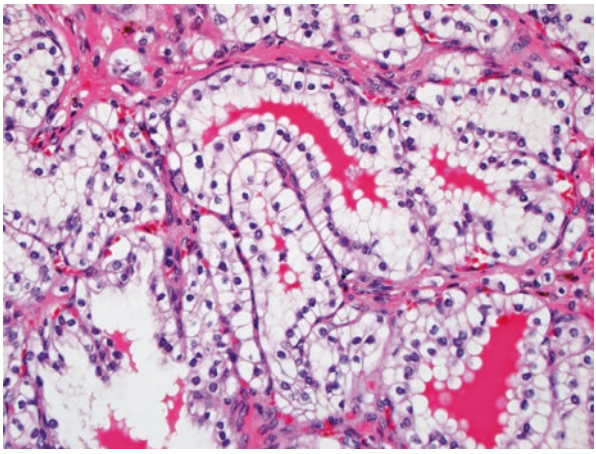

Fig. 2.6 H&E, high magnification, clear cell papillary renal cell carcinoma

association with oncocytosis (Fig. 2.7) or in patients with Birt-Hogg-Dubé syndrome. Sporadic HOCTs tend to be solitary, while those associated with Birt-Hogg-Dubé syndrome and oncocytosis are often multifocal and bilateral. Most of these tumors present at a low pathologic stage and have an indolent behavior [45].

Sporadic HOCTs form well-circumscribed, tan-brown masses that may have a central scar, similar to oncocytomas. Tumor cells have overlapping histologic features seen in oncocytoma and chromophobe RCC. The cells have mild cytologic atypia and abundant eosinophilic cytoplasm. Binucleate cells and perinuclear cytoplasmic clearing are common; however raisinoid nuclei are absent. Tumor cells grow in sheets with occasional small tubules. HOCTs associated with Birt-Hogg-Dubé syndrome will have areas of classic chromophobe RCC and oncocytoma within the same tumor. Chromophobe cells with wrinkled nuclei and perinuclear halos can be found within the fibromyxoid background typically associated with oncocytomas (Fig. 2.8). HOCTs will be positive for CK7 and CD117 [42, 43]. Sporadic HOCTs have been found to have abnormalities of chromosomes 1, 2, 6, 9,

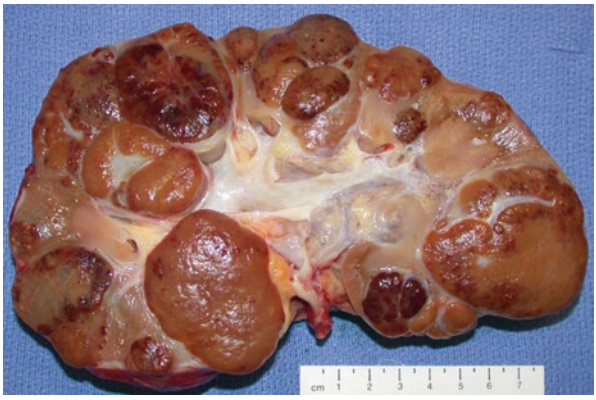

Fig. 2.7 Gross image of a kidney with oncocytosis showing numerous mahogany brown nodules

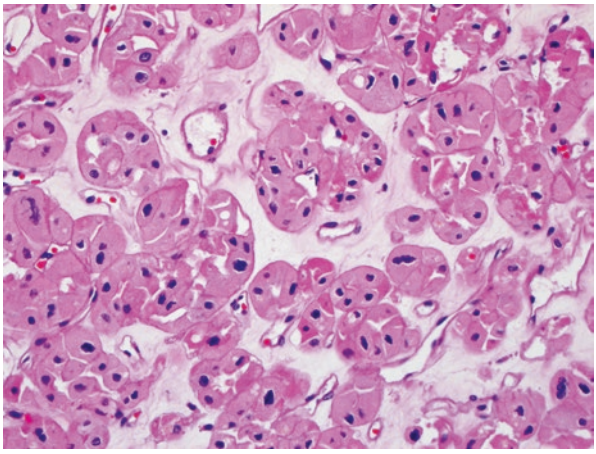

Fig. 2.8 H&E, high magnification, hybrid oncocytic/chromophobe tumor

10, 13, 17, 20, 21, and 22 [43, 46]. Monosomy of chromosome 20 is the most common mutation, which is a rare finding in oncocytoma and chromophobe RCC [3]. Oncocytosis-associated HOCTs and those associated with Birt-Hogg-Dubé syndrome have a non-specific genetic phenotype.

Collecting Duct Carcinoma

Collecting duct carcinoma (CDC) is a rare, aggressive, malignant renal tumor [47–49]. Most patients with CDC are symptomatic and present with high stage and metastatic disease [49]. These tumors have a poor response to chemotherapy and immunotherapy [49].

CDC arises from the medulla and appears as a firm, gray-white mass. Hemorrhage and necrosis are a common finding. Unlike conventional RCC, which is typically well-circumscribed, CDCs have an irregular infiltrative border. Criteria for the diagnosis of CDC includes at least some involvement of the medulla, predominance of tubule formation, a desmoplastic stromal reaction, and exclusion of other RCC subtypes as well as urothelial carcinoma [3]. CDCs should have significant cytologic atypia and a high mitotic rate with atypical mitotic figures. Lymphovascular and renal sinus invasion are common. CDCs have a morphologic overlap with renal medullary carcinoma, urothelial carcinoma, and metastatic carcinomas to the kidney.

Immunohistochemistry can be useful in confirming the diagnosis of CDC. Tumor cells should be positive for PAX8 and negative for GATA3 and p63 and show loss of INI1 [47, 48]. CDCs have a variable genetic profile. DNA losses and loss of heterozygosity have been reported on multiple chromosomes [50]. In addition, studies have shown amplifications of *HER2/neu* and mutations involving *INI1* [50, 51].

Renal Medullary Carcinoma

Renal medullary carcinoma (RMC) is an aggressive malignant renal tumor that is associated with sickle cell trait [41, 52–54]. Most patients present with metastatic disease and the prognosis is exceptionally poor [41, 52–54]. It is thought that RMC occurs in the medulla where the microenvironment is particularly susceptible to sickling of red blood cells and ischemic damage. Chronic reparative changes promote carcinogenesis, particularly via *HIF-1α*, TP53, and *VEGF* mutations [54].

RMC forms a poorly circumscribed mass centered in the renal medulla. Tumors are usually gray-white and firm. Areas of necrosis are common. Tumor cells form tubules and glands that are high-grade with marked cytologic atypia (Fig. 2.9). Tumor cells often produce mucin. The background shows a pronounced myxoid, desmoplastic reaction, and inflammation that is often predominated by neutrophils.

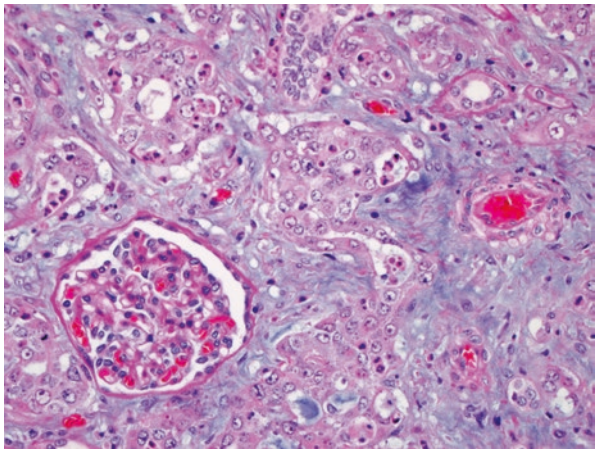

Fig. 2.9 H&E, high magnification, renal medullary carcinoma

Tumor cells show positivity for PAX8, CK7, and CAM5.2 and loss of INI1 [54]. The tumor's genetic profile involves mutations in genes involved in the hypoxia-induced signaling pathways, including *HIF-1α* [54]. Loss of heterozygosity involving *INI1* has also been reported [54].

MiT Family Translocation Renal Cell Carcinomas

The MiT group of transcription factors include, among others, TFE3 and TFEB. RCCs with either a *TFE3* or *TFEB* gene aberrations are collectively known as the MiT family translocation renal cell carcinomas [55–59]. Among this group of RCCs, those with *TFE3* (located at the Xp11.2 locus) alterations are the most common [59]. The *ASPSCR1* (*ASPL*) and *PRCC* genes are the most common fusion partners with *TFE3*, resulting in either the t(X;17)(p11;q25) or the t(X;1)(p11;q21) translocation, respectively [57]. The second, less common, group within the MiT family translocation RCCs are those that show fusions of the *TFEB* gene, located at chromosome 6p21, with the *MALAT1* gene on chromosome 11q12, forming a t(6:11)(p21;q12) fusion [3].

MiT family translocation RCCs have a tendency to disproportionally affect younger patients, representing about 40% of pediatric RCCs [57, 59]. However, about 1–4% of RCCs in adults are MiT family translocation RCCs [56]. Given that RCCs are much more common in adults than children, the absolute numbers of MiT family translocation RCC are actually higher in adults [57]. MiT family translocation RCCs are associated with prior exposure to cytotoxic chemotherapy [55]. The prognosis for these tumors appear to be similar to clear cell RCC but worse than papillary RCC [55]. While data is currently limited, the MiT family translocation RCCs with the *TFEB-MALAT1* fusion appear to behave in a more indolent manner than those with *TFE3* alterations [56]. Both the TFE3- and TFEB-associated MiT family translocation RCCs have the potential to recur many years after initial diagnosis [55].

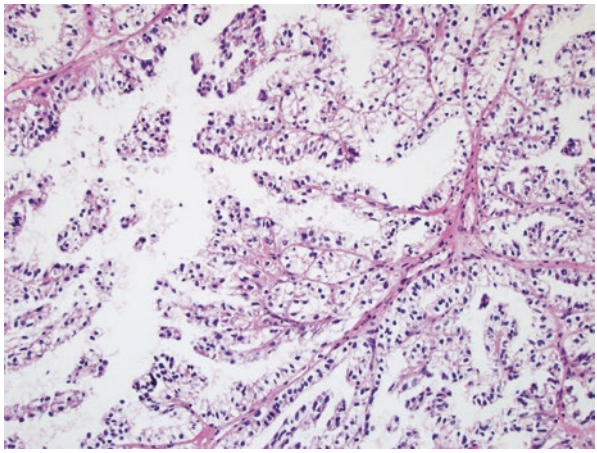

Fig. 2.10 H&E, high magnification, Xp11.2 translocation renal cell carcinoma

MiT family translocation RCCs have no distinguishing gross characteristics and are often similar to the conventional type of RCC. While there can be considerable histologic overlap between the TFE3 and TFEB types, there are some differences. Those with *TFE3* translocations often show mixtures of nested and papillary architecture with variable clear and eosinophilic cells with prominent nucleoli (Fig. 2.10). Psammoma bodies are often present [55, 57]. Those with *TFEB* translocations may show a biphasic tumor composed of small and large epithelial cells among basement membrane material. Melanin pigment can be seen in some MiT family translocation RCCs.

MiT family translocation RCCs are positive for PAX8 and CD10 but are typically negative for CK7 [54]. Unlike other forms of RCC, MiT family translocation RCCs can express cathepsin K and often can express the melanocytic markers HMB-45 and Melan-A [59]. Unlike melanoma, MiT family translocation RCCs are negative for S100 protein and MITF. Both the TFE3 and TFEB fusion products target similar segments of DNA, resulting in transcription of similar downstream targets, such as cathepsin K, HMB-45, and Melan-A [59]. The activation of these targets also explains the presence of melanin pigment in some tumors.

Multilocular Cystic Renal Neoplasm of Low Malignant Potential

Multilocular cystic renal neoplasm of low malignant potential (MCRNLMP) was formally known as multilocular cystic renal cell carcinoma [3, 4, 60–62]. MCRNLMP is a rare renal tumor that typically presents as a solitary mass. Most tumors are discovered incidentally on imaging and are considered to be of low malignant potential as there are no reports of metastatic disease or disease recurrence.

These tumors are entirely composed of multiple cystic spaces. The presence of a solid tumor component excludes the diagnosis of MCRNLMP. Cyst walls and septa are lined by low-grade, clear cells. Individual cells or small groups of clear cells should be present within the septa, but these foci should lack expansile growth. MCRNLMP should not have necrosis, vascular invasion, or sarcomatoid features. Clear cell RCC with cystic degeneration, cystic nephroma, and tubulocystic renal cell carcinoma can mimic MCRNLMP and needs to be excluded.

Tumor cells are positive for PAX8 and CAIX, similar to clear cell RCC [63]. Deletions of chromosome 3p are present in the majority of cases [64].

Mucinous Tubular and Spindle Cell Carcinoma

Mucinous tubular and spindle cell carcinoma (MTSC) is a rare renal tumor typically seen in middle-aged women [3, 65, 66]. This tumor has an association with end-stage renal disease and nephrolithiasis. Most patients present with organ-confined disease. Although these tumors are thought to have a good prognosis, there have been reported cases of metastatic disease [65, 66].

MTSC tends to be well-circumscribed and can grow to be large in size. Tumors are often homogenous tan-gray and have a mucoid appearance. Tumor cells are low-grade and arranged in long, tightly packed tubules that can lie in parallel or show branching (Fig. 2.11a). The background stroma contains abundant extracellular mucin (Fig. 2.11b). Tubules classically transition into the spindle component, which is also low-grade (Fig. 2.11c). MTSC with high-grade features, necrosis, mitoses, or sarcomatoid change is rarely seen.

Tumor cells show positivity for PAX8, CK7, EMA, AMACR, and E-cadherin [65, 66]. These tumors have a variable genetic profile, with losses and gains of multiple chromosomes reported [65, 66]. Gains in chromosome 7 and 17 and loss of chromosome Y have not been described in MTSC, making this tumor distinct from papillary RCC [65, 66].

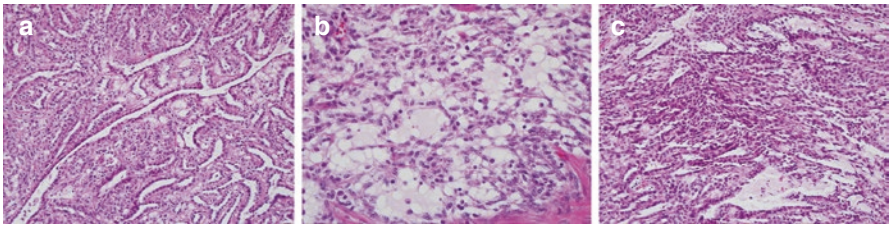

Fig. 2.11 H&E, high magnification, mucinous tubular and spindle cell carcinoma, (**a**) tubule component, (**b**) mucinous component, and (**c**) spindle cell component

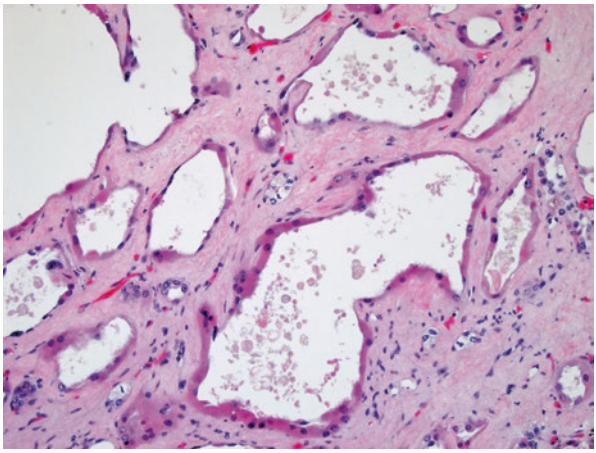

Fig. 2.12 H&E, high magnification, tubulocystic renal cell carcinoma

Tubulocystic Renal Cell Carcinoma

Tubulocystic RCC is a newly recognized renal tumor by the WHO [3, 4]. Tubulocystic RCC is thought to have an indolent biologic behavior with rare cases of metastases reported in the literature [67].

Tubulocystic RCC presents as a well-circumscribed mass composed of multiple cysts. These tumors are typically small (around 4 cm) and organ confined. The tubules are small to medium sized and are lined by a single layer of flat to cuboidal cells (Fig. 2.12). Hobnail cells are usually present. Tubulocystic RCC has high-grade nuclear features with large nucleoli, which help distinguish it from benign tumors such as cystic nephroma. Similar to papillary RCC, tubulocystic carcinoma has gains in chromosome 7 and 17 and loss of chromosome Y [68, 69].

Acquired Cystic Kidney Disease-Associated Renal Cell Carcinoma

Acquired cystic disease (ACD)-associated RCC is another newly recognized renal tumor by the WHO [3, 4]. This malignant tumor is the predominant subtype of RCC arising in the setting of end-stage renal disease and its associated acquired cystic kidney disease [70, 71]. As opposed to other tumors that can be seen in patients with end-stage renal disease and the general population, this tumor is only found in the setting of acquired cystic kidney disease. The incidence of the tumor increases with the time spent on dialysis [70, 71]. ACD-associated RCC is often multifocal and bilateral. Most tumors are small and are thought to have an indolent clinical outcome. However, this is likely confounded by the early detection of these tumors due to frequent imaging in patients with chronic kidney disease. Sarcomatoid features and metastases have been reported in the literature [70, 71].

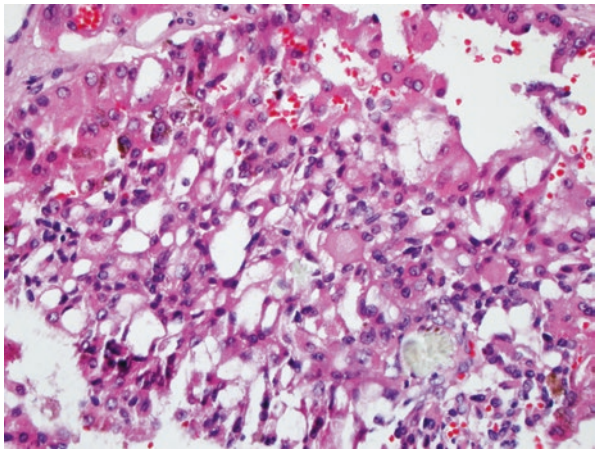

Fig. 2.13 H&E, high magnification, acquired cystic kidney disease-associated renal cell carcinoma

ACD-associated RCC forms a well-circumscribed tan-yellow mass that can arise within a renal cyst or be associated with the renal parenchyma. Necrosis and hemorrhage can be present. The background kidney will be atrophic with multiple small cortical cysts. This tumor can have several morphologic patterns including papillary, tubulocystic, and solid. The classic growth pattern shows a cribriform−/sieve-like appearance with the presence of calcium oxalate crystals (Fig. 2.13). However, calcium oxalate crystals may not always be present and the lack of this finding does not exclude the diagnosis. Tumor cells are high-grade with prominent nucleoli and abundant eosinophilic cytoplasm.

On immunohistochemistry, ACD-associated RCC shows positivity for CD10, RCC marker, and AMACR [70]. CK7 is typically negative in contrast to papillary RCC [70]. This tumor has a variable genetic profile; however the most common abnormalities include gains in chromosomes 3, 7, and 16 [70]. Gains of the sex chromosomes have also been reported [70]. Mutations in the *VHL* gene have not been identified [70].

Hereditary Leiomyomatosis and Renal Cell Carcinoma

Hereditary leiomyomatosis and RCC (HLRCC) is an autosomal dominant syndrome that arises in patients with a germline mutation of fumarate hydratase [72–74]. The mutation causes an increase in fumarate, which impairs the function of HIF prolyl hydroxylase. This leads to increased levels of HIF1α. Patients develop cutaneous and uterine leiomyomas as well as RCC. This RCC subtype is a newly recognized classification by the WHO [3, 4]. These tumors tend to be aggressive and have a poor prognosis.

RCCs associated with the hereditary leiomyomatosis and RCC syndrome can grow to a large size, and extrarenal extension is common. Both cystic and solid

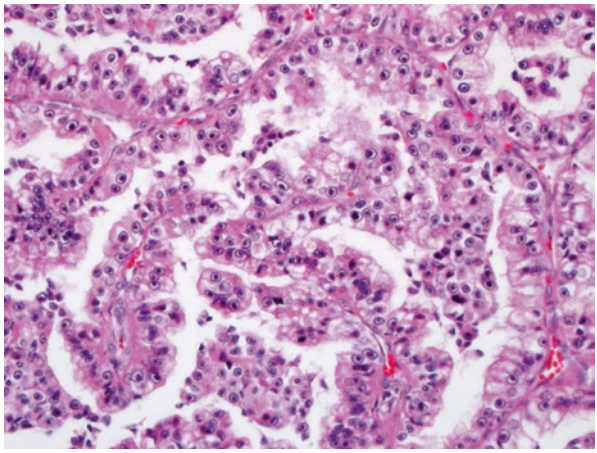

Fig. 2.14 H&E, high magnification, hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma

growth have been reported. Tumor cells can be arranged in tubular, solid, or papillary patterns. Tumor cells are large with prominent nucleoli and abundant eosinophilic cytoplasm. Previously, many of these tumors were classified as type 2 papillary RCC due to the overlapping morphology. Classically, tumor cells have a large eosinophilic nucleolus with cytoplasmic clearing around the nucleolus, creating a cytomegalovirus viral inclusion look (Fig. 2.14). Immunohistochemistry will show loss of fumarate hydratase staining in tumor cells and overexpression of S-(2-succino)cysteine [72–74].

Succinate Dehydrogenase-Deficient Renal Cell Carcinoma

Succinate dehydrogenase (SDH)-deficient RCC is a newly recognized malignant renal tumor by the WHO [3, 4]. This is a rare tumor that comprises less than 1% of all RCCs. Most patients present in early adulthood with the mean age in the fourth decade of life. SDH-deficient RCC is typically hereditary, and the vast majority of cases arise in the setting of a germline mutation on one of the SDH genes [75, 76]. The most commonly involved gene is *SDHB*. Knockout of the SDH genes leads to dysfunction of mitochondrial complex II [75, 76]. Patients have an increased risk of paraganglioma, gastrointestinal stromal tumor, and pituitary adenoma. It is recommended that all patients with SDH-deficient RCC be offered genetic testing for a germline mutation.

Most tumors form a well-circumscribed mass that is organ confined on presentation. Multifocal and bilateral disease is found in up to 30% of patients [75, 76]. Tumor cells have eosinophilic cytoplasm and inconspicuous nucleoli. Solid, nested, and tubular growth patterns can be seen. The classic histologic feature of this tumor is cytoplasmic vacuoles or eosinophilic inclusions that can impart a bubbly appearance to the cells. However, this finding can be found only focally in some tumors.

Higher-grade nuclear features, sarcomatoid change, and necrosis have been reported and suggest a worse prognosis.

Tumor cells are positive for PAX8 and typically negative for CD117 and CK7 [75, 76]. Neuroendocrine markers should be negative, and loss of staining for SDHB by immunohistochemistry is required for the diagnosis.

Nephroblastoma (Wilms Tumor)

Nephroblastoma is the most common childhood renal malignancy [77–80]. It accounts for 90% of all newly diagnosed childhood renal tumors and is the fourth most common overall cancer in this age group. Nephroblastoma is thought to originate from remnants of metanephric tissue, known as nephrogenic blastemal rests. Most patients present at an average age of 2–4 years with a non-painful, palpable abdominal mass. Some children may be symptomatic with abdominal pain, hematuria, fever, hypertension, or an acute abdomen. Most tumors are unilateral and organ confined at presentation, with approximately 5% occurring bilaterally. Advances in chemotherapy have greatly improved the prognosis for patients with nephroblastoma, with an overall survival >90%. Nephroblastoma is associated with a genetic syndrome in 10% of cases. WAGR (Wilms tumor, aniridia, genitourinary anomalies, and mental retardation) and Denys-Drash syndrome (Wilms tumor, pseudohermaphroditism, and mesangial sclerosis) have *WT1* gene mutations. Beckwith-Wiedemann syndrome (asymmetric growth with hemihypertrophy, macroglossia, omphalocele, and visceromegaly) arises from mutations in the *WT2* gene. Patients with a germline mutation present at an earlier age and are more likely to have bilateral disease.

Nephroblastoma presents as a well-circumscribed, encapsulated mass. The cut surface is soft, homogenous, and gray to tan-pink in color. The presence of hemorrhage, cystic change, and necrosis is common. Classically, tumor cells show triphasic differentiation consisting of blastemal, stromal, and epithelial components (Fig. 2.15). The blastemal component is composed of small blue cells with closely packed nuclei, coarse chromatin, and scant cytoplasm. The epithelial component consists of primitive tubules with elongated nuclei. The stroma contains spindled cells, with some cases showing soft tissue differentiation. Nephroblastoma will have a high mitotic index. Many cases are associated with perilobar or intralobar nephrogenic rests. It is thought that nephrogenic rests are preneoplastic in nature and the risk of malignant transformation is higher for intralobar rests. Anaplasia is defined as markedly enlarged nuclei (3x the size of blastemal nuclei) with hyperchromasia and hyperdiploid (multipolar) mitotic figures. Diffuse anaplasia is associated with *TP53* gene mutations, resistance to chemotherapy, disease recurrence, metastases, and death.

On immunohistochemistry, tumor cells show staining for WT1 and CD56 [79, 80]. The majority of tumors arise from sporadic mutations on the *WT1* gene (chromosome 11p13) or the *WT2* gene (chromosome 11p15). Abnormalities in other

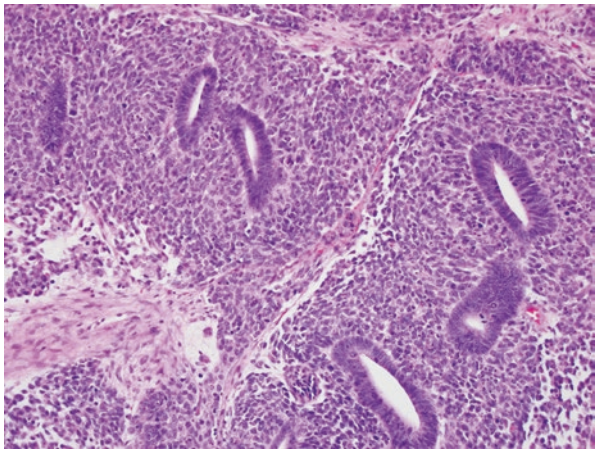

Fig. 2.15 H&E, high magnification, nephroblastoma

genes may also be seen including *WTX*, *CTNNB1*, and *TP53* [79, 80]. Nephroblastomas with loss of heterozygosity at 1p and 16q are associated with a poor prognosis [79, 80].

Benign Renal Tumors

Oncocytoma

Oncocytoma is the most common benign renal tumors, accounting for approximately 9% of all renal cortical neoplasms [81–85]. Most oncocytomas are incidentally discovered on imaging and are otherwise asymptomatic. While capable of local extension, oncocytomas are incapable of metastatic spread.

Oncocytomas present as solid, well-circumscribed masses that classically have a mahogany brown cut surface and the presence of a central stellate scar. A central scar is not diagnostic of oncocytoma, as this feature has been described in malignant renal tumors. Oncocytomas can have foci of hemorrhage, but the finding of necrosis, clear cells, papillary structures, or mitoses excludes this diagnosis. Rare cases have been reported to invade the perinephric fat or the renal vein, a finding that should not be mistaken for malignancy [82]. Tumor cells are uniform with abundant eosinophilic cytoplasm. The tumor grows in small, solid nests within a fibromyxoid background (Fig. 2.16). Cases can also show tubular, cystic, or solid growth.

Oncocytomas will show positivity for CD117 on immunohistochemistry, and CK7 should be negative or only focally positive [83]. This is in contrast to chromophobe RCC, a common diagnostic differential, which is diffusely positive for CK7 [81, 83]. Multifocal oncocytomas and oncocytosis are associated with Birt-

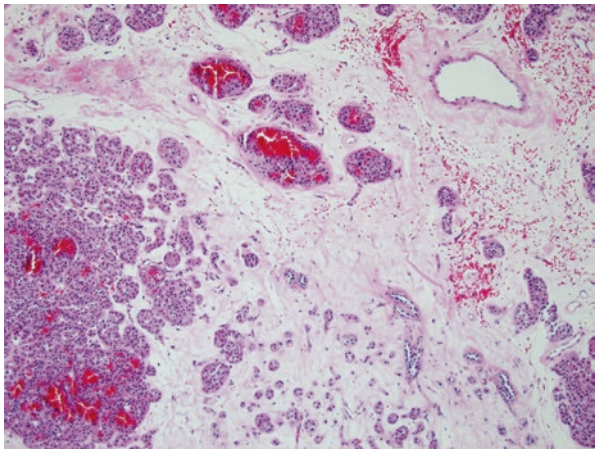

Fig. 2.16 H&E, high magnification, oncocytoma

Hogg-Dubé syndrome. Genetic mutations include loss of chromosomes Y, loss of chromosome 1, rearrangements of 11q13, and deletion of chromosome 14 [84].

Angiomyolipoma

Angiomyolipoma (AML) is a renal tumor that is a member of the perivascular epithelioid cell tumor family [86–89]. The majority of AMLs are benign; however, those with epithelioid features can have malignant behavior [87]. Most tumors are small and can be managed with active surveillance. However, larger tumors (>4 cm) can spontaneously bleed and cause significant morbidity [86]. AMLs are also capable of local invasion. Pregnancy and hormonal therapy have been known to cause increased growth.

AMLs typically present as an unencapsulated, well-circumscribed mass. The color of the cut surface varies with the content of fat present in the lesion. Fat-poor tumors appear tan-white to pink, while those that are fat-rich are more yellow. As the name suggests, AMLs are composed of three components: thick-walled vessels, smooth muscle, and adipose tissue (Fig. 2.17). The diagnosis of fat-poor lesions should be reserved for tumors that contain <25% fat. Hyalinization, cystic change, or calcifications have also been reported. Epithelioid cells may be present in a minority of cases. The presence of ≥70% atypical epithelioid cells, ≥2 mitoses per 10 high power fields, atypical mitotic figures, and necrosis is associated with increased risk of malignant behavior.

Tumor cells will show positivity for SMA, desmin, HMB-45, and Melan-A [88]. Fat-poor tumors are typically negative for Melan-A [88]. Although the majority of AMLs occur sporadically, this tumor presents in up to 90% of patients with tuberous sclerosis complex (TSC), an autosomal dominant syndrome caused by germline mutations of *TSC1* on 9q34 and *TSC2* on 16p13 [88]. Renal AMLs associated with TSC are often multifocal and bilateral. Mutations of *TSC2* can also be seen in sporadic AML. AML is also associated with lymphangioleiomyomatosis.

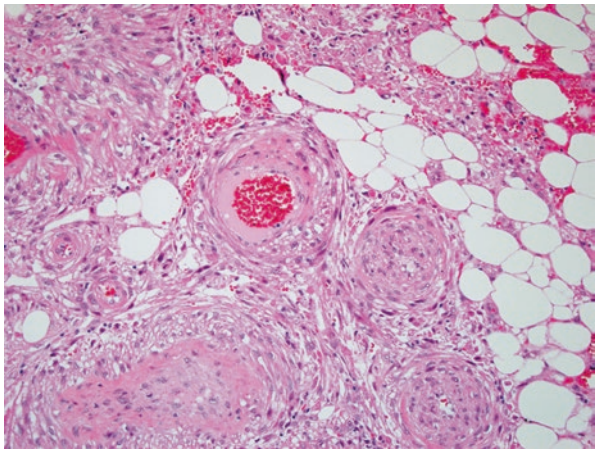

Fig. 2.17 H&E, high magnification, angiomyolipoma

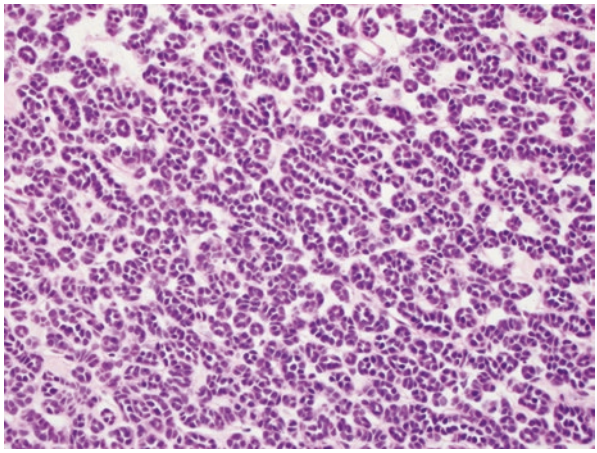

Fig. 2.18 H&E, high magnification, metanephric adenoma

Metanephric Adenoma

Metanephric adenoma is a benign kidney tumor with morphologic resemblance to the fetal kidney [90–92]. It affects a wide age range of patients and is more common in women. Metanephric adenoma is typically an incidental finding but can be associated with hematuria, flank pain, abdominal mass, or polycythemia [90, 92]. Metanephric adenoma is the kidney tumor most likely to cause polycythemia via secretion of erythropoietin [90].

Grossly, metanephric adenomas are solitary, well-circumscribed tan to gray tumors typically 3–6 cm in size. Microscopically, they resemble the fetal metanephric kidney. Tumor cells are arranged in tightly packed acini with inconspicuous lumens set in a scant loose stroma (Fig. 2.18). Acini can focally be elongated with intraluminal tufts forming glomeruloid and short papillary structures. Psammoma

bodies are common. The neoplastic cells are small with fine, evenly distributed chromatin, inconspicuous nucleoli and scant cytoplasm. Mitotic activity and necrosis should be absent.

By immunohistochemistry, the cells show characteristic expression of WT1 and CD57 [91]. They are negative for CK7 and racemase and are diploid for chromosomes 7 and 17 [91].

Mixed Epithelial and Stromal Tumor Family

The mixed epithelial and stromal tumor (MEST) family includes the adult cystic nephroma (which is predominantly cystic) and the MEST (which has cystic and solid areas) [93–95]. Adult cystic nephromas are now recognized to be a separate entity from pediatric cystic nephromas, which have *DICER1* mutations [95]. Most tumors are benign; however malignant transformation has been reported in the literature [93, 94].

These tumors are always solitary, unilateral masses with variable cystic and solid components. Most are well-circumscribed and unencapsulated. The cut surface shows thin-walled cysts with white, firm solid areas. The epithelial component consists of cysts, glands, and tubules. Some glands may have an endometrioid or tubal appearance. Less commonly, intestinal and urothelial morphology has been reported. The cysts are lined by flat to cuboidal epithelium, with hobnail cells being a common finding (Fig. 2.19). Stromal cellularity is variable and in many cases stromal condensation is seen around the epithelial component. The stroma can be composed of blue, spindle cells, creating an ovarian-like appearance. Smooth muscle metaplasia is also a common finding. Cytologic atypia, mitotic activity, necrosis, and hemorrhage are rare.

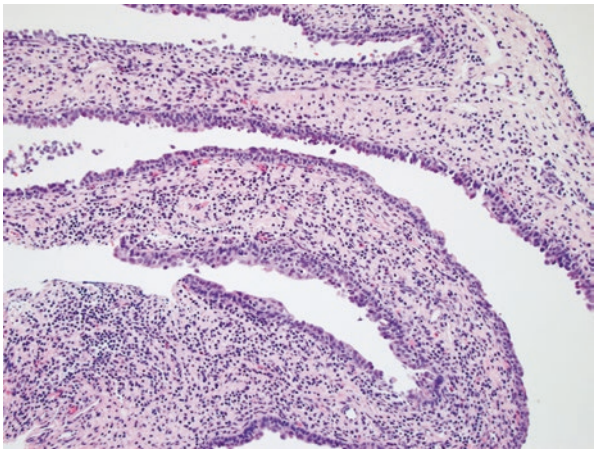

Fig. 2.19 H&E, high magnification, mixed epithelial and stromal tumor

Tumors of the MEST family show immunohistochemical staining for actin, desmin, CD10, estrogen receptor, and progesterone receptor in the stromal component [95]. Inhibin and calretinin may be positive in cases with luteinized stroma [95].

References

1. (CAP) CoAP. Cancer protocol templates AJCC cancer staging manual 2016 [cited 2016 09/26/17]. Available from: www.cap.org/web/oracle/webcenter/portalapp/pagehierarchy/cancer_protocol_templates.jspx?_adf.ctrl-state=mgbufglyx_4&_afrLoop=50758928733115#!%40%40%3F_afrLoop%3D50758928733115%26_adf.ctrl-state%3D3jlqfweu7_4.
2. Amin MB, Edge SB. In: Cancer AJCo, editor. AJCC cancer staging manual. Chicago: Springer; 2017.
3. Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. The International Society of Urological Pathology (ISUP) vancouver classification of renal neoplasia. Am J Surg Pathol. 2013;37(10):1469–89.
4. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of tumours of the urinary system and male genital organs-part a: renal, penile, and testicular tumours. Eur Urol. 2016;70(1):93–105.
5. Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol. 2013;37(10):1490–504.
6. Przybycin CG, Magi-Galluzzi C, McKenney JK. Hereditary syndromes with associated renal neoplasia: a practical guide to histologic recognition in renal tumor resection specimens. Adv Anat Pathol. 2013;20(4):245–63.
7. Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v58–68.
8. Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. J Urol. 2001;166(5):1611–23.
9. Bonsib SM. The renal sinus is the principal invasive pathway: a prospective study of 100 renal cell carcinomas. Am J Surg Pathol. 2004;28(12):1594–600.
10. Bonsib SM. Renal veins and venous extension in clear cell renal cell carcinoma. Mod Pathol. 2007;20(1):44–53.
11. Delahunt B, Bethwaite PB, Nacey JN. Outcome prediction for renal cell carcinoma: evaluation of prognostic factors for tumours divided according to histological subtype. Pathology. 2007;39(5):459–65.
12. Nguyen DP, Vertosick EA, Corradi RB, Vilaseca A, Benfante NE, Touijer KA, et al. Histological subtype of renal cell carcinoma significantly affects survival in the era of partial nephrectomy. Urol Oncol. 2016;34(6):259.e1–8.
13. Hirsch MS, Signoretti S, Dal Cin P. Adult renal cell carcinoma: a review of established entities from morphology to molecular genetics. Surg Pathol Clin. 2015;8(4):587–621.
14. Su D, Singer EA, Srinivasan R. Molecular pathways in renal cell carcinoma: recent advances in genetics and molecular biology. Curr Opin Oncol. 2015;27(3):217–23.
15. Reuter VE, Argani P, Zhou M, Delahunt B. Best practices recommendations in the application of immunohistochemistry in the kidney tumors: report from the International Society of Urologic Pathology consensus conference. Am J Surg Pathol. 2014;38(8):e35–49.
16. Tan PH, Cheng L, Rioux-Leclercq N, Merino MJ, Netto G, Reuter VE, et al. Renal tumors: diagnostic and prognostic biomarkers. Am J Surg Pathol. 2013;37(10):1518–31.
17. Zhou M, Roma A, Magi-Galluzzi C. The usefulness of immunohistochemical markers in the differential diagnosis of renal neoplasms. Clin Lab Med. 2005;25(2):247–57.

18. Zucchi A, Novara G, Costantini E, Antonelli A, Carini M, Carmignani G, et al. Prognostic factors in a large multi-institutional series of papillary renal cell carcinoma. BJU Int. 2012;109(8):1140–6.
19. Delahunt B, Egevad L, Samaratunga H, Martignoni G, Nacey JN, Srigley JR. Gleason and Fuhrman no longer make the grade. Histopathology. 2016;68(4):475–81.
20. Antonelli A, Tardanico R, Balzarini P, Arrighi N, Perucchini L, Zanotelli T, et al. Cytogenetic features, clinical significance and prognostic impact of type 1 and type 2 papillary renal cell carcinoma. Cancer Genet Cytogenet. 2010;199(2):128–33.
21. Bigot P, Bernhard JC, Gill IS, Vuong NS, Verhoest G, Flamand V, et al. The subclassification of papillary renal cell carcinoma does not affect oncological outcomes after nephron sparing surgery. World J Urol. 2016;34(3):347–52.
22. Cornejo KM, Dong F, Zhou AG, Wu CL, Young RH, Braaten K, et al. Papillary renal cell carcinoma: correlation of tumor grade and histologic characteristics with clinical outcome. Hum Pathol. 2015;46(10):1411–7.
23. Linehan WM, Spellman PT, Ricketts CJ, Creighton CJ, Fei SS, Davis C, et al. Comprehensive molecular characterization of papillary renal-cell carcinoma. N Engl J Med. 2016;374(2):135–45.
24. Kovac M, Navas C, Horswell S, Salm M, Bardella C, Rowan A, et al. Recurrent chromosomal gains and heterogeneous driver mutations characterise papillary renal cancer evolution. Nat Commun. 2015;6:6336.
25. Yang XJ, Tan MH, Kim HL, Ditlev JA, Betten MW, Png CE, et al. A molecular classification of papillary renal cell carcinoma. Cancer Res. 2005;65(13):5628–37.
26. Amin MB, Paner GP, Alvarado-Cabrero I, Young AN, Stricker HJ, Lyles RH, et al. Chromophobe renal cell carcinoma: histomorphologic characteristics and evaluation of conventional pathologic prognostic parameters in 145 cases. Am J Surg Pathol. 2008;32(12):1822–34.
27. Gordetsky J, Zarzour J. Correlating preoperative imaging with histologic subtypes of renal cell carcinoma and common mimickers. Curr Urol Rep. 2016;17(7):52.
28. Volpe A, Novara G, Antonelli A, Bertini R, Billia M, Carmignani G, et al. Chromophobe renal cell carcinoma (RCC): oncological outcomes and prognostic factors in a large multicentre series. BJU Int. 2012;110(1):76–83.
29. Schmidt LS, Linehan WM. Molecular genetics and clinical features of Birt-Hogg-Dube syndrome. Nat Rev Urol. 2015;12(10):558–69.
30. Ng KL, Morais C, Bernard A, Saunders N, Samaratunga H, Gobe G, et al. A systematic review and meta-analysis of immunohistochemical biomarkers that differentiate chromophobe renal cell carcinoma from renal oncocytoma. J Clin Pathol. 2016;69(8):661–71.
31. Abbosh P, Sundararajan S, Millis SZ, Hauben A, Reddy S, Geynisman DM, Uzzo R. Molecular and genomic profiling to identify actionable targets in chromophobe renal cell cancer. Eur Urol Focus. 2017. pii:S2405–4569(17)30008-1.
32. Alexiev BA, Drachenberg CB. Clear cell papillary renal cell carcinoma: incidence, morphological features, immunohistochemical profile, and biologic behavior: a single institution study. Pathol Res Pract. 2014;210(4):234–41.
33. Aydin H, Chen L, Cheng L, Vaziri S, He H, Ganapathi R, et al. Clear cell tubulopapillary renal cell carcinoma: a study of 36 distinctive low-grade epithelial tumors of the kidney. Am J Surg Pathol. 2010;34(11):1608–21.
34. Diolombi ML, Cheng L, Argani P, Epstein JI. Do clear cell papillary renal cell carcinomas have malignant potential? Am J Surg Pathol. 2015;39(12):1621–34.
35. Gobbo S, Eble JN, Grignon DJ, Martignoni G, MacLennan GT, Shah RB, et al. Clear cell papillary renal cell carcinoma: a distinct histopathologic and molecular genetic entity. Am J Surg Pathol. 2008;32(8):1239–45.
36. Rohan SM, Xiao Y, Liang Y, Dudas ME, Al-Ahmadie HA, Fine SW, et al. Clear-cell papillary renal cell carcinoma: molecular and immunohistochemical analysis with emphasis on the von Hippel-Lindau gene and hypoxia-inducible factor pathway-related proteins. Mod Pathol. 2011;24(9):1207–20.

37. Tickoo SK, dePeralta-Venturina MN, Harik LR, Worcester HD, Salama ME, Young AN, et al. Spectrum of epithelial neoplasms in end-stage renal disease: an experience from 66 tumor-bearing kidneys with emphasis on histologic patterns distinct from those in sporadic adult renal neoplasia. Am J Surg Pathol. 2006;30(2):141–53.
38. Wang K, Zarzour J, Rais-Bahrami S, Gordetsky J. Clear cell papillary renal cell carcinoma: new clinical and imaging characteristics. Urology. 2017;103:136–41.
39. Wolfe A, Dobin SM, Grossmann P, Michal M, Donner LR. Clonal trisomies 7,10 and 12, normal 3p and absence of VHL gene mutation in a clear cell tubulopapillary carcinoma of the kidney. Virchows Arch. 2011;459(4):457–63.
40. Zhou H, Zheng S, Truong LD, Ro JY, Ayala AG, Shen SS. Clear cell papillary renal cell carcinoma is the fourth most common histologic type of renal cell carcinoma in 290 consecutive nephrectomies for renal cell carcinoma. Hum Pathol. 2014;45(1):59–64.
41. Shah AY, Karam JA, Malouf GG, Rao P, Lim ZD, Jonasch E, et al. Management and outcomes of patients with renal medullary carcinoma: a multicentre collaborative study. BJU Int. 2016;120:782.
42. Gobbo S, Eble JN, Delahunt B, Grignon DJ, Samaratunga H, Martignoni G, et al. Renal cell neoplasms of oncocytosis have distinct morphologic, immunohistochemical, and cytogenetic profiles. Am J Surg Pathol. 2010;34(5):620–6.
43. Petersson F, Gatalica Z, Grossmann P, Perez Montiel MD, Alvarado Cabrero I, Bulimbasic S, et al. Sporadic hybrid oncocytic/chromophobe tumor of the kidney: a clinicopathologic, histomorphologic, immunohistochemical, ultrastructural, and molecular cytogenetic study of 14 cases. Virchows Arch. 2010;456(4):355–65.
44. Tickoo SK, Reuter VE, Amin MB, Srigley JR, Epstein JI, Min KW, et al. Renal oncocytosis: a morphologic study of fourteen cases. Am J Surg Pathol. 1999;23(9):1094–101.
45. Waldert M, Klatte T, Haitel A, Ozsoy M, Schmidbauer J, Marberger M, et al. Hybrid renal cell carcinomas containing histopathologic features of chromophobe renal cell carcinomas and oncocytomas have excellent oncologic outcomes. Eur Urol. 2010;57(4):661–5.
46. Pote N, Vieillefond A, Couturier J, Arrufat S, Metzger I, Delongchamps NB, et al. Hybrid oncocytic/chromophobe renal cell tumours do not display genomic features of chromophobe renal cell carcinomas. Virchows Arch. 2013;462(6):633–8.
47. Gonzalez-Roibon N, Albadine R, Sharma R, Faraj SF, Illei PB, Argani P, et al. The role of GATA binding protein 3 in the differential diagnosis of collecting duct and upper tract urothelial carcinomas. Hum Pathol. 2013;44(12):2651–7.
48. Kobayashi N, Matsuzaki O, Shirai S, Aoki I, Yao M, Nagashima Y. Collecting duct carcinoma of the kidney: an immunohistochemical evaluation of the use of antibodies for differential diagnosis. Hum Pathol. 2008;39(9):1350–9.
49. Sui W, Matulay JT, Robins DJ, James MB, Onyeji IC, RoyChoudhury A, et al. Collecting duct carcinoma of the kidney: disease characteristics and treatment outcomes from the National Cancer Database. Urol Oncol. 2017;35(9):540.e13–8.
50. Zambrano NR, Lubensky IA, Merino MJ, Linehan WM, Walther MM. Histopathology and molecular genetics of renal tumors toward unification of a classification system. J Urol. 1999;162(4):1246–58.
51. Elwood H, Chaux A, Schultz L, Illei PB, Baydar DE, Billis A, et al. Immunohistochemical analysis of SMARCB1/INI-1 expression in collecting duct carcinoma. Urology. 2011;78(2):474.e1–5.
52. Ezekian B, Englum B, Gilmore BF, Nag UP, Kim J, Leraas HJ, et al. Renal medullary carcinoma: a national analysis of 159 patients. Pediatr Blood Cancer. 2017;64(11):e26609.
53. Hakimi AA, Koi PT, Milhoua PM, Blitman NM, Li M, Hugec V, et al. Renal medullary carcinoma: the Bronx experience. Urology. 2007;70(5):878–82.
54. Swartz MA, Karth J, Schneider DT, Rodriguez R, Beckwith JB, Perlman EJ. Renal medullary carcinoma: clinical, pathologic, immunohistochemical, and genetic analysis with pathogenetic implications. Urology. 2002;60(6):1083–9.
55. Armah HB, Parwani AV. Xp11.2 translocation renal cell carcinoma. Arch Pathol Lab Med. 2010;134(1):124–9.
56. Classe M, Malouf GG, Su X, Yao H, Thompson EJ, Doss DJ, et al. Incidence, clinicopathological features and fusion transcript landscape of translocation renal cell carcinomas. Histopathology. 2017;70(7):1089–97.

57. Ellis CL, Eble JN, Subhawong AP, Martignoni G, Zhong M, Ladanyi M, et al. Clinical heterogeneity of Xp11 translocation renal cell carcinoma: impact of fusion subtype, age, and stage. Mod Pathol. 2014;27(6):875–86.
58. Kauffman EC, Ricketts CJ, Rais-Bahrami S, Yang Y, Merino MJ, Bottaro DP, et al. Molecular genetics and cellular features of TFE3 and TFEB fusion kidney cancers. Nat Rev Urol. 2014;11(8):465–75.
59. Martignoni G, Pea M, Gobbo S, Brunelli M, Bonetti F, Segala D, et al. Cathepsin-K immunoreactivity distinguishes MiTF/TFE family renal translocation carcinomas from other renal carcinomas. Mod Pathol. 2009;22(8):1016–22.
60. Matoso A, Chen YB, Rao V, Wang L, Cheng L, Epstein JI. Atypical renal cysts: a morphologic, immunohistochemical, and molecular study. Am J Surg Pathol. 2016;40(2):202–11.
61. Suzigan S, Lopez-Beltran A, Montironi R, Drut R, Romero A, Hayashi T, et al. Multilocular cystic renal cell carcinoma: a report of 45 cases of a kidney tumor of low malignant potential. Am J Clin Pathol. 2006;125(2):217–22.
62. Williamson SR, MacLennan GT, Lopez-Beltran A, Montironi R, Tan PH, Martignoni G, et al. Cystic partially regressed clear cell renal cell carcinoma: a potential mimic of multilocular cystic renal cell carcinoma. Histopathology. 2013;63(6):767–79.
63. Williamson SR, Halat S, Eble JN, Grignon DJ, Lopez-Beltran A, Montironi R, et al. Multilocular cystic renal cell carcinoma: similarities and differences in immunoprofile compared with clear cell renal cell carcinoma. Am J Surg Pathol. 2012;36(10):1425–33.
64. Halat S, Eble JN, Grignon DJ, Lopez-Beltran A, Montironi R, Tan PH, et al. Multilocular cystic renal cell carcinoma is a subtype of clear cell renal cell carcinoma. Mod Pathol. 2010;23(7):931–6.
65. Kenney PA, Vikram R, Prasad SR, Tamboli P, Matin SF, Wood CG, et al. Mucinous tubular and spindle cell carcinoma (MTSCC) of the kidney: a detailed study of radiological, pathological and clinical outcomes. BJU Int. 2015;116(1):85–92.
66. Zhao M, He XL, Teng XD. Mucinous tubular and spindle cell renal cell carcinoma: a review of clinicopathologic aspects. Diagn Pathol. 2015;10:168.
67. Tran T, Jones CL, Williamson SR, Eble JN, Grignon DJ, Zhang S, et al. Tubulocystic renal cell carcinoma is an entity that is immunohistochemically and genetically distinct from papillary renal cell carcinoma. Histopathology. 2016;68(6):850–7.
68. Ulamec M, Skenderi F, Zhou M, Kruslin B, Martinek P, Grossmann P, et al. Molecular genetic alterations in renal cell carcinomas with tubulocystic pattern: tubulocystic renal cell carcinoma, tubulocystic renal cell carcinoma with heterogenous component and familial leiomyomatosis-associated renal cell carcinoma. Clinicopathologic and molecular genetic analysis of 15 cases. Appl Immunohistochem Mol Morphol. 2016;24(7):521–30.
69. Zhou M, Yang XJ, Lopez JI, Shah RB, Hes O, Shen SS, et al. Renal tubulocystic carcinoma is closely related to papillary renal cell carcinoma: implications for pathologic classification. Am J Surg Pathol. 2009;33(12):1840–9.
70. Foshat M, Eyzaguirre E. Acquired cystic disease-associated renal cell carcinoma: review of pathogenesis, morphology, ancillary tests, and clinical features. Arch Pathol Lab Med. 2017;141(4):600–6.
71. Kuroda N, Ohe C, Mikami S, Hes O, Michal M, Brunelli M, et al. Review of acquired cystic disease-associated renal cell carcinoma with focus on pathobiological aspects. Histol Histopathol. 2011;26(9):1215–8.
72. Grubb RL 3rd, Franks ME, Toro J, Middelton L, Choyke L, Fowler S, et al. Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer. J Urol. 2007;177(6):2074–9; discussion 9–80.
73. Merino MJ, Torres-Cabala C, Pinto P, Linehan WM. The morphologic spectrum of kidney tumors in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. Am J Surg Pathol. 2007;31(10):1578–85.
74. Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet. 2002;30(4):406–10.
75. Gill AJ, Hes O, Papathomas T, Sedivcova M, Tan PH, Agaimy A, et al. Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. Am J Surg Pathol. 2014;38(12):1588–602.

76. Williamson SR, Eble JN, Amin MB, Gupta NS, Smith SC, Sholl LM, et al. Succinate dehydrogenase-deficient renal cell carcinoma: detailed characterization of 11 tumors defining a unique subtype of renal cell carcinoma. Mod Pathol. 2015;28(1):80–94.
77. Al-Hussain T, Ali A, Akhtar M. Wilms tumor: an update. Adv Anat Pathol. 2014;21(3):166–73.
78. Brok J, Treger TD, Gooskens SL, van den Heuvel-Eibrink MM, Pritchard-Jones K. Biology and treatment of renal tumours in childhood. Eur J Cancer. 2016;68:179–95.
79. Cone EB, Dalton SS, Van Noord M, Tracy ET, Rice HE, Routh JC. Biomarkers for Wilms tumor: a systematic review. J Urol. 2016;196(5):1530–5.
80. Ooms AH, Gadd S, Gerhard DS, Smith MA, Guidry Auvil JM, Meerzaman D, et al. Significance of TP53 mutation in Wilms tumors with diffuse anaplasia: a report from the children's oncology group. Clin Cancer Res. 2016;22(22):5582–91.
81. Cochand-Priollet B, Molinie V, Bougaran J, Bouvier R, Dauge-Geffroy MC, Deslignieres S, et al. Renal chromophobe cell carcinoma and oncocytoma. A comparative morphologic, histochemical, and immunohistochemical study of 124 cases. Arch Pathol Lab Med. 1997;121(10):1081–6.
82. Hes O, Michal M, Sima R, Vanecek T, Brunelli M, Martignoni G, et al. Renal oncocytoma with and without intravascular extension into the branches of renal vein have the same morphological, immunohistochemical and genetic features. Virchows Arch. 2008;452(3):285–93.
83. Kryvenko ON, Jorda M, Argani P, Epstein JI. Diagnostic approach to eosinophilic renal neoplasms. Arch Pathol Lab Med. 2014;138(11):1531–41.
84. Kuroda N, Toi M, Hiroi M, Shuin T, Enzan H. Review of renal oncocytoma with focus on clinical and pathobiological aspects. Histol Histopathol. 2003;18(3):935–42.
85. Perez-Ordonez B, Hamed G, Campbell S, Erlandson RA, Russo P, Gaudin PB, et al. Renal oncocytoma: a clinicopathologic study of 70 cases. Am J Surg Pathol. 1997;21(8):871–83.
86. Bhatt JR, Richard PO, Kim NS, Finelli A, Manickavachagam K, Legere L, et al. Natural history of renal angiomyolipoma (AML): most patients with large AMLs >4cm can be offered active surveillance as an initial management strategy. Eur Urol. 2016;70(1):85–90.
87. Brimo F, Robinson B, Guo C, Zhou M, Latour M, Epstein JI. Renal epithelioid angiomyolipoma with atypia: a series of 40 cases with emphasis on clinicopathologic prognostic indicators of malignancy. Am J Surg Pathol. 2010;34(5):715–22.
88. Flum AS, Hamoui N, Said MA, Yang XJ, Casalino DD, McGuire BB, et al. Update on the diagnosis and management of renal angiomyolipoma. J Urol. 2016;195(4 Pt 1):834–46.
89. Mehta V, Venkataraman G, Antic T, Rubinas TC, Le Poole IC, Picken MM. Renal angiomyolipoma, fat-poor variant–a clinicopathologic mimicker of malignancy. Virchows Arch. 2013;463(1):41–6.
90. Bastide C, Rambeaud JJ, Bach AM, Russo P. Metanephric adenoma of the kidney: clinical and radiological study of nine cases. BJU Int. 2009;103(11):1544–8.
91. Kinney SN, Eble JN, Hes O, Williamson SR, Grignon DJ, Wang M, et al. Metanephric adenoma: the utility of immunohistochemical and cytogenetic analyses in differential diagnosis, including solid variant papillary renal cell carcinoma and epithelial-predominant nephroblastoma. Mod Pathol. 2015;28(9):1236–48.
92. McNeil JC, Corbett ST, Kuruvilla S, Jones EA. Metanephric adenoma in a five-year-old boy presenting with chyluria: case report and review of literature. Urology. 2008;72(3):545–7.
93. Calio A, Eble JN, Grignon DJ, Delahunt B. Mixed epithelial and stromal tumor of the kidney: a clinicopathologic study of 53 cases. Am J Surg Pathol. 2016;40(11):1538–49.
94. Calio A, Eble JN, Grignon DJ, Delahunt B. Cystic nephroma in adults: a clinicopathologic study of 46 cases. Am J Surg Pathol. 2016;40(12):1591–600.
95. Li Y, Pawel BR, Hill DA, Epstein JI, Argani P. Pediatric cystic nephroma is morphologically, immunohistochemically, and genetically distinct from adult cystic nephroma. Am J Surg Pathol. 2017;41(4):472–81.

Chapter 3
Genetics of Renal Cell Carcinoma

Mark W. Ball and W. Marston Linehan

Introduction

Renal cell carcinoma (RCC) is the most common primary tumor of the kidney, resulting in approximately 64,000 new diagnoses and 14,000 deaths each year in the United States [1]. Currently, the World Health Organization recognizes 16 subtypes of RCC [2], and up to 12 hereditary conditions have been identified with increased lifetime risk of developing renal tumors [3]. Each of the recognized subtypes of RCC is clinically, genetically, and morphologically distinct.

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

Understanding the genes and pathways altered in RCC directly translates to how patients are managed both with surgery [7] and systemic therapy [8] (Table 3.1). This chapter will review the genetics of kidney cancer and how these changes affect patient management.

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Table 3.1 Summary of hereditary conditions associated with renal cell carcinoma

Name	Gene	RCC histology	Nonrenal manifestations	Preferred surgical approach	Surveillance
Von Hippel-Lindau (VHL)	*VHL* (3p25)	Clear cell RCC, cystic RCC	CNS hemangioblastomas, retinal angiomas, pheochromocytoma	Enucleation	Until largest tumor reaches 3 cm
Familial translocation RCC	Chromosome 3 translocation	Clear cell RCC	None	Enucleation	Until largest tumor reaches 3 cm
BAP1-associated RCC	*BAP1* (3p21)	Clear cell RCC	Benign melanocytic tumors, malignant uveal and cutaneous melanoma, and malignant mesothelioma	Partial nephrectomy with wide excision	No surveillance
Hereditary papillary renal carcinoma (HPRC)	c-*MET* proto-oncogene (7q34)	Type 1 papillary RCC	None	Enucleation	Until largest tumor reaches 3 cm
Hereditary leiomyomatosis and renal cell carcinoma	*FH* (1q42)	Type 2 papillary RCC	Cutaneous leiomyomas Uterine leiomyomas	Partial nephrectomy with wide excision, consider lymphadenectomy	No surveillance
Birt-Hogg-Dube (BHD)	*BHD1/FLCN* (chromosome 17p11.2)	Chromophobe RCC, oncocytoma, hybrid oncocytic tumors	Cutaneous fibrofolliculomas, lung cysts, spontaneous pneumothorax	Enucleation	Until largest tumor reaches 3 cm
MITF family translocation RCC	*TFE3* (Xp11), *TFEB* (6p21), *MITF*	Various RCC histologies	*MITF*: melanoma	Partial nephrectomy with wide excision	No surveillance
Tuberous sclerosis complex (TSC)	*TSC1* (9q34) *TSC2* (16p13)	Angiomyolipomas, RCC, renal cysts	Facial angiofibromas, ungual/periungual fibroma, shagreen patch, retinal hamartomas, subependymal nodule, cortical hamartoma	Enucleation	RCC: Until the largest tumor reaches 3 cm. AML: surveillance until 4 cm or symptomatic
Succinate dehydrogenase-deficient RCC	*SDHB* (1p36), *SDHC* (1q21) or *SDHD* (11q23)	*SDHB*: oncocytic RCC *SDHC/D*: clear cell RCC	Pheochromocytomas, paragangliomas, gastrointestinal stromal tumors	Partial nephrectomy with wide excision, consider lymphadenectomy	No surveillance

Clear Cell RCC and von Hippel-Lindau Disease

Clear cell RCC is the most common form of sporadic RCC and accounts for 75% of all kidney cancers [9]. It is characterized by inactivation of the von Hippel-Lindau *(VHL)* gene, which is either mutated or epigenetically silenced in over 90% cases of sporadic clear cell RCC cases. This results in the loss of the VHL protein (pVHL), which is a member of an E3 ubiquitin ligase complex that includes elongins B and C, cullin-2, and Rbx1 [10]. The E3 ligase complex targets proteins, including hypoxia-inducible factor alpha (HIFα), for ubiquitin-mediated degradation by the proteasome. Under normoxic conditions, HIFα is hydroxylated by prolyl hydroxylase (PHD), enabling pVHL within the E3 ligase complex to recognize and target HIFα for ubiquitination and degradation [10]. Under hypoxic conditions, PHD is unable to hydroxylate HIFα, evading recognition by pVHL and accumulates in the cell to drive transcription of HIF target genes. Similarly, when *VHL* is mutated, HIF accumulates and transcriptionally upregulates the expression of target genes including *VEGF*, *GLUT1*, and *PDGF-β*, supporting tumor angiogenesis and growth [11–16].

The genetic basis of clear cell RCC was uncovered by studying patients with VHL disease. VHL is an autosomal dominant inherited multisystem disorder in which affected individuals are predisposed to develop clear cell RCC, renal cysts, pheochromocytomas, paragangliomas, pancreatic neuroendocrine tumors, pancreatic cysts, hemangioblastomas of the central nervous system and retina, endolymphatic sac tumors, and cystadenomas of the epididymis and broad ligament [17]. Linkage analysis of families with VHL led to the identification of a novel gene at chromosome 3p25 [18]. *VHL* was identified as a tumor suppressor gene in which both copies of the gene are inactivated to drive tumorigenesis. Nearly all VHL-associated renal tumors demonstrate loss of chromosome 3p or somatic "second-hit" *VHL* mutations [19, 20]. VHL patients inherit one mutant copy of the gene, and then the second functional copy is damaged or lost, leading to tumorigenesis. As a result of improved mutation detection methods, germline *VHL* mutations have been identified in over 900 families worldwide who present with >200 different mutations [17, 21, 22].

Management of VHL-associated renal tumors is focused on preventing metastasis while preserving the renal function. To that end, our institutional practice has been to perform active surveillance when tumors are less than 3 cm in diameter and resecting all ipsilateral tumors with a nephron-sparing approach once the largest tumor has reached 3 cm [23]. Considering the multiple small tumors and the need to preserve normal renal parenchyma, enucleation of tumors is used and has been demonstrated to be a safe surgical technique [24]. In general, the overarching goal of the surgeon is to "reset the clock," meaning removal of as many lesions as possible in one surgery in an attempt to prolong the interval between ipsilateral renal surgeries. Toward that end, all solid and complex lesions are removed with frequent use of intraoperative ultrasound to localize and ensure complete removal of all tumors.

Recently, efforts by The Cancer Genome Atlas have identified other recurrent somatic alterations in sporadic clear cell RCC, including the chromatin remodeling genes *PBRM1* (32.9%), *SETD2* (11.5%), and *BAP1* (10.1%), PI3K/AKT pathway genes (such as *MTOR*, *PTEN*, and *PIK3CA*), loss of chromosome 14q, and gain of chromosome 5q [25]. In other cohorts, *BAP1* was reported to be mutated in up to 14% of sporadic clear cell RCC and is associated with more aggressive tumors and poor patient prognosis [26]. Poor overall survival has been correlated with *BAP1* mutations and evidence of a metabolic shift in high-stage tumors involving down-regulation of the AMPK complex and Krebs cycle genes along with upregulation of the pentose phosphate pathway and fatty acid synthesis, a phenotype consistent with the Warburg effect [25, 27].

Recently, genomic analysis of multiple areas within large clear cell RCC tumors has demonstrated that these lesions display a large degree of genomic heterogeneity [28, 29]. While mutations in *VHL* are nearly ubiquitous in clear cell RCC and are thought to be "truncal" mutations, i.e., occurring early in oncogenesis, a subset of tumors also contain truncal *BPRM1* mutations [29]. In contrast, other commonly mutated genes in clear cell RCC include the chromatin remodeling genes, *SETD2*, *KDM5C*, and *BAP1*, are thought to develop subsequent to *VHL* later in the tumor's evolution, and they exhibit a branched evolutionary pattern, occurring at varying points in carcinogenesis [25].

Other recent efforts have sought to correlate the degree of genomic changes with pathologic features, survival, and response to therapy. Among genitourinary malignancies, clear cell RCC had the fourth lowest level of somatic mutations and second lowest level of copy number alterations across the genome; yet, greater CNV was associated with higher Fuhrman and longer recurrence-free survival [30]. Because greater somatic alterations have been shown to correlate with response to immunotherapy [31–33], these data may have implications for systemic therapy options, although this hypothesis has yet to be confirmed in RCC.

Familial Chromosome 3 Translocation RCC

The identification of a family with recurrent multifocal clear cell RCC without VHL identified a different genetic alteration involving chromosome 3: a balanced germline (3;8)(p14;q24) translocation [34]. Subsequently, germline chromosome 3 translocations have been identified involving chromosomes 1, 2, 4, 6, and 8 [35, 36]. Histologically, familial translocation tumors are similar to VHL-associated RCC tumors, and patients are at risk for the development of bilateral and multifocal RCC. The average age of onset is later than in VHL, in the fourth to fifth decade of life. Some clear cell kidney tumors in patients affected with chromosome 3 translocations have been shown to have loss of the 3p derivative chromosome and mutation in the *VHL* gene. These findings led to the proposition of a "three-hit" hypothesis for the carcinogenesis of these tumors where the first hit is inheritance of the germline chromosome 3 translocation, the second hit is loss of the derivative

chromosome, and somatic mutation of the remaining allele of a chromosome 3p (i.e., *VHL* or others) is the third hit.

Management of familial chromosome 3 translocation RCC is similar to VHL. The diagnosis is established by demonstrating an absence of germline *VHL* alterations, and a chromosome 3 translocation is made on germline karyotype. Patients should undergo regular cross-sectional imaging to identify kidney tumors that require surgical resection. Nephron-sparing surgery should be utilized to preserve renal function.

BAP1-Associated Renal Tumors

BRCA1-associated protein-1 (BAP1)-associated tumor predisposition syndrome is an autosomal dominant inherited disorder in which patients are at risk for the development of a variety of tumors, including benign melanocytic tumors, malignant uveal and cutaneous melanoma, and malignant mesothelioma [37, 38]. RCCs, most frequently with clear cell histology and with a more aggressive clinical course, have been recently confirmed as part of the BAP1-associated clinical phenotype occurring in about 10% of *BAP1* mutation carriers [38]. Several families with *BAP1* germline mutations have been reported for which RCC is the only manifestation [37, 39]. Loss of chromosome 3p or somatic second-hit *BAP1* mutations have been identified in BAP1-associated tumors supporting a tumor suppressor role for BAP1 [37–39]. BAP1 interacts with multiple complexes to influence a variety of cell functions including cell differentiation, cell death, and gluconeogenesis [40].

The potentially aggressive nature of BAP1-associated tumors requires individualized management. It is recommended that patients with germline *BAP1* alteration have annual abdominal imaging to evaluate for the presence of renal tumors. Unlike other types of genetically defined clear cell RCC, active surveillance is not recommended in these patients. Patients affected by germline mutations of the *BAP1* gene are at risk for the development of bilateral, multifocal, and recurrent renal tumors, and preservation of renal function is recommended whenever possible [7, 41, 42].

Type 1 Papillary RCC and Hereditary Papillary Renal Carcinoma

Papillary RCC accounts for 15–20% of kidney cancers and is further subdivided into Type 1 papillary RCC and Type 2 papillary RCC [9]. Type 1 papillary RCC is characterized by papillae and tubular structures composed of small cells with basophilic cytoplasm and small, uniform nuclei and commonly presents as multifocal disease. Type 1 papillary RCC is associated with whole copy number gains of chromosomes 7 and 17 in most cases and somatic mutation of the *MET* oncogene on chromosome 7 in ~15% of cases [43].

Hereditary papillary renal carcinoma (HPRC) is an autosomal dominant inherited disorder in which affected individuals are at risk to develop bilateral, multifocal Type 1 papillary RCC [44]. HPRC-associated renal tumors are characterized by "incipient lesions" in the apparently "normal" surrounding kidney parenchyma, with an estimation of >3000 of these microscopic papillary tumors in a single kidney that suggest multiple, independent, early events [45, 46]. HPRC patients are at risk to develop renal tumors during the fifth and sixth decades of life [47, 48]; however, early-onset HPRC families have also been reported [49]. Age-dependent penetrance has been estimated at 67% by the age of 60 years with complete penetrance by 80 years of age [48]. Fewer than 40 families with HPRC have been reported to date, underscoring the rarity of this inherited renal cancer syndrome.

The disease locus for HPRC was localized to chromosome 7q31 by genetic linkage analysis in HPRC families [50]. Since papillary Type 1 renal tumors are characterized by trisomy of chromosome 7 [51], an oncogene was considered a likely candidate. Indeed, mutations in the *MET* proto-oncogene located at 7q31 were identified in the germline of individuals affected with HPRC [50]. Missense mutations located in the intracellular tyrosine kinase domain of *MET* are predicted to activate Met kinase [48, 50, 52].

MET encodes the receptor for hepatocyte growth factor (HGF). Binding of HGF to MET through its extracellular domain leads to a conformational change, autophosphorylation of critical tyrosines in the intracellular kinase domain, and recruitment of second messenger molecules, triggering downstream signaling cascades that drive a number of cellular programs controlling motility, proliferation, differentiation, and branching morphogenesis [53]. The missense *MET* mutations identified in the germline of individuals affected with HPRC are predicted by molecular modeling to cause conformational changes of the protein that activate the Met kinase in the absence of HGF binding [54], which is also supported in in vitro and in vivo models [55, 56]. Since papillary RCC is characterized by trisomy of chromosome 7 [51], the demonstration that nonrandom duplication of the chromosome 7 bearing the mutant *MET* allele occurs in HPRC-associated renal tumors [57] supports the concept that increased mutant *MET* copy number may provide a growth advantage to kidney tumor cells. It is unlikely that somatic *MET* mutations are the primary driver in sporadic Type 1 papillary renal cancer, since fewer than 15% of sporadic papillary renal tumors have been reported with *MET* mutations [43, 52].

Patients with HPRC are identified by family history or may be incidentally discovered by cross-sectional imaging performed for another reason. Affected individuals do not uncommonly undergo their initial renal surgery at 50–60 years of age, which is later onset than many of the other hereditary renal cancer patients. The lesions are often hypoechoic to the renal parenchyma and may be poorly enhancing. Hypoenhancing CT lesions can be confused with hyperdense cysts, and therefore MRI may be more useful than CT scan for detecting and monitoring HPRC renal lesions.

Similar to the approach with patients affected with VHL, active surveillance until the largest renal tumors reaches the 3 cm threshold is recommended for patients affected with HPRC. Nephron-sparing surgical approaches are recom-

mended for HPRC-associated renal tumors as HPRC renal tumors tend to be bilateral and multifocal and numerous surgical procedures may be required to treat recurrent tumors.

Type 2 Papillary RCC and Hereditary Leiomyomatosis and Renal Cell Carcinoma

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is a familial cancer syndrome associated with a predisposition to develop cutaneous and uterine leiomyomas and a potentially aggressive form of papillary RCC [58–61]. Cutaneous leiomyomas are a common clinical feature that can occur on the arms or trunk. Affected females are at risk to develop early-onset uterine leiomyomas [62, 63]. Papillary RCCs, which present in approximately 10–15% of HLRCC patients, may be solitary, multifocal, and/or bilateral. These tumors have the potential to spread, even when they are small (0.5–2 cm) [59, 62, 63]. HLRCC-associated renal tumors demonstrate a distinct histologic staining pattern that is characterized by cells with abundant eosinophilic cytoplasm and a large nucleus containing prominent inclusion-like nucleoli surrounded by peri-nucleolar halos [59].

HLRCC is characterized by an autosomal dominant inheritance pattern and is associated with germline mutations of the chromosome 1p42.1 gene which encodes the Krebs cycle enzyme, fumarate hydratase (*FH)* [62–64]. A spectrum of germline mutations are associated with HLRCC with missense mutations being the most common. Currently, specific genotype/phenotype correlations have not been observed in HLRCC [62–64]. Somatic loss of the remaining functional wild-type copy of *FH* is observed within HLRCC renal tumors resulting in biallelic loss of FH activity. Inactivation of this enzyme leads to an alteration of metabolism of glucose through the Krebs cycle as well as increased levels of intracellular fumarate. The tumors undergo a metabolic shift to aerobic glycolysis with decreased oxidative phosphorylation. FH-deficient cells become more dependent upon glycolysis for energy production, have decreased levels of AMPK, and increased fatty acid synthesis [65, 66]. The increased intracellular fumarate oncometabolite inhibits several α-ketoglutarate-dependent dioxygenases including the PHD enzymes leading to increased levels of HIF and activation of the HIF pathway [65, 67]. Additionally, increased intracellular fumarate functions as an oncometabolite that induces the succination of multiple proteins, such as KEAP1. Succination of KEAP1 impairs its ability to inhibit the NRF2 transcription factor and results in the upregulation of the antioxidant response pathway that can combat the increased levels of reactive oxygen species associated with FH-deficient RCC [68, 69].

Our practice is to recommend lifelong annual abdominal screening by contrast-enhanced CT or MRI, beginning at age 8. Patients with HLRCC-associated renal cysts should be watched closely for tumor growth within the cysts. A cyst which is not simple is regarded as possibly malignant until proven otherwise. Because patients affected with HLRCC are at risk for the development of bilateral renal

tumors over their lifetime, nephron-sparing approaches are recommended when possible. HLRCC-associated renal tumors have an invasive growth pattern, and an open surgical procedure with intraoperative ultrasound, a wide surgical margin, and ipsilateral hilar lymphadenectomy is recommended. In contradistinction to the recommended management approach for VHL-, HPRC-, and Birt-Hogg-Dubé (BHD)-associated renal tumors, active surveillance is not recommended for patients with HLRCC [7, 41].

Chromophobe RCC and Birt-Hogg-Dubé

BHD is an autosomal dominant inherited cancer syndrome in which affected individuals are at risk for developing benign hair follicle hamartomas (fibrofolliculomas), pulmonary cysts, spontaneous pneumothoraces, and renal tumors [70, 71]. BHD syndrome is phenotypically heterogeneous within and between families. The most common manifestations of BHD are fibrofolliculomas and lung cysts, occurring in >83% of affected individuals and most commonly after puberty [71–73]. Approximately 24–38% of BHD-affected individuals will experience at least one spontaneous pneumothorax event during their lifetime with a median age of occurrence of 38 years [71–73].

BHD-affected individuals have a 6.9-fold greater risk for developing renal tumors compared to unaffected family members [71]. Bilateral, multifocal renal tumors have been reported to develop in 29–34% of BHD-affected patients [72, 73], but this rate may reflect ascertainment bias since the frequency of renal tumors was considerably lower in other BHD cohorts [74]. The median age of renal tumor diagnosis is 48–51 years [71, 72]. BHD-associated renal tumors may present with variable histologies including hybrid oncocytic/chromophobe tumors (50%) that contain features of chromophobe RCC and oncocytoma, chromophobe RCC (34%), clear cell RCC (9%), and oncocytoma (5%) [75]. Renal tumors with different histologies can arise even in a single kidney of a BHD patient. Microscopic oncocytic lesions ("oncocytosis") can be seen scattered throughout the "normal" renal parenchyma of most patients and may represent precursors of BHD-associated renal tumors [75].

The genetic locus for BHD syndrome was mapped to chromosome 17p11 by genetic linkage analysis, and subsequently mutations in a novel gene, *folliculin* (*FLCN*), were identified in the germline of patients affected with BHD [76]. The majority of *FLCN* mutations are predicted to prematurely truncate the protein and result in loss of FLCN function. Additionally, mutations that result in amino acid substitutions and partial gene deletions have been reported, with a mutation detection rate approaching 90% [72–74]. Inactivation of the remaining wild-type *FLCN* allele by somatic mutation or chromosome 17p loss is found in BHD-associated renal tumors [77]. Demonstration of the tumorigenic potential of *FLCN*-deficient renal tumor cell lines in vivo supports a tumor suppressor function for FLCN [78].

Patients with BHD should have imaging of their kidneys starting from the age of 20 to 25 years [41]. Abdominal imaging every 3 years is recommended for affected individuals with no renal masses. In recommending the frequency of imaging for individuals with renal masses, the surgeon should take into consideration tumor size, location, and growth rate. Renal ultrasound is not recommended as the sole modality for screening. As with VHL and HPRC, it is recommended that BHD-associated tumors be monitored until the largest tumor reaches the 3 cm threshold, at which time surgical intervention is recommended [7, 41]. In our experience, patients with BHD will most often require only one surgical procedure per kidney. Occasionally multiple procedures will be required over a BHD patient's lifetime to successfully manage the renal tumors. As BHD patients are at risk for the development of bilateral, multifocal tumors, partial nephrectomy is recommended whenever possible.

MITF Family Translocation RCC

The microphthalmia-associated transcription factor (MiTF) family of genes includes *TFE3*, *TFEB*, and *MITF*. Members of this transcription factor family share similar protein structures, recognize identical DNA sequences upon homo- and heterodimerization with each other, and drive the transcription of similar genes. While *MITF* mutations have been implicated in conferring a hereditary susceptibility to RCC, *TFE3* and *TFEB* have been associated with chromosomal rearrangements, resulting in tumors that are termed MITF family translocation RCC. Translocation RCCs are defined as a histologically variable subtype of sporadic kidney cancer and make up approximately 1–5% of RCCs [79].

TFE3 is located on the X chromosome at Xp11, and *TFE3* translocation accounts for 20–45% of renal tumors in children and young adults [80]. Xp11 translocation tumors can show a wide spectrum of morphology. Histologically, tumors frequently display a papillary architecture formed by clear cells with granular eosinophilic cytoplasm. Psammoma bodies can sometimes be found [80]. TFE3 translocation-associated RCC is most common in pediatric patients, females, and individuals with prior exposure to cytotoxic chemotherapy [80].

TFEB translocation RCC has similar clinical features to TFE3 RCC. TFEB-fusion RCC is characterized by a chromosomal translocation involving *TFEB*, another member of the MITF transcription factor family, located on chromosome 6p21. RCCs involving chromosome 6p21 translocations, which are less common than chromosome Xp11 translocation RCCs, can be found in children and adults and have been reported in patients with previous chemotherapy. Histologically, TFEB-fusion RCCs typically present with a biphasic microscopic architecture, characterized by large, epithelioid cells with clear and eosinophilic cytoplasm (mimicking clear cell RCC) and small, eosinophilic cells with hyperchromatic nuclei forming rosette-like structures [80].

MITF is located at 3p13 and regulates a transcriptional program involved in the development and differentiation of melanocytes, osteoclasts, and mast cells [81]. Accordingly, germline mutations in *MITF* are responsible for the autosomal dominant Waardenburg syndrome Type 2 and the more severe and rare Tietze syndrome, both characterized by hearing loss and hypopigmentation of the skin, hair, and eyes [81]. Somatic *MITF* amplification is common in melanoma, especially in the *BRAF* mutant subtype [82]. A germline mutation of *MITF* (p.E318K) has been shown to constitute a risk factor for the development of melanoma and RCC [81]. Compared to the general population, carriers of this variant have a >5-fold increased risk to develop RCC and co-occurrence of RCC and melanoma. The p.E318K mutant MITF protein is affected by impaired sumoylation, differentially regulates DNA binding, and drives enhanced transcriptional activity of genes involved in cell growth, proliferation, and inflammation. This may explain the oncogenic role of the *MITF* p.E318K mutation. TFE3 RCC can spread when the tumors are small (2 cm), and therefore we do not recommend active surveillance for MITF family translocation RCC. TFE3-fusion RCCs have been seen with late-onset metastasis which makes long clinical follow-up necessary [80].

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a multisystem, autosomal dominant inherited hamartomatous disorder affecting both adults and children. Affected individuals are predisposed to develop a variety of skin lesions including facial angiofibromas, hypopigmented macules, shagreen patches, and ungula fibromas. Pulmonary lymphangiomyomatosis characterized by proliferation of abnormal smooth muscle cells and cystic changes in the lung affects adolescent girls and women with TSC. Cerebral cortex tubers develop in >80% of TSC patients and can lead to a number of neurologic manifestations including epilepsy, cognitive disability, and neurobehavioral abnormalities. Bilateral, multifocal renal angiomyolipomas (AMLs), which are benign tumors of the kidney consisting of abnormal vessels, immature smooth muscle cells, and fat cells, develop in an estimated 55–75% of TSC patients occurring as early as 10 years of age [83]. Additionally, RCCs with a variety of histologies may develop in TSC-affected individuals. Although the lifetime risk is similar to the general population (2–3%), the age of onset of renal tumor in TSC patients is younger, an average age of 36 years [83, 84].

TSC1 and TSC2 proteins form a heterotrimer with TBC1 domain family member 7 (TBC1D7) that negatively regulates the activity of mTORC1 through the conversion of the small GTPase RHEB from the active GTP-bound state to the inactive GDP-bound state through the action of the TSC2 GTPase-activating domain [85]. Mutations in either *TSC1* or *TSC2* in TSC-associated tumors cause hyperactivation of RAS homologue expressed in the brain (RHEB) which in turn activates mTORC1 leading to increased protein translation and extensive metabolic reprograming [85].

Efforts are underway to develop a systemic therapeutic approach for patients with TSC-associated renal masses, with a focus on mTOR inhibitors. In 2008, a clinical trial of sirolimus in patients with TSC-associated AML showed encouraging results [86]. Everolimus, which is approved for TSC-associated central nervous lesions, is currently being evaluated in trials for renal manifestations of TSC [87].

Management of renal masses in patients with TSC is aimed at renal function preservation. AMLs greater than 4 cm may be at risk for spontaneous bleeding, although some studies suggest a bleeding risk for 3 cm lesions [88]. Historically embolization has been used; however recent advances in microwave ablation have also shown to be successful for the treatment of AMLs [89].

Succinate Dehydrogenase-Deficient Kidney Cancer

Familial paraganglioma/pheochromocytoma is an inherited cancer syndrome associated with an increased risk for pheochromocytoma, paraganglioma, gastrointestinal stromal tumor, and RCC. This syndrome demonstrates an autosomal dominant pattern of inheritance and is associated with germline mutations within one of the four succinate dehydrogenase complex subunit genes, *SDHA*, *SDHB*, *SDHC*, and *SDHD*, or a succinate dehydrogenase complex assembly factor, *SDHAF2* [90]. Germline mutations in all five genes have been associated with the development of bilateral or multifocal pheochromocytomas or paragangliomas, while succinate dehydrogenase-deficient RCC (SDH-RCC) has been associated with germline mutation of *SDHB*, *SDHC*, and *SDHD*. Somatic loss of the remaining functional copy of the germline mutated SHD complex subunit results in loss of enzyme activity in a "second-hit" fashion.

SDH-RCC can be aggressive, and patients have demonstrated locally advanced or disseminated disease when tumors are still relatively small (1–2 cm) [90]. These tumors demonstrate a variety of histologic staining patterns including clear cell and oncocytic neoplastic patterns [90, 91]. Our institutional practice involves annual imaging with contrast-enhanced CT or MRI. These patients are monitored and managed in a similar fashion as patients with HLRCC since even small renal SDH-RCC masses have been known to metastasize [90]. As these tumors are considered aggressive, active surveillance is not recommended. Nephron-sparing approaches, with wide surgical margin, are recommended when possible [7, 41].

Conclusion

The genetic and genomic characterization of kidney cancer has broad implications for disease management in both the localized and advanced setting. For genetically defined cancers, the decisions of when to perform surveillance, when to operate, and how much of a margin to resect are predicated on the tumor's genetics. In

advanced disease, systemic therapy regimens are also tailored based on the patient's genetics. Future work with a focus on gene discovery and the metabolic composition of kidney tumors will continue to refine treatment strategies.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67:7–30.
2. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of tumours of the urinary system and male genital organs-part a: renal, penile, and testicular tumours. Eur Urol. 2016;70:93–105.
3. Linehan WM. Genetic basis of kidney cancer: role of genomics for the development of disease-based therapeutics. Genome Res. 2012;22:2089–100.
4. Kletscher BA, Qian J, Bostwick DG, Andrews PE, Zincke H. Prospective analysis of multifocality in renal cell carcinoma: influence of histological pattern, grade, number, size, volume and deoxyribonucleic acid ploidy. J Urol. 1995;153:904–6.
5. Whang M, O'Toole K, Bixon R, Brunetti J, Ikeguchi E, Olsson CA, et al. The incidence of multifocal renal cell carcinoma in patients who are candidates for partial nephrectomy. J Urol. 1995;154:968–70; discussion 70–1.
6. Gudbjartsson T, Jonasdottir TJ, Thoroddsen A, Einarsson GV, Jonsdottir GM, Kristjansson K, et al. A population-based familial aggregation analysis indicates genetic contribution in a majority of renal cell carcinomas. Int J Cancer. 2002;100:476–9.
7. Shuch B, Singer EA, Bratslavsky G. The surgical approach to multifocal renal cancers: hereditary syndromes, ipsilateral multifocality, and bilateral tumors. Urol Clin N Am. 2012;39:133–48, v.
8. Ball MW, Singer EA, Srinivasan R. Renal cell carcinoma: molecular characterization and evolving treatment paradigms. Curr Opin Oncol. 2017;29:201–9.
9. Linehan WM, Srinivasan R, Schmidt LS. The genetic basis of kidney cancer: a metabolic disease. Nat Rev Urol. 2010;7:277–85.
10. Gossage L, Eisen T, Maher ER. VHL, the story of a tumour suppressor gene. Nat Rev Cancer. 2015;15:55–64.
11. Majmundar AJ, Wong WJ, Simon MC. Hypoxia-inducible factors and the response to hypoxic stress. Mol Cell. 2010;40:294–309.
12. Maxwell PH, Wiesener MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature. 1999;399:271–5.
13. Ohh M, Park CW, Ivan M, Hoffman MA, Kim TY, Huang LE, et al. Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. Nat Cell Biol. 2000;2:423–7.
14. Ivan M, Kondo K, Yang H, Kim W, Valiando J, Ohh M, et al. HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. Science. 2001;292:464–8.
15. Jaakkola P, Mole DR, Tian YM, Wilson MI, Gielbert J, Gaskell SJ, et al. Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science. 2001;292:468–72.
16. Kaelin WG Jr. Molecular basis of the VHL hereditary cancer syndrome. Nat Rev Cancer. 2002;2:673–82.
17. Nielsen SM, Rhodes L, Blanco I, Chung WK, Eng C, Maher ER, et al. Von Hippel-Lindau disease: genetics and role of genetic counseling in a multiple neoplasia syndrome. J Clin Oncol. 2016;34:2172–81.

18. Latif F, Tory K, Gnarra JR, Yao M, Duh FM, Orcutt ML, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science. 1993;260:1317–20.
19. Tory K, Brauch H, Linehan WM, Barba D, Oldfield E, Filling-Katz M, et al. Specific genetic change in tumors associated with von Hippel-Lindau disease. J Natl Cancer Inst. 1989;81:1097–101.
20. Mandriota SJ, Turner KJ, Davies DR, Murray PG, Morgan NV, Sowter HM, et al. HIF activation identifies early lesions in VHL kidneys: evidence for site-specific tumor suppressor function in the nephron. Cancer Cell. 2002;1:459–68.
21. Beroud C, Joly D, Gallou C, Staroz F, Orfanelli MT, Junien C. Software and database for the analysis of mutations in the VHL gene. Nucleic Acids Res. 1998;26:256–8.
22. Nordstrom-O'Brien M, van der Luijt RB, van Rooijen E, van den Ouweland AM, Majoor-Krakauer DF, Lolkema MP, et al. Genetic analysis of von Hippel-Lindau disease. Hum Mutat. 2010;31:521–37.
23. Duffey BG, Choyke PL, Glenn G, Grubb RL, Venzon D, Linehan WM, et al. The relationship between renal tumor size and metastases in patients with von Hippel-Lindau disease. J Urol. 2004;172:63–5.
24. Singer EA, Vourganti S, Lin KY, Gupta GN, Pinto PA, Rastinehad AR, et al. Outcomes of patients with surgically treated bilateral renal masses and a minimum of 10 years of followup. J Urol. 2012;188:2084–8.
25. Cancer Genome Atlas Research N. Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature. 2013;499:43–9.
26. Pena-Llopis S, Vega-Rubin-de-Celis S, Liao A, Leng N, Pavia-Jimenez A, Wang S, et al. BAP1 loss defines a new class of renal cell carcinoma. Nat Genet. 2012;44:751–9.
27. Hakimi AA, Ostrovnaya I, Reva B, Schultz N, Chen YB, Gonen M, et al. Adverse outcomes in clear cell renal cell carcinoma with mutations of 3p21 epigenetic regulators BAP1 and SETD2: a report by MSKCC and the KIRC TCGA research network. Clin Cancer Res. 2013;19:3259–67.
28. Gerlinger M, Horswell S, Larkin J, Rowan AJ, Salm MP, Varela I, et al. Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregion sequencing. Nat Genet. 2014;46:225–33.
29. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366:883–92.
30. Ball MW, Gorin MA, Drake CG, Hammers HJ, Allaf ME. The landscape of whole-genome alterations and pathologic features in genitourinary malignancies: an analysis of the cancer genome atlas. Eur Urol Focus. 2017;3:584.
31. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015;348:124–8.
32. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med. 2014;371:2189–99.
33. Ball MW, Johnson MH, Gorin MA, Rodriguez M, Diaz LA, Haffner M, et al. Clinical, pathologic, and genomic profiles of exceptional responders to anti−PD1 therapy in renal cell carcinoma. J Clin Oncol. 2016;34:625.
34. Cohen AJ, Li FP, Berg S, Marchetto DJ, Tsai S, Jacobs SC, et al. Hereditary renal-cell carcinoma associated with a chromosomal translocation. N Engl J Med. 1979;301:592–5.
35. van Kessel AG, Wijnhoven H, Bodmer D, Eleveld M, Kiemeney L, Mulders P, et al. Renal cell cancer: chromosome 3 translocations as risk factors. J Natl Cancer Inst. 1999;91:1159–60.
36. Rodriguez-Perales S, Melendez B, Gribble SM, Valle L, Carter NP, Santamaria I, et al. Cloning of a new familial t(3;8) translocation associated with conventional renal cell carcinoma reveals a 5 kb microdeletion and no gene involved in the rearrangement. Hum Mol Genet. 2004;13:983–90.

37. Farley MN, Schmidt LS, Mester JL, Pena-Llopis S, Pavia-Jimenez A, Christie A, et al. Germline BAP1 mutation predisposes to familial clear-cell renal cell carcinoma. Mol Cancer Res. 2013;11:1061.
38. Rai K, Pilarski R, Cebulla CM, Abdel-Rahman MH. Comprehensive review of BAP1 tumor predisposition syndrome with report of two new cases. Clin Genet. 2016;89:285–94.
39. Popova T, Hebert L, Jacquemin V, Gad S, Caux-Moncoutier V, Dubois-d'Enghien C, et al. Germline BAP1 mutations predispose to renal cell carcinomas. Am J Hum Genet. 2013;92:974–80.
40. Carbone M, Yang H, Pass HI, Krausz T, Testa JR, Gaudino G. BAP1 and cancer. Nat Rev Cancer. 2013;13:153–9.
41. Leung C, Pan S, Shuch B. Management of renal cell carcinoma in young patients and patients with hereditary syndromes. Curr Opin Urol. 2016;26:396–404.
42. Mir MC, Derweesh I, Porpiglia F, Zargar H, Mottrie A, Autorino R. Partial nephrectomy versus radical nephrectomy for clinical T1b and T2 renal tumors: a systematic review and meta-analysis of comparative studies. Eur Urol. 2016;71:606.
43. Linehan WM, Spellman PT, Ricketts CJ, Creighton CJ, Fei SS, Davis C, et al. Comprehensive molecular characterization of papillary renal-cell carcinoma. N Engl J Med. 2016;374:135–45.
44. Zbar B, Tory K, Merino MJ, Schmidt LS, Glenn GM, Choyke P, et al. Hereditary papillary renal cell carcinoma. J Urol. 1994;151:561–6.
45. Lubensky IA, Schmidt LS, Zhuang Z, Weirich G, Pack S, Zambrano N, et al. Hereditary and sporadic papillary renal carcinomas with c-met mutations share a distinct morphological phenotype. Am J Pathol. 1999;155:517–26.
46. Ornstein DK, Lubensky IA, Venzon D, Zbar B, Linehan WM, Walther MM. Prevalence of microscopic tumors in normal appearing renal parenchyma of patients with hereditary papillary renal cancer. J Urol. 2000;163:431–3.
47. Zbar B, Glenn GM, Lubensky IA, Choyke P, Magnusson G, Bergerheim U, et al. Hereditary papillary renal cell carcinoma: clinical studies in 10 families. J Urol. 1995;153:907–12.
48. Schmidt LS, Junker K, Weirich G, Glenn G, Choyke P, Lubensky I, et al. Two North American families with hereditary papillary renal carcinoma and identical novel mutations in the MET proto-oncogene. Cancer Res. 1998;58:1719–22.
49. Schmidt LS, Nickerson ML, Angeloni D, Glenn GM, Walther MM, Albert PS, et al. Early onset hereditary papillary renal carcinoma: germline missense mutations in the tyrosine kinase domain of the met proto-oncogene. J Urol. 2004;172:1256–61.
50. Schmidt LS, Duh FM, Chen F, Kishida T, Glenn GM, Choyke P, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet. 1997;16:68–73.
51. Kovacs G, Fuzesi L, Emanual A, Kung HF. Cytogenetics of papillary renal cell tumors. Genes Chromosomes Cancer. 1991;3:249–55.
52. Schmidt LS, Junker K, Nakaigawa N, Kinjerski T, Weirich G, Miller M, et al. Novel mutations of the MET proto-oncogene in papillary renal carcinomas. Oncogene. 1999;18:2343–50.
53. Birchmeier C, Birchmeier W, Gherardi E, Vande Woude GF. Met, metastasis, motility and more. Nat Rev Mol Cell Biol. 2003;4:915–25.
54. Schiering N, Knapp S, Marconi M, Flocco MM, Cui J, Perego R, et al. Crystal structure of the tyrosine kinase domain of the hepatocyte growth factor receptor c-Met and its complex with the microbial alkaloid K-252a. Proc Natl Acad Sci U S A. 2003;100:12654–9.
55. Jeffers M, Schmidt LS, Nakaigawa N, Webb CP, Weirich G, Kishida T, et al. Activating mutations for the met tyrosine kinase receptor in human cancer. Proc Natl Acad Sci U S A. 1997;94:11445–50.
56. Jeffers M, Fiscella M, Webb CP, Anver M, Koochekpour S, Vande Woude GF. The mutationally activated Met receptor mediates motility and metastasis. Proc Natl Acad Sci U S A. 1998;95:14417–22.
57. Zhuang Z, Park WS, Pack S, Schmidt LS, Pak E, Pham T, et al. Trisomy 7 – harboring non-random duplication of the mutant MET allele in hereditary papillary renal carcinomas. Nat Genet. 1998;20:66–9.
58. Launonen V, Vierimaa O, Kiuru M, Isola J, Roth S, Pukkala E, et al. Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proc Natl Acad Sci U S A. 2001;98:3387–2.

59. Merino MJ, Torres-Cabala C, Pinto PA, Linehan WM. The morphologic spectrum of kidney tumors in hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome. Am J Surg Pathol. 2007;31:1578–85.
60. Grubb RL III, Franks ME, Toro J, Middelton L, Choyke L, Fowler S, et al. Hereditary leiomyomatosis and renal cell cancer: a syndrome associated with an aggressive form of inherited renal cancer. J Urol. 2007;177:2074–80.
61. Schmidt LS, Linehan WM. Hereditary leiomyomatosis and renal cell carcinoma. Int J Nephrol Renov Dis. 2014;7:253–60.
62. Toro JR, Nickerson ML, Wei MH, Warren MB, Glenn GM, Turner ML, et al. Mutations in the fumarate hydratase gene cause hereditary leiomyomatosis and renal cell cancer in families in North America. Am J Hum Genet. 2003;73:95–106.
63. Wei MH, Toure O, Glenn GM, Pithukpakorn M, Neckers L, Stolle C, et al. Novel mutations in FH and expansion of the spectrum of phenotypes expressed in families with hereditary leiomyomatosis and renal cell cancer. J Med Genet. 2006;43:18–27.
64. Tomlinson IP, Alam NA, Rowan AJ, Barclay E, Jaeger EE, Kelsell D, et al. Germline mutations in FH predispose to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer. Nat Genet. 2002;30:406–10.
65. Tong WH, Sourbier C, Kovtunovych G, Jeong SY, Vira M, Ghosh M, et al. The glycolytic shift in fumarate-hydratase-deficient kidney cancer lowers AMPK levels, increases anabolic propensities and lowers cellular iron levels. Cancer Cell. 2011;20:315–27.
66. Yang Y, Lane AN, Ricketts CJ, Sourbier C, Wei MH, Shuch B, et al. Metabolic reprogramming for producing energy and reducing power in fumarate hydratase null cells from hereditary leiomyomatosis renal cell carcinoma. PLoS One. 2013;8:e72179.
67. Isaacs JS, Jung YJ, Mole DR, Lee S, Torres-Cabala C, Chung YL, et al. HIF overexpression correlates with biallelic loss of fumarate hydratase in renal cancer: novel role of fumarate in regulation of HIF stability. Cancer Cell. 2005;8:143–53.
68. Adam J, Hatipoglu E, O'Flaherty L, Ternette N, Sahgal N, Lockstone H, et al. Renal cyst formation in Fh1-deficient mice is independent of the Hif/Phd pathway: roles for fumarate in KEAP1 succination and Nrf2 signaling. Cancer Cell. 2011;20:524–37.
69. Ooi A, Wong JC, Petillo D, Roossien D, Perrier-Trudova V, Whitten D, et al. An antioxidant response phenotype shared between hereditary and sporadic type 2 papillary renal cell carcinoma. Cancer Cell. 2011;20:511–23.
70. Birt AR, Hogg GR, Dube WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol. 1977;113:1674–7.
71. Zbar B, Alvord WG, Glenn GM, Turner M, Pavlovich CP, Schmidt LS, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. Cancer Epidemiol Biomarkers Prev. 2002;11:393–400.
72. Schmidt LS, Nickerson ML, Warren MB, Glenn GM, Toro JR, Merino MJ, et al. Germline BHD-mutation spectrum and phenotype analysis of a large cohort of families with Birt-Hogg-Dub, syndrome. Am J Hum Genet. 2005;76:1023–33.
73. Toro JR, Wei MH, Glenn GM, Weinreich M, Toure O, Vocke CD, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dube syndrome: a new series of 50 families and a review of published reports. J Med Genet. 2008;45:321–31.
74. Schmidt LS, Linehan WM. Molecular genetics and clinical features of Birt-Hogg-Dube syndrome. Nat Rev Urol. 2015;12:558–69.
75. Pavlovich CP, Walther MM, Eyler RA, Hewitt SM, Zbar B, Linehan WM, et al. Renal tumors in the Birt-Hogg-Dub, syndrome. Am J Surg Pathol. 2002;26:1542–52.
76. Nickerson ML, Warren MB, Toro JR, Matrosova V, Glenn GM, Turner ML, et al. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dube syndrome. Cancer Cell. 2002;2:157–64.
77. Vocke CD, Yang Y, Pavlovich CP, Schmidt LS, Nickerson ML, Torres-Cabala CA, et al. High frequency of somatic frameshift BHD gene mutations in Birt-Hogg-Dube-associated renal tumors. J Natl Cancer Inst. 2005;97:931–5.
78. Hong SB, Oh H, Valera VA, Stull J, Ngo DT, Baba M, et al. Tumor suppressor FLCN inhibits tumorigenesis of a FLCN-null renal cancer cell line and regulates expression of key molecules in TGF-beta signaling. Mol Cancer. 2010;9:160.

79. Kauffman EC, Ricketts CJ, Rais-Bahrami S, Yang Y, Merino MJ, Bottaro DP, et al. Molecular genetics and cellular features of TFE3 and TFEB fusion kidney cancers. Nat Rev Urol. 2014;11:465–75.
80. Argani P. MiT family translocation renal cell carcinoma. Semin Diagn Pathol. 2015;32:103–13.
81. Bertolotto C, Lesueur F, Giuliano S, Strub T, de LM, Bille K, et al. A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma. Nature. 2011;480:94–8.
82. Cancer Genome Atlas N. Genomic classification of cutaneous melanoma. Cell. 2015;161:1681–96.
83. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med. 2006;355:1345–56.
84. Bjornsson J, Short MP, Kwiatkowski DJ, Henske EP. Tuberous sclerosis-associated renal cell carcinoma. Clinical, pathological, and genetic features. Am J Pathol. 1996;149:1–8.
85. Henske EP, Jozwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. Nat Rev Dis Primers. 2016;2:16035.
86. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med. 2008;358:140–51.
87. Tsai JD, Wei CC, Yang SH, Fan HC, Hsu CC, Tung MC, et al. Effects of everolimus on tuberous sclerosis complex-associated renal angiomyolipoma: a preliminary report. Nephrology (Carlton). 2017;22:1017–22.
88. Kothary N, Soulen MC, Clark TW, Wein AJ, Shlansky-Goldberg RD, Crino PB, et al. Renal angiomyolipoma: long-term results after arterial embolization. J Vasc Interv Radiol. 2005;16:45–50.
89. Cristescu M, Abel EJ, Wells S, Ziemlewicz TJ, Hedican SP, Lubner MG, et al. Percutaneous microwave ablation of renal angiomyolipomas. Cardiovasc Intervent Radiol. 2016;39:433–40.
90. Ricketts CJ, Shuch B, Vocke CD, Metwalli AR, Bratslavsky G, Middelton L, et al. Succinate dehydrogenase kidney cancer: an aggressive example of the Warburg effect in cancer. J Urol. 2012. https://doi.org/10.1016/j.juro.2012.08.030.
91. Gill AJ, Hes O, Papathomas T, Sedivcova M, Tan PH, Agaimy A, et al. Succinate dehydrogenase (SDH)-deficient renal carcinoma: a morphologically distinct entity: a clinicopathologic series of 36 tumors from 27 patients. Am J Surg Pathol. 2014;38:1588–602.

Chapter 4
Imaging of Renal Tumors

Steven P. Rowe, Yafu Yin, and Michael A. Gorin

Introduction

The incidence of clinically localized renal tumors has gradually increased in recent decades, paralleling the growing use of cross-sectional imaging across the field of medicine [1, 2]. The most common primary tumor of the kidney is renal cell carcinoma (RCC), representing up to 90% of all renal masses [3]. The International Society of Urologic Pathology now recognizes a number of histologic subtypes of RCC, each with their own molecular underpinnings and metastatic potential [4]. The most common of these are the clear cell (~75%), papillary (~15%), and chromophobe (~5%) RCC subtypes. In general, clear cell RCC and type II papillary RCC are categorized as aggressive, whereas type I papillary RCC and chromophobe RCC are thought to behave in a more indolent manner. Less common RCC subtypes include clear cell papillary RCC, translocation-associated RCC, medullary RCC, and collecting duct RCC. Benign renal tumor histologies include oncocytomas, angiomyolipomas (AMLs), and mixed epithelial stromal tumors (MESTs).

Anatomical imaging with X-ray computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US) plays an important role in the detection and characterization of renal masses. However, these conventional imaging

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techniques are often unable to provide specific information regarding the histology of a renal mass. This information is of clinical importance, as a significant portion of renal tumors will be a benign or indolent histology not requiring surgical intervention [5]. To aid in minimizing the overtreatment of clinically insignificant renal tumors, investigational techniques such as molecular imaging are being evaluated for their ability to noninvasively determine the histology of renal tumors [6, 7]. In this chapter, we review the role of anatomical and molecular imaging in the evaluation of renal masses.

Imaging of Renal Tumors

X-Ray Computed Tomography

The most commonly used modality for renal mass characterization is multiphase CT. CT is widely available and provides for high intrinsic spatial resolution. Initial evaluation of a renal mass with CT should be carried out in four phases with a non-contrast acquisition followed by post-contrast imaging in the arterial, venous, and delayed phases. This study is commonly referred to as a renal protocol CT. Of note, at least one of the post-contrast CT acquisitions can be extended beyond the kidney to cover the entire chest, abdomen, and pelvis in order to evaluate for the presence of metastatic disease.

When performing a renal protocol CT, a non-contrast phase is acquired just prior to contrast administration. This allows for differentiation between hyperdense renal cysts and true enhancing masses by providing a baseline attenuation that can be compared to subsequent contrast phases. More specifically, a cyst will remain the same density throughout all phases of the study (±10 Hounsfield units), whereas a solid mass will show increased attenuation following intravenous contrast administration. Next, arterial or corticomedullary phase images are acquired 25–30 s following the administration of intravenous contrast. Many common renal tumors, most notably clear cell RCC and oncocytomas, are highly conspicuous at this imaging time point owing to brisk arterial enhancement (Fig. 4.1) [8]. It should be noted, however, that the high level of enhancement of the cortex can obscure small and peripherally located masses.

A venous or nephrographic phase is next acquired. This is performed at approximately 80–90 s after contrast administration. This phase has particular utility in the identification of small renal masses and can aid in identifying tumor invasion of the ipsilateral main renal vein and/or inferior vena cava (Fig. 4.2) [9]. Finally, a delayed or urographic phase is performed 5–8 min following contrast administration in order to evaluate the renal collecting system, which can be useful for detecting coexisting pathologies such as transitional cell carcinoma.

Renal protocol CT can also provide other potentially important information regarding a renal mass. For example, any of the CT phases can be utilized to examine for the presence of extension of tumor beyond the kidney capsule, albeit with lim-

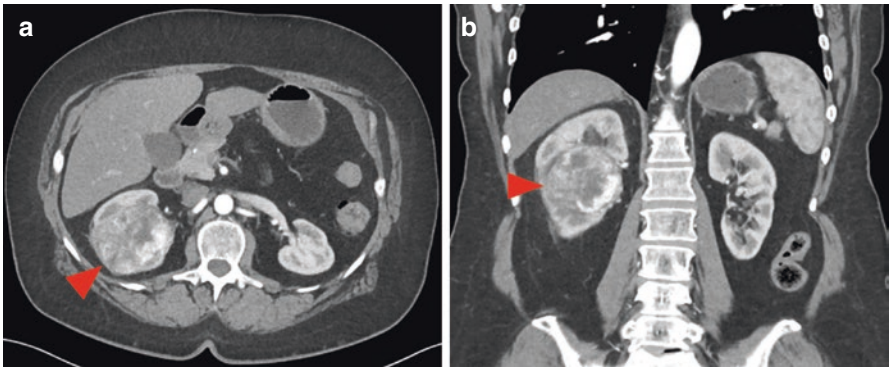

Fig. 4.1 CT images of a clinically localized clear cell RCC. (**a**) Axial and (**b**) coronal, arterial phase images. Note the brisk arterial enhancement in this tumor (red arrowheads) particularly along the inferomedial aspects of the lesion. This enhancement pattern is typical for clear cell RCC

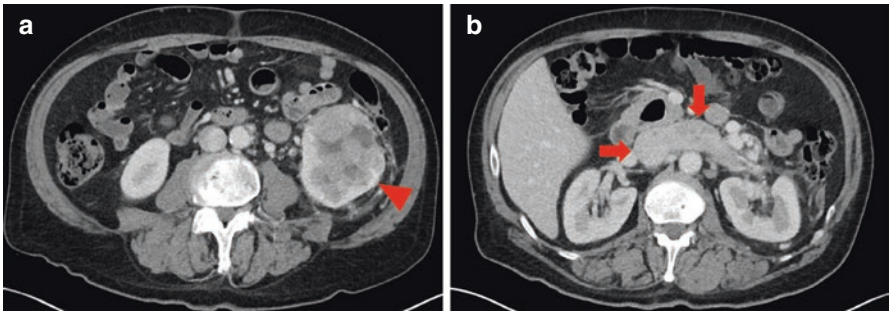

Fig. 4.2 CT images of a clear cell RCC with venous invasion. (**a**) Axial, venous phase image shows a large heterogeneously enhancing left-sided renal mass (red arrowhead). (**b**) In a more superior axial, venous phase CT image, the left renal vein and inferior vena cava are enlarged with internal heterogeneous enhancement (red arrows), compatible with venous invasion of the tumor. Following imaging the mass was surgically resected and was found to be clear cell RCC

ited sensitivity [10]. Additionally, this study can be useful for determining the histology of selected renal masses. Perhaps the best example of this is for AMLs, as the vast majority of these lesions contain macroscopic fat that is visualized as areas of negative Hounsfield units on CT (Fig. 4.3). Aside from AMLs, the ability of CT to characterize the histology of a given renal mass is limited, although some general trends are worth noting. For example, papillary RCC generally demonstrates a low and relatively homogeneous level of enhancement in comparison to clear cell RCC and oncocytomas, with chromophobe RCC most often having an intermediate enhancement level [8].

Cystic renal lesions are well-characterized by CT and are deserving of detailed discussion. The Bosniak classification of renal cysts has been in common use since its introduction in 1986 [11]. With this classification system, cystic lesions are divided into five categories (I, II, IIF, III, and IV) with an

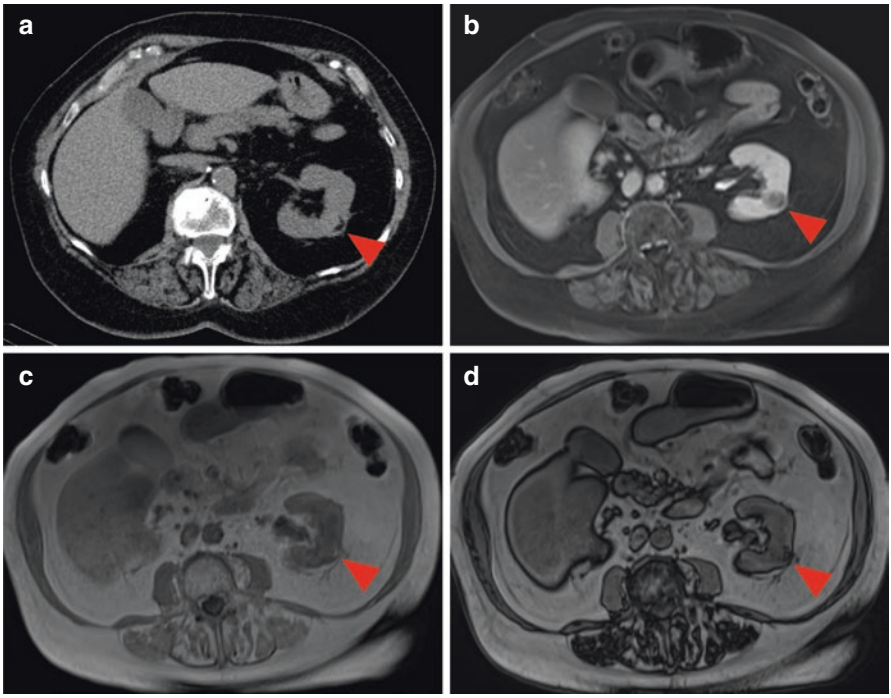

Fig. 4.3 CT and MRI images of a renal AML. (**a**) Axial, non-contrast CT image of a patient with a left-sided renal mass containing macroscopic fat (red arrowhead). Note that the attenuation of the fat in the mass is identical to the perinephric fat surrounding the kidney. (**b**) Axial, T1, fat-saturation, post-contrast MR image in the same patient delineates the borders of this relatively hypoenhancing tumor and also demonstrates the presence of macroscopic fat. Just as on CT, the crescentic area of fat within the AML appears identical to the perinephric fat. (**c**) Axial, in-phase and (**d**) axial, out-of-phase MR images show the area of macroscopic fat in the AML as bright/high signal on the in-phase image (**c**), whereas the periphery of the macroscopic fat becomes dark/low signal on the out-of-phase image. This finding is known as the India ink artifact

increasing risk of underlying malignancy in the higher numerical categories. Bosniak I lesions are simple epithelial cysts which are a common incidental finding on CT. These lesions are not true tumors of the kidney, as they lack any solid component and are universally benign. Bosniak I cysts are simple fluid attenuation on CT (generally taken to be ≤20 Hounsfield units) and do not have any visible septa or calcifications. The Bosniak II classification includes benign cystic lesions that are not pure simple epithelial cysts. These lesions can contain a few thin septations (without visible or measurable enhancement), minimal associated calcifications, or measure greater than simple fluid attenuation [12]. Both Bosniak I and II cysts should be well-circumscribed with easily definable boundaries with the adjacent normal renal parenchyma. Lesions in either of these categories do not require any specific follow-up or intervention except for in symptomatic individuals.

Bosniak IIF cysts are often the most difficult to accurately categorize as many different features can place a cystic lesion in this category (Fig. 4.4). Characteristics of Bosniak IIF lesions include the presence of several thin septa, apparent visual but not measurable enhancement of a cyst wall or septum, non-enhancing smooth or nodular thickening of a wall or septum, and more-than-minimal associated calcifications. The risk of malignancy with these lesions is thought to be on the order of 5%; thus follow-up but not immediate treatment is required [13].

Bosniak III (Fig. 4.5) and IV (Fig. 4.6) cystic lesions harbor a high likelihood of malignancy and should be managed with surgical resection. Bosniak III cysts demonstrate measurably enhancing walls or septa, which can be smooth or irregular, and approximately 50% of these lesions are malignant [14]. Bosniak IV lesions contain

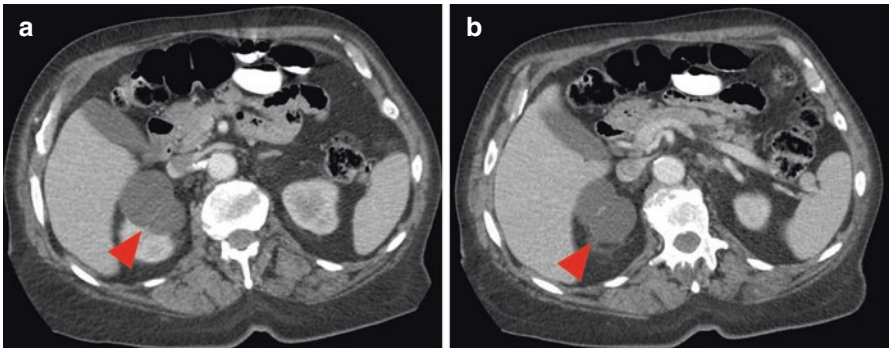

Fig. 4.4 CT images of a Bosniak IIF renal cyst. (**a**) Axial, venous phase image of a minimally complex right-sided renal cystic lesion. A thin septation (red arrowhead) is apparent within the cystic lesion. (**b**) On a more superior axial, venous phase image, a smooth thickening of the septation is apparent with visual enhancement, although the septation is too thin to reliably measure this enhancement (red arrowhead)

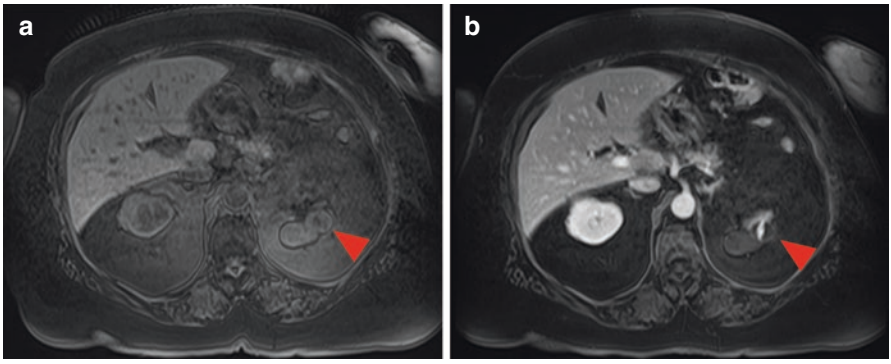

Fig. 4.5 MRI images of a multi-lobulated Bosniak III cyst. (**a**) Axial, T1, fat-saturation, non-contrast image and (**b**) axial, T1, fat-saturation, post-contrast MR image. Note the thick, avidly enhancing septum in the lesion (red arrowheads)

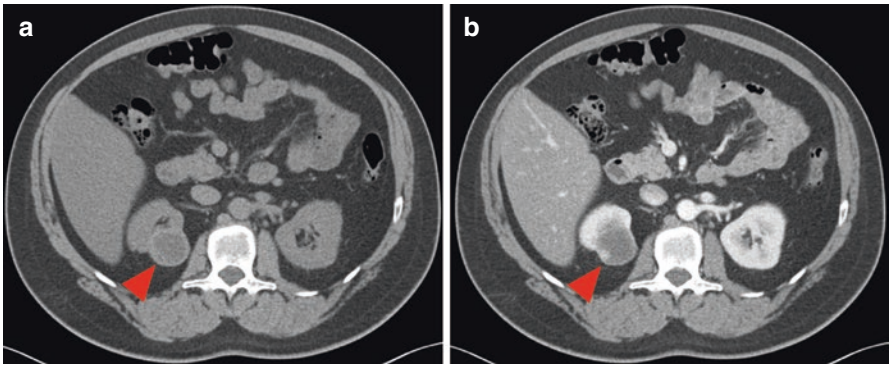

Fig. 4.6 CT images of a Bosniak IV renal cyst. (**a**) Axial, non-contrast image of a predominantly low-density right renal lesion that does visually appear to be a simple cyst (red arrowhead). (**b**) Axial, venous phase CT demonstrates that much of the lesion does not enhance; however a nodular, enhancing component is present within the wall of this cystic lesion (red arrowhead)

definitive, enhancing solid components and are true renal tumors. These lesions are most often cystic RCCs and should be treated as malignant, although some other rare renal neoplasms may present as Bosniak IV cysts [15].

Magnetic Resonance Imaging

MRI of renal tumors parallels the evaluation that takes place with CT, with some important differences imposed by the longer scan acquisition time and other technical parameters. The American College of Radiology considers multiphase CT to be the best method by which to evaluate an indeterminate renal mass, although multiphase MRI is also considered appropriate [16]. MRI offers advantages in soft tissue characterization and functional imaging. Additionally, MRI lacks ionizing radiation, which may be an important consideration in younger patients with renal malignancies requiring multiple examinations for surveillance. Renal protocol MRI provides much of the same information as CT such as anatomic delineation of a renal tumor and its enhancement characteristics. Generally, renal protocol MRI should be carried out on a closed MRI operating at 1.5 T or 3.0 T field strength. Typically, the pulse sequences included in a renal protocol MRI include T1-weighted pre-contrast images (with both in-phase and opposed-phase acquisitions allowing for identification of fat and water within a single voxel), T2-weighted images, and post-contrast T1 imaging in multiple phases as is performed for CT [17]. The renal collecting system is best evaluated on delayed-phase post-contrast imaging with fat saturation. Modern renal protocol MRI often also includes diffusion-weighted imaging (DWI), which measures restriction in the motion of water and is often regarded as a surrogate for cellularity. DWI is interpreted in conjunction with an apparent diffusion coefficient (ADC) map that confirms that high signal on DWI is

true diffusion restriction and is not a manifestation of high T2 signal in the tumor. True diffusion restriction will demonstrate low signal on an ADC map, whereas a falsely high DWI signal as the result of associated high T2 signal will also have high signal on an ADC map.

The determination of renal mass histology is somewhat limited with MRI, although there are some advantages relative to CT. As with CT, the most definitive diagnosis can often be made with AMLs, again through the identification of macroscopic fat within the tumor which will have high signal intensity on both T1- and T2-weighted images with signal drop-out with chemical shift fat saturation and India ink artifact at fat-soft tissue interfaces with opposed-phase imaging (Fig. 4.3). Interestingly, the presence of intracellular or microscopic fat can cause a more generalized loss of signal on opposed-phase imaging than what is seen with the India ink artifact, and this non-specific finding can be present with either clear cell RCC or AMLs [18].

As with CT, the general rule applies with contrast-enhanced MRI that clear cell RCC and oncocytomas are the most hyperenhancing renal masses, with papillary RCC being overall hypoenhancing and chromophobe RCC demonstrating intermediate levels of enhancement. However, the improved soft tissue characterization of MRI relative to CT and the inclusion of the functional information available from DWI may allow for relative confidence in the differentiation of some tumor types [19]. For example, although both clear cell RCC and AMLs can demonstrate signal drop on opposed-phase imaging, this finding in a solid renal mass that is homogeneous and demonstrates low signal on T2-weighted imaging is diagnostic of an AML [20]. DWI has shown promise in differentiating aggressive from benign tumors, with significantly lower ADC values present in RCCs in comparison to oncocytomas [21]. Among RCC subtypes, papillary RCC often demonstrates very low ADC values compatible with restricted diffusion, although other subtypes with high nucleolar grades can also be low signal on ADC maps [22].

Cystic renal lesions on MRI are also well-characterized, and the previously described Bosniak categories can still be used [23]. Most cystic renal lesions will have the same Bosniak classification whether imaged with CT or MRI, although MRI does appear to have a higher sensitivity for septa, wall and septal thickening, and subtle enhancement of the wall and septa. As such, some cystic lesions will have higher Bosniak classifications on MRI, which can affect the preferred management strategy [23]. A pure, benign, Bosniak I epithelial cyst should appear on MRI as a very T2 bright and T1 dark lesion without any evidence of contrast enhancement, following the signal characteristics of simple fluid. Calcifications in Bosniak II–IV cysts will show up as areas of low T1 and T2 signal. Any enhancing features in Bosniak II–IV cysts are evaluated on pre- and post-contrast T1 images and will show increased signal on the post-contrast acquisition (Fig. 4.5).

Imaging of the chest is often difficult to perform with MRI due to respiratory and cardiac motion. Although many pulse sequences can now acquire slices during single breath-holds, slice selection can limit evaluation for subtle findings such as small pulmonary nodules. As a result, staging of RCC is often performed with a renal protocol MRI of the abdomen and pelvis along with dedicated chest imaging (preferably CT).

Ultrasound

US evaluation of renal masses is somewhat limited in comparison to CT and MRI, although the emergence of US-compatible intravenous contrast agents may result in evolving practice patterns in coming years. US lacks ionizing radiation and nephrotoxic contrast; however, US can be limited by poor visualization of the kidneys in patients that have a large body habitus. Additionally, this imaging modality is highly operator dependent, a limitation that is not present with CT and MRI. Furthermore, the sensitivity of US for renal masses is lower than other cross-sectional modalities [24]. However, the lack of ionizing radiation of US makes it particularly well suited to following known renal masses for growth. For example, US is used heavily for follow-up in the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry that aims to decrease overtreatment of small renal masses [25].

As with CT and MRI, the underlying histology of a solid renal mass is often unable to be characterized on US. Solid renal masses can demonstrate a variety of echoic properties, with RCCs potentially being hypoechoic, isoechoic, or hyperechoic relative to the background renal parenchyma. Classically, the macroscopic fat in AMLs causes them to be hyperechoic, but this finding can be subtle and is not nearly as definitive as the identification of fat on CT or MRI.

US has excellent discriminatory ability for solid versus cystic masses, particularly when a relatively hypodense lesion is identified on CT that is not a definitive hyperdense cyst [26]. Additionally, US has a high sensitivity for septa, debris within cystic lesions, and calcifications. Other than definitive Bosniak I simple epithelial cysts, which appear completely anechoic on US and demonstrate increased through-transmission, other cystic lesions must be graded with renal protocol CT or MRI.

An exciting development in the field of US imaging has been the introduction of intravenous contrast agents. Although the use of US contrast for renal mass imaging is off-label in the United States, early data suggest that contrast agents provide useful information in the characterization of renal tumors [27, 28]. The imaging mechanism of intravenous microbubbles involves the reflection of sonographic signal off of many echogenic surfaces, thus increasing the signal of vascularized tissues. Contrast-enhanced US has shown promise in the characterization of cystic renal lesions [27] and may have improved sensitivity for subtle blood flow within solid renal tumors in comparison to CT [28]. The ultimate utility of contrast-enhanced US in renal tumor imaging does, however, require further exploration.

Molecular Imaging of Renal Tumors

General Background

Although the anatomic information available from conventional imaging is invaluable in the work-up of patients with renal tumors, in most circumstances a histologic characterization of an enhancing renal mass is not readily feasible with these

modalities, as has been noted above. In particular, distinguishing hyperenhancing clear cell RCC from similarly hyperenhancing oncocytomas is particularly difficult. This is distinctly problematic given that these represent the most common malignant and benign renal mass types, respectively. Investigational work has been done to derive additional information from available conventional imaging data, with particularly promising recent work demonstrating that CT texture analysis can somewhat successfully differentiate among different renal tumor histologies, including clear cell RCC and oncocytomas [29]. These methods, however, remain investigational, and larger volumes of data with advanced machine learning/artificial intelligence algorithms are needed in order to utilize standard CT, MRI, and US datasets to adequately classify renal tumors.

The limitations of characterizing renal tumors with CT, MRI, and US have contributed to an interest in developing molecular imaging approaches to better distinguish benign and indolent renal masses from those that are likely to behave in an aggressive manner. The Society of Nuclear Medicine and Molecular Imaging broadly defines the field of molecular imaging as "a type of medical imaging that provides detailed pictures of what is happening inside the body at the molecular and cellular level [30]." Thus, molecular imaging is able to provide functional information about a tumor's underlying biology that is not available from anatomical cross-sectional imaging.

The two most common modalities employed in molecular imaging are positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Fundamentally, PET makes use of positron-emitting radionuclides (including ^{18}F, ^{11}C, ^{68}Ga, ^{124}I, and ^{89}Zr) that are covalently or non-covalently bonded or conjugated to molecules that allow for localization of the radionuclide to a cellular or molecular process of interest. The decay of such radionuclides produces a positron that interacts with surrounding matter, comes to rest, and then annihilates with a nearby electron. This annihilation process produces two 511-keV photons that are given off in opposite directions and are detected at nearly exactly the same time at opposite points around a ring of detectors that surrounds the patient. This process is often referred to as "coincidence detection." The sophisticated electronics of the PET scanner are able to localize these coincidence detection events and record a line of response connecting the two detectors triggered coincidentally. Because the original positron decay event must have occurred along that line or response, the coincidence detection encodes spatial information on where the positron-emitting decay event occurred. Through the collection of many such coincidence events, the system is able to reconstruct images that reflect the distribution of the radiotracer within the patient's body.

SPECT makes use of a fundamentally different process than PET. SPECT relies on single-photon-emitting radionuclides (including ^{99m}Tc, ^{111}In, and ^{123}I), and the coincidence detection that underlies PET is not possible with these radioisotopes. Single-photon emission is an omnidirectional process, with emission of the photons from the radiotracer occurring in such a way that any direction of photon emission is equally likely as any other direction. As such, the imaging process places a collimator between the patient and the detector. A collimator allows only those photons that travel through its holes, which are positioned perpendicular to the patient, to

reach the detector thereby excluding photons that arrive at an angle to the collimator holes, thus imparting spatial information to the created image. A SPECT detector and its associated collimator are slowly rotated around the patient in either a stepwise or continuous manner so that complete volumetric data can be acquired.

The data acquired from these imaging methods are usually reconstructed in a tomographic manner and then combined with anatomic information from CT or less commonly MRI. As such, most modern molecular imaging is actually a combination of molecular and anatomic information.

Radiotracers and Their Targets

The most commonly used molecular imaging agent is the PET radiotracer and glucose analog 2-deoxy-2-[^{18}F]fluoro-D-glucose (^{18}F-FDG). ^{18}F-FDG is a profoundly important radiotracer that has revolutionized the imaging of many malignancies. This imaging agent, however, has not shown an ability to reliably identify or characterize renal tumors [31]. As such, other radiotracers have been investigated for these purposes.

The best studied target for renal mass molecular imaging is carbonic anhydrase IX (CAIX), a cell surface enzyme with a role in maintaining extracellular pH [32]. While in many nonrenal malignancies, CAIX expression is inducible and related to the low oxygen tension of hypoxia, the vast majority of clear cell RCCs constitutively overexpress CAIX as a result of loss of the von Hippel-Lindau tumor suppressor gene [33, 34]. Further enhancing the appeal of CAIX as a target is that it is not found to any measurable extent in normal renal parenchyma or on renal masses other than the clear cell subtype [35–37]. An ^{124}I-labeled monoclonal antibody against CAIX (^{124}I-girentuximab) has proven particularly promising. A pilot study of 26 patients with renal tumors who underwent ^{124}I-girentuximab PET/CT imaging prior to surgical resection found a sensitivity of 94% for the detection of clear cell RCC with no false-positive results [38]. A larger multicenter trial with 195 patients was also promising with a reported sensitivity of 86.2% and specificity of 85.9% for the identification of clear cell RCC [39]. Overall, ^{124}I-girentuximab PET/CT was found to be significantly more sensitive and specific than conventional imaging with contrast-enhanced CT. Given these promising results, other CAIX-targeting agents, including small molecule radiotracers, are also being investigated [40, 41].

^{11}C-acetate, a radiolabeled cholesterol and fatty acid precursor, has also been studied in the context of characterizing otherwise indeterminate renal masses. Imaging with this radiotracer has demonstrated an overall higher sensitivity for detecting RCCs in comparison to ^{18}F-FDG. Additionally, this radiotracer may have a role in the identification of fat-poor AMLs, which have been shown to take up significant amounts of ^{11}C-acetate [42].

Recently, there has been an interest in applying the widely available and inexpensive single-photon-emitting radiotracer ^{99m}Tc-sestamibi for the characterization of anatomically indeterminate renal tumors (Fig. 4.7). ^{99m}Tc-sestamibi is a lipophilic

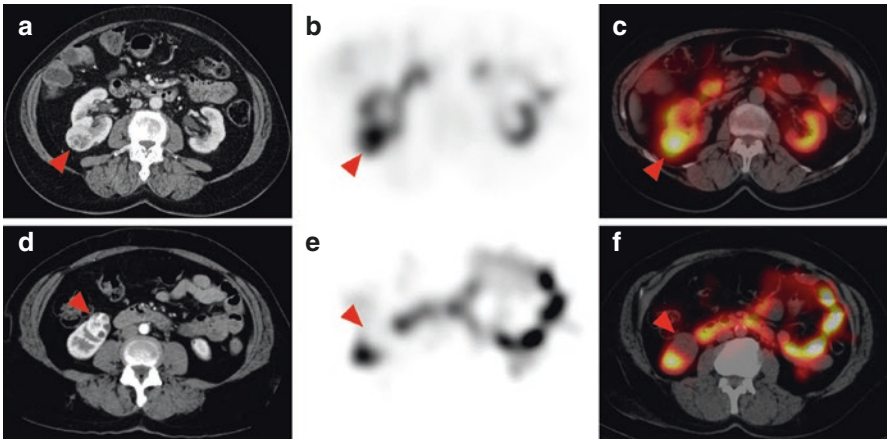

Fig. 4.7 Characterization of renal tumor histology using ^{99m}Tc-sestamibi SPECT/CT. (**a**) Axial, late arterial phase CT image from a patient with an indeterminate right renal mass (red arrowhead). (**b**) Axial ^{99m}Tc-sestamibi SPECT and (**c**) SPECT/CT images from the same patient show intense radiotracer uptake (red arrowheads), most compatible with a benign or indolent histology. This tumor was biopsied and found to be an oncocytic renal neoplasm. The patient is currently on active surveillance. (**d**) Axial, arterial phase CT from another patient with an indeterminate right renal mass (red arrowhead). (**e**) Axial ^{99m}Tc-sestamibi SPECT and (**f**) SPECT/CT images from the same patient demonstrate a lack of radiotracer uptake in the mass (red arrowheads), most compatible with an aggressive histology. This mass was resected and found to be a clear cell RCC

cation that has an intrinsic affinity for the high negative charge potential associated with mitochondrial membranes. Current common uses of ^{99m}Tc-sestamibi include myocardial perfusion imaging and localization of parathyroid adenomas. Interestingly, as early as 1996, Gormley and coworkers had the insight that mitochondria-rich oncocytomas might demonstrate differential uptake of ^{99m}Tc-sestamibi in comparison to other renal tumors [43]. Indeed, in a proof-of-principle study using non-tomographic imaging, the authors successfully identified an oncocytoma among several renal tumors [43]. Approximately 20 years later, Rowe et al. utilized the more detailed fusion of molecular and anatomic imaging available with SPECT/CT to further suggest the usefulness of ^{99m}Tc-sestamibi imaging in this context [44]. In their study, the authors successfully utilized ^{99m}Tc-sestamibi SPECT/CT to differentiate three oncocytomas apart from three aggressive RCCs. In a follow-up study that included 50 patients, Gorin and coworkers reported a sensitivity of 87.5% and a specificity of 95.2% for preoperatively identifying oncocytomas and closely related hybrid oncocytic/chromophobe tumors from other renal tumor types [45]. Additionally, initial results of a large diagnostic trial taking place in Sweden supported the high accuracy of this method for characterizing renal tumors as benign/indolent [46].

Beyond aiding in the characterization of clinically localized renal masses, molecular imaging also has potential to assist in staging patients with RCC. More specifically, ^{18}F-FDG PET/CT has proven to have a high degree of sensitivity for detecting sites of metastatic RCC [47]. It should be noted, however, that current

guidelines from the National Comprehensive Cancer Network do not endorse the routine use of this imaging modality due to a relative paucity of data to suggest that this expensive imaging modality is superior to contrast-enhanced CT [48]. Additional investigational PET agents that show promise for the detection of RCC metastases include ^{89}Zr-labeled bevacizumab (a monoclonal antibody against vascular endothelial growth factor [49]) and ^{18}F- and ^{68}Ga-labeled small molecular radiotracers targeted against prostate-specific membrane antigen [50, 51].

Conclusions

A number of modalities exist for imaging renal tumors including conventional anatomic methods (CT, MRI, and US) and molecular imaging approaches (PET and SPECT). Conventional imaging will most often be the means by which renal tumors are detected, either incidentally when a patient is being imaged for non-genitourinary complaints or when a patient is undergoing an evaluation for clinical signs and symptoms such as hematuria or flank pain. Conventional imaging provides important information regarding a detected renal mass including its solid or cystic nature, size, and stage in cases of malignancy. However, anatomic imaging often fails to differentiate benign from malignant clinically localized renal masses. For this reason, there is currently an increasing emphasis on using molecular imaging data to provide additional information on the underlying biology of renal masses. At the time of this writing, there is not a widely accepted molecular imaging test for characterizing renal tumors; however, several promising agents are in various stages of preclinical or early clinical development. In the future, it seems quite likely that molecular imaging will play an important role in the noninvasive risk stratification of clinically localized renal masses.

References

1. Gill IS, Aron M, Gervais DA, Jewett MA. Clinical practice. Small renal mass. N Engl J Med. 2010;362(7):624–34.
2. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst. 2006;98(18):1331–4.
3. Holger Moch PAH, Ulbright TM, Reuter VE. WHO classification of tumours of the urinary system and male genital organs: International Agency for Research on Cancer (IARC) 69372 Lyon Cedex 08, France; 2016.
4. Srigley JR, Delahunt B, Eble JN, Egevad L, Epstein JI, Grignon D, et al. The International Society of Urological Pathology (ISUP) Vancouver classification of renal neoplasia. Am J Surg Pathol. 2013;37(10):1469–89.
5. Johnson DC, Vukina J, Smith AB, Meyer AM, Wheeler SB, Kuo TM, et al. Preoperatively misclassified, surgically removed benign renal masses: a systematic review of surgical series and United States population level burden estimate. J Urol. 2015;193(1):30–5.
6. Gorin MA, Rowe SP, Allaf ME. Nuclear imaging of renal tumours: a step towards improved risk stratification. Nat Rev Urol. 2015;12(8):445–50.

7. Gorin MA, Rowe SP, Allaf ME. Noninvasive determination of renal tumor histology utilizing molecular imaging. Urol Oncol. 2016;34(12):525–8.
8. Pierorazio PM, Hyams ES, Tsai S, Feng Z, Trock BJ, Mullins JK, et al. Multiphasic enhancement patterns of small renal masses (</=4 cm) on preoperative computed tomography: utility for distinguishing subtypes of renal cell carcinoma, angiomyolipoma, and oncocytoma. Urology. 2013;81(6):1265–71.
9. Gakis G, Kramer U, Schilling D, Kruck S, Stenzl A, Schlemmer HP. Small renal oncocytomas: differentiation with multiphase CT. Eur J Radiol. 2011;80(2):274–8.
10. Gorin MA, Ball MW, Pierorazio PM, Tanagho YS, Bhayani SB, Kaouk JH, et al. Outcomes and predictors of clinical T1 to pathological T3a tumor up-staging after robotic partial nephrectomy: a multi-institutional analysis. J Urol. 2013;190(5):1907–11.
11. Bosniak MA. The current radiological approach to renal cysts. Radiology. 1986;158(1):1–10.
12. Jonisch AI, Rubinowitz AN, Mutalik PG, Israel GM. Can high-attenuation renal cysts be differentiated from renal cell carcinoma at unenhanced CT? Radiology. 2007;243(2):445–50.
13. Israel GM, Bosniak MA. Follow-up CT of moderately complex cystic lesions of the kidney (Bosniak category IIF). AJR Am J Roentgenol. 2003;181(3):627–33.
14. Smith AD, Remer EM, Cox KL, Lieber ML, Allen BC, Shah SN, et al. Bosniak category IIF and III cystic renal lesions: outcomes and associations. Radiology. 2012;262(1):152–60.
15. Gorin MA, Rowe SP, Allaf ME, Argani P. Angiomyolipoma with epithelial cysts: add one to the differential of cystic renal lesions. Int J Urol. 2015;22(11):1081–2.
16. Heilbrun ME, Remer EM, Casalino DD, Beland MD, Bishoff JT, Blaufox MD, et al. ACR Appropriateness Criteria indeterminate renal mass. J Am Coll Radiol. 2015;12(4):333–41.
17. Kang SK, Kim D, Chandarana H. Contemporary imaging of the renal mass. Curr Urol Rep. 2011;12(1):11–7.
18. Outwater EK, Bhatia M, Siegelman ES, Burke MA, Mitchell DG. Lipid in renal clear cell carcinoma: detection on opposed-phase gradient-echo MR images. Radiology. 1997;205(1):103–7.
19. Ramamurthy NK, Moosavi B, McInnes MD, Flood TA, Schieda N. Multiparametric MRI of solid renal masses: pearls and pitfalls. Clin Radiol. 2015;70(3):304–16.
20. Sasiwimonphan K, Takahashi N, Leibovich BC, Carter RE, Atwell TD, Kawashima A. Small (<4 cm) renal mass: differentiation of angiomyolipoma without visible fat from renal cell carcinoma utilizing MR imaging. Radiology. 2012;263(1):160–8.
21. Lassel EA, Rao R, Schwenke C, Schoenberg SO, Michaely HJ. Diffusion-weighted imaging of focal renal lesions: a meta-analysis. Eur Radiol. 2014;24(1):241–9.
22. Wang H, Cheng L, Zhang X, Wang D, Guo A, Gao Y, et al. Renal cell carcinoma: diffusion-weighted MR imaging for subtype differentiation at 3.0 T. Radiology. 2010;257(1):135–43.
23. Israel GM, Hindman N, Bosniak MA. Evaluation of cystic renal masses: comparison of CT and MR imaging by using the Bosniak classification system. Radiology. 2004;231(2):365–71.
24. Jamis-Dow CA, Choyke PL, Jennings SB, Linehan WM, Thakore KN, Walther MM. Small (< or = 3-cm) renal masses: detection with CT versus US and pathologic correlation. Radiology. 1996;198(3):785–8.
25. Pierorazio PM, Johnson MH, Ball MW, Gorin MA, Trock BJ, Chang P, et al. Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. Eur Urol. 2015;68(3):408–15.
26. Zirinsky K, Auh YH, Rubenstein WA, Williams JJ, Pasmantier MW, Kazam E. CT of the hyperdense renal cyst: sonographic correlation. AJR Am J Roentgenol. 1984;143(1):151–6.
27. Park BK, Kim B, Kim SH, Ko K, Lee HM, Choi HY. Assessment of cystic renal masses based on Bosniak classification: comparison of CT and contrast-enhanced US. Eur J Radiol. 2007;61(2):310–4.
28. Tamai H, Takiguchi Y, Oka M, Shingaki N, Enomoto S, Shiraki T, et al. Contrast-enhanced ultrasonography in the diagnosis of solid renal tumors. J Ultrasound Med. 2005;24(12):1635–40.
29. Raman SP, Chen Y, Schroeder JL, Huang P, Fishman EK. CT texture analysis of renal masses: pilot study using random forest classification for prediction of pathology. Acad Radiol. 2014;21(12):1587–96.

30. About Nuclear Medicine and Molecular Imaging [Internet]. Society of Nuclear Medicine and Molecular Imaging Website. Accessed 3 June 2017. Available from: http://www.snmmi.org/AboutSNMMI/Content.aspx?ItemNumber=6433.
31. Ozulker T, Ozulker F, Ozbek E, Ozpacaci T. A prospective diagnostic accuracy study of F-18 fluorodeoxyglucose-positron emission tomography/computed tomography in the evaluation of indeterminate renal masses. Nucl Med Commun. 2011;32(4):265–72.
32. Supuran CT. Carbonic anhydrases: novel therapeutic applications for inhibitors and activators. Nat Rev Drug Discov. 2008;7(2):168–81.
33. Grabmaier K, AdW MC, Verhaegh GW, Schalken JA, Oosterwijk E. Strict regulation of CAIX(G250/MN) by HIF-1alpha in clear cell renal cell carcinoma. Oncogene. 2004;23(33):5624–31.
34. Shuch B, Amin A, Armstrong AJ, Eble JN, Ficarra V, Lopez-Beltran A, et al. Understanding pathologic variants of renal cell carcinoma: distilling therapeutic opportunities from biologic complexity. Eur Urol. 2015;67(1):85–97.
35. Ivanov S, Liao SY, Ivanova A, Danilkovitch-Miagkova A, Tarasova N, Weirich G, et al. Expression of hypoxia-inducible cell-surface transmembrane carbonic anhydrases in human cancer. Am J Pathol. 2001;158(3):905–19.
36. Potter C, Harris AL. Hypoxia inducible carbonic anhydrase IX, marker of tumour hypoxia, survival pathway and therapy target. Cell Cycle. 2004;3(2):164–7.
37. Clare BW, Supuran CT. A perspective on quantitative structure-activity relationships and carbonic anhydrase inhibitors. Expert Opin Drug Metab Toxicol. 2006;2(1):113–37.
38. Divgi CR, Pandit-Taskar N, Jungbluth AA, Reuter VE, Gonen M, Ruan S, et al. Preoperative characterisation of clear-cell renal carcinoma using iodine-124-labelled antibody chimeric G250 (124I-cG250) and PET in patients with renal masses: a phase I trial. Lancet Oncol. 2007;8(4):304–10.
39. Divgi CR, Uzzo RG, Gatsonis C, Bartz R, Treutner S, Yu JQ, et al. Positron emission tomography/computed tomography identification of clear cell renal cell carcinoma: results from the REDECT trial. J Clin Oncol. 2013;31(2):187–94.
40. Yang X, Minn I, Rowe SP, Banerjee SR, Gorin MA, Brummet M, et al. Imaging of carbonic anhydrase IX with an 111In-labeled dual-motif inhibitor. Oncotarget. 2015;6(32):33733–42.
41. Minn I, Koo SM, Lee HS, Brummet M, Rowe SP, Gorin MA, et al. [64Cu]XYIMSR-06: a dual-motif CAIX ligand for PET imaging of clear cell renal cell carcinoma. Oncotarget. 2016;7(35):56471–9.
42. Ho CL, Chen S, Ho KM, Chan WK, Leung YL, Cheng KC, et al. Dual-tracer PET/CT in renal angiomyolipoma and subtypes of renal cell carcinoma. Clin Nucl Med. 2012;37(11):1075–82.
43. Gormley TS, Van Every MJ, Moreno AJ. Renal oncocytoma: preoperative diagnosis using technetium 99m sestamibi imaging. Urology. 1996;48(1):33–9.
44. Rowe SP, Gorin MA, Gordetsky J, Ball MW, Pierorazio PM, Higuchi T, et al. Initial experience using 99mTc-MIBI SPECT/CT for the differentiation of oncocytoma from renal cell carcinoma. Clin Nucl Med. 2015;40(4):309–13.
45. Gorin MA, Rowe SP, Baras AS, Solnes LB, Ball MW, Pierorazio PM, et al. Prospective evaluation of (99m)Tc-sestamibi SPECT/CT for the diagnosis of renal oncocytomas and hybrid oncocytic/chromophobe tumors. Eur Urol. 2016;69(3):413–6.
46. Tzortzakakis AGO, Karlsson M, Ekstrom-Ehn L, Ghaffarpour R, Axelsson R. Visual evaluation and differentiation of renal oncocytomas from renal cell carcinomas by means of 99mTc-Sestamibi SPECT/CT. EJNMMI Res. 2017;7:29.
47. Wang HY, Ding HJ, Chen JH, Chao CH, Lu YY, Lin WY, et al. Meta-analysis of the diagnostic performance of [18F]FDG-PET and PET/CT in renal cell carcinoma. Cancer Imaging. 2012;12:464–74.
48. Motzer RJ, Jonasch E, Agarwal N, Bhayani S, Bro WP, Chang SS, et al. Kidney Cancer, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2017;15(6):804–34.

49. Oosting SF, Brouwers AH, van Es SC, Nagengast WB, Oude Munnink TH, Lub-de Hooge MN, et al. 89Zr-bevacizumab PET visualizes heterogeneous tracer accumulation in tumor lesions of renal cell carcinoma patients and differential effects of antiangiogenic treatment. J Nucl Med. 2015;56(1):63–9.
50. Rowe SP, Gorin MA, Hammers HJ, Som Javadi M, Hawasli H, Szabo Z, et al. Imaging of metastatic clear cell renal cell carcinoma with PSMA-targeted (18)F-DCFPyL PET/CT. Ann Nucl Med. 2015;29(10):877–82.
51. Sawicki LM, Buchbender C, Boos J, Giessing M, Ermert J, Antke C, et al. Diagnostic potential of PET/CT using a 68Ga-labelled prostate-specific membrane antigen ligand in whole-body staging of renal cell carcinoma: initial experience. Eur J Nucl Med Mol Imaging. 2017;44(1):102–7.

Chapter 5
Renal Mass Biopsy

Matthew D. Ingham and Adam S. Feldman

Introduction

Within the United States, renal cell carcinoma represents the sixth and 10th most commonly diagnosed cancer in men and women, respectively [1]. Over the past number of decades, the incidence of renal cell carcinoma have been largely on the rise [2, 3]. Though some studies looking at European countries have suggested that this trend may be starting to slow, more recent studies from the United States tell a different story [4]. Using data from the National Program of Cancer Registries and the Surveillance, Epidemiology, and End Results registry, King and colleagues noted a continued trend toward an increasing incidence of renal cell carcinoma – rising from 10.6/100,000 in 2001 to 12.4/100,00 in 2010 [5]. Undoubtedly, much of this increase in incidence stems from the rapidly increasing utilization of cross-sectional abdominal imaging [6, 7]. A majority of renal masses are found incidentally, with 13–27% of all abdominal imaging having some form of incidental renal finding [8, 9]. As renal masses are increasingly discovered at an early stage where nearly 20% may be benign lesions, we are often faced with a need to further risk-stratify before deciding on a management strategy [10, 11]. Percutaneous renal mass biopsy is a diagnostic option which can be utilized to help address this clinical dilemma. Interestingly, renal mass biopsy is utilized infrequently in the clinical evaluation of renal masses, with many stating a lack of influence on clinical management as rationale [12, 13]. The goals of this chapter are to discuss the clinical indications for percutaneous renal mass biopsy, the technique of the procedure, clinical outcomes, and potential complications.

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Indications for Renal Mass Biopsy

When assessing the various indications to pursue renal mass biopsy, both well-established and emerging indications exist [14]. The main guiding principle behind these indications is that the renal mass biopsy should be performed in cases where the outcome will significantly change the clinical management strategy offered. One common indication is in the patient in whom another known malignancy exists. For these patients, the possibility of a renal mass representing a metastasis is real and must be further clarified before appropriate treatment may be offered. Although some cancers exhibit a significant predilection to metastasize to the kidney, the risk of a new primary renal malignancy cannot be ignored. In one series, nearly 50% of biopsies confirmed a renal primary despite a concurrent diagnosis of lung cancer [15].

Similar to a diagnosis of a separate, non-renal malignancy, infectious processes may mimic a suspicious renal mass. Cases of pyelonephritis may result in small focal abscesses or lobar nephronia, which may make a clear radiologic diagnosis difficult [16]. Although infectious causes can often be differentiated clinically, there are cases in which the clinical picture is not as clear and biopsy can significantly help direct care.

Beyond simply needing to clarify a confusing lesion noted on imaging, renal mass biopsy may also play a role in those patients in whom the standard therapy of surgical extirpation is not an option. In cases of surgically unresectable disease, renal mass biopsy can provide a tissue diagnosis to help guide systemic medical therapy. Similarly, as the general population continues to live longer and, as such, often does so in the setting of increasing chronic disease burden, we commonly find ourselves faced with renal masses diagnosed in patients who pose significant operative risk. Pathologic clarification as facilitated by renal mass biopsy can be critical in appropriately risk-stratifying these patients. As noted earlier, radiographically suspicious renal masses still carry a significant risk of benign pathology or may represent a less-aggressive histology [7, 10]. In these cases, the risks of operative intervention may not warrant the potential benefit.

As the incidental discovery of small renal masses increases, so too does the experience with active surveillance as a primary management strategy. In a recently reported large study from the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry, active surveillance appears to offer cancer-specific survival rates which were non-inferior to primary intervention [17]. Many will argue that those patients being selected for active surveillance should only be eligible following a renal mass biopsy to ensure the absence of overly aggressive pathology [18]. Admittedly, this remains a debatable point, though studies have shown some benefit in quality of life when patients on watchful waiting have an increased certainty regarding their disease state [19, 20].

Similar to the rise of active surveillance as a management option for the small renal mass, the field has seen an increase in the utilization of ablative therapies. In these cases, it is imperative to perform a renal mass biopsy to both confirm the

diagnosis and also to ensure a pathologic specimen is available to guide follow-up and additional therapy should any late recurrence or metastasis develop [21]. Although cystic lesions pose a significant risk of a nondiagnostic biopsy, in carefully selected patients with cystic masses containing a significant solid component, there may be a role for renal mass biopsy as radiologic diagnosis can be even more difficult than for a purely solid renal mass [14].

In patients with multiple or bilateral renal masses, renal mass biopsy offers a potential advantage in two respects. First, establishing a diagnosis of renal cell carcinoma can help direct decisions about testing for germline genetic mutations and thus guide planning for treatment versus observation based on tumor size. Second, assessing for a benign lesion may be prudent prior to intervening on both kidneys in patients with bilateral renal lesions. In patients with known genetic syndromes, decisions about a biopsy can be directed by the specific syndrome. In von Hippel-Lindau disease, a biopsy to confirm renal cell carcinoma is likely not necessary. However, in tuberous sclerosis complex, the risk of a lipid-poor angiomyolipoma is significant, and therefore treatment may be avoidable in many of these patients [22]. A listing of indications for performing renal mass biopsy is presented in Table 5.1.

Clinical Guidelines

A number of societal guidelines have been updated to include guidance on the utilization of renal mass biopsy. The 2017 Renal Mass and Localized Renal Cancer Guideline from the American Urological Association states that renal mass biopsy should be considered when a mass is suspected to be hematologic, metastatic, infectious, or inflammatory and after a thorough discussion of the risks and benefits [23]. The National Comprehensive Cancer Network 2017 kidney cancer guidelines endorse similar indications for biopsy but go slightly further, noting that a biopsy may be considered in small masses to help guide decisions regarding active surveillance and the various ablative techniques [24]. Similarly, the 2014 European Association of Urology guidelines on renal cell carcinoma suggest that renal mass

Table 5.1 Indications for renal mass biopsy

Indications for biopsy
Planned renal mass ablation[a]
Increased operative risk/advanced age
Solitary kidney/significant renal insufficiency
Known non-renal malignancy and concern for metastasis
Multiple suspicious renal masses
Select genetic syndromes (e.g., tuberous sclerosis complex)
Surgically unresectable disease
Suspicion of an infectious process

[a]We view biopsy in ablation cases as an absolute indication

biopsy is reasonable prior to either surveillance or ablation but report only a grade C level of evidence [25].

Outlined in Fig. 5.1 is a simple decision algorithm for when to employ renal mass biopsy [19]. While this algorithm gives some helpful guidance, there remains significant room for subjectivity in determining the true "clinical benefit" of the procedure.

Renal Mass Biopsy Techniques

A number of different technical aspects of renal mass biopsy must be considered to help maximize the diagnostic utility and minimize potential complications. These include imaging guidance, equipment and passage technique, and amount of specimen taken. In addition to these, one must ensure that a thorough pre-procedural evaluation has been completed. Specific attention must be paid to any known bleeding disorders or pre-procedural use of anticoagulants and/or antiplatelet agents. We typically recommend stopping these 5–7 days before the planned procedure, although in patients with a known history of cardiovascular disease on daily 81 mg of aspirin, we do continue this medication through the procedure.

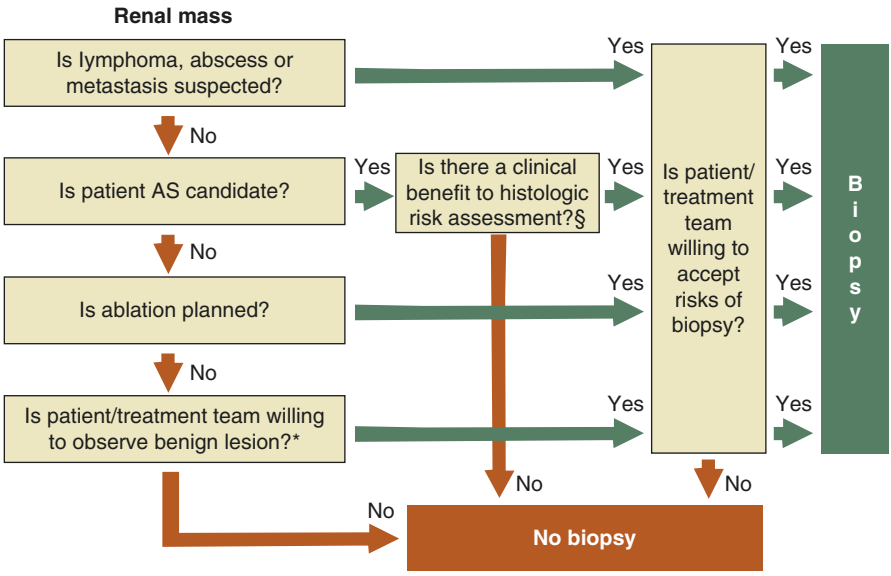

Fig. 5.1 Algorithm for performing renal mass biopsy. (From Kutikov et al. [19], fig 1 with permission from Elsevier)

Imaging Guidance

Renal mass biopsy has traditionally been performed under guidance with either ultrasound or computed tomography (CT), although more recently use of magnetic resonance imaging (MRI) has gained some favor. To our knowledge, no significant head-to-head studies have been conducted to specifically address which imaging modality is most efficacious. Each, instead, offers its own set of benefits. In ultrasound guidance, the practitioner gains the advantage of real-time image acquisition and needle tracking – one can continually confirm that the needle is appropriately targeted. Additionally, ultrasound does not expose the patient to any ionizing radiation. From a cost perspective, ultrasound remains an economical option for image guidance. In light of the relative ease of use and ubiquity in the urologic community, some have even advocated for the feasibility of office-based ultrasound-guided renal biopsy [26]. While these are all strong points in favor of ultrasound, one cannot discount the fact that ultrasound may not demonstrate the renal lesion with appropriate accuracy and it is not suited for clearly highlighting surrounding structures at risk of injury.

In contrast to ultrasound, CT guidance offers an excellent modality for accurately imaging the renal mass in question along with the surrounding structures of concern including the colon, pleural cavity, spleen, and liver. To help improve accuracy, a radiopaque skin grid is employed as imaging is not real-time as is the case with ultrasound. Exposure to ionizing radiation is a consideration for CT guidance but can be minimized using contemporary scanners with low- and ultra-low-dose imaging protocols. Lastly, MRI guidance has gained some prominence as many ablative techniques also utilize this imaging modality. While these techniques have been described for more than 20 years, recent refinements in equipment and technique have improved its adoption [27].

Equipment and Technique

While many factors may affect the diagnostic accuracy of renal mass biopsy, perhaps the most basic of these is the chosen needle size. At our center, an 18G needle is typically used [28]. Studies have shown that a lowest threshold of an 18G needle should be used, as diagnostic accuracy rates drop from the mid to high 90% range down to a less acceptable 81% with use of a smaller 20G needle [29].

Traditionally, fine-needle aspiration was the main technique utilized for sample acquisition but has been supplemented or supplanted by core biopsy in recent years. During fine-needle aspiration, the sample is often processed by the cytopathology lab as opposed to formal tissue pathology as in the case of the core sample. Reports have shown that sample adequacy, ability to determine tumor subtype, and overall diagnostic accuracy are significantly reduced in fine-needle aspiration as compared to core biopsy [30, 31]. While core biopsy outperforms fine-needle aspiration as a

stand-alone technique, combination of both methods shows yet further improvement in diagnostic accuracy with improvements of up to 14% [31, 32]. At our center, we advocate for this combined method and typically take six fine-needle aspirate samples along with three core biopsies [28].

Another important aspect to consider involves the number of percutaneous needle passes made. In a traditional non-coaxial technique, multiple passes of the needle are made percutaneously to obtain the various samples needed. In contrast, coaxial technique limits the number of percutaneous needle passes by using a common access needle that is placed into the tissue in question. Multiple passes of the sampling needle are then made through this initial needle such that only one percutaneous pass is made. In a randomized, prospective, head-to-head study of these two techniques, the coaxial approach yielded a significantly faster procedure time, lower complication rate, and improved diagnostic yield as compared to the non-coaxial approach [33].

Finally, one must consider how much tissue is needed to obtain an accurate diagnosis. As stated, our institution prefers to do six fine-needle aspirates in addition to three core biopsies [28]. When looking at an ex vivo model, Lane and colleagues demonstrated that use of three cores significantly improves diagnostic rates, finding 85% accuracy in comparison to only 59% for a single core [34]. Similar improvements in three versus one core were noted in the ability to subtype the samples, with rates rising from 44% to 67% [34]. While multiple cores are needed, it may also prove beneficial to specifically obtain these cores from distinct regions of the mass, especially in cases of larger masses, due to tumor heterogeneity. Abel and colleagues described a novel method utilizing a multi-quadrant strategy wherein at least four separate tumor regions are sampled [35]. Using this technique, the authors were able to lower their nondiagnostic rate from 10.9% to 0%.

Diagnostic Accuracy and Histologic Subtyping

Adequacy of Sample and Overall Diagnostic Accuracy

In early series, the ability to arrive at a diagnosis from biopsy was somewhat poor. For patients with a renal mass ≤3 cm, the nondiagnostic rate was 16% with a negative predictive value of 60% [15]. In more contemporary series, the nondiagnostic rates range from 7.7% to 19.4% on initial biopsy [36–40]. These rates tend to improve when repeat biopsy is utilized, which typically carries a roughly 80% diagnostic rate [36–40]. This trend was also shown by Lane et al. in a meta-analysis that found that, when looking pre- vs post-2001, the nondiagnostic rate improved from 9% to 5% [41]. A number of features have been shown to contribute to higher nondiagnostic rates, namely, cystic and non-enhancing lesions, very small masses, and a skin-to-tumor distance ≥13 cm [42]. Our series demonstrated a high nondiagnostic rate of 64% in cystic renal masses as compared to 12% in solid masses. In regard to tumor size, we identified an inflection point in the nondiagnostic rate at 1.5 cm, such that tumors <1.5 cm in diameter had a significantly greater risk of a nondiagnostic biopsy than larger tumors [43].

Among those biopsies that are adequate for histologic diagnosis, the rates of concordance for determining the presence or absence of malignancy when compared against resected tumor specimens are quite good. Multiple studies have reported concordance rates in the range of 91–98% [36, 38, 39, 44]. These results are echoed in a recent meta-analysis from Patel et al. that reported values of sensitivity and specificity of 96% [36]. Similarly, a meta-analysis by Marconi et al. demonstrated an overall diagnostic rate of 92% among 5200 patients [45].

Histologic Subtyping and Grading

Beyond simply determining when a malignancy is or is not present, renal mass biopsy can play a role in assessing the tumor type and grade. Many feel that this is, in actuality, the more important information gleaned from the biopsy as it can help to determine tumor aggressiveness. Concordance rates of 91–96% were reported in the meta-analysis of Patel et al. [36]. Similarly, a rate of 90.3% was noted by Marconi and coworkers [45].

When looking at the ability to accurately assess tumor-grade concordance between biopsy and resected tumor specimens, far greater variability between series can be seen. Rates range from 52% to 94%, with a fairly even distribution throughout that range [37, 39, 40, 44]. In the meta-analysis by Patel et al., concordance rates for tumor grade ranged from 51.5% to 75.9% [36]. Marconi et al. reported a similar rate of 62.5% [45]. When dichotomized into low (I–II) versus high grade (III–IV), the accuracy improved to 87% [45]. This is an important dichotomy to make, as many series showed very high levels of upgrading from low to high Fuhrman grade on final pathology. Rates for this upgrading ranged from 16% to 32% [36, 38].

Complications

Any discussion of renal mass biopsy would not be complete without addressing the potential procedural complications. With improvements in imaging and biopsy technique, the overall morbidity of renal mass biopsy has significantly improved. Today, only 0.1% of patients experience some form of life-threatening complication, and even minor complications arise <2% of the time [46, 47]. The most commonly encountered complications include bleeding and injury to adjacent structures.

Tract Seeding

Concern over the possibility of seeding the biopsy tract was traditionally viewed as a significant reason to avoid ever performing percutaneous renal biopsy in the setting of presumed malignancy. This view, however, has largely changed as relatively

few historical cases of tract seeding can be found in the world literature [48]. It is felt with the use of modern biopsy techniques, including the use of a coaxial sheath, the risk of tract seeding is nearly zero [28, 37]. We would, however, continue to recommend counseling patients on the negligible risk of seeding associated with biopsy using a contemporary technique.

Bleeding

Renal mass biopsy carries with it a risk of bleeding in the form of perinephric hematoma or gross hematuria. However, these events are most often clinically insignificant. Uncommonly, they can lead to hospital admission for observation, transfusion, or even the need for intervention. These risks can be minimized by a thorough preprocedural assessment of any potential factors that may predispose the patient to bleeding. It is important to note that an uncorrected coagulopathy is an absolute contraindication to percutaneous renal biopsy. Use of smaller needles can help to minimize bleeding risk. A study of renal biopsies performed for medical renal disease showed that use of a 14G needle led to a 2.1% transfusion rate as opposed to only 0.5% for smaller needles [49]. Similarly low rates were noted in a large recent meta-analysis, with transfusion being needed in 0.7% of cases [45]. Of note, one study in which a CT scan was routinely performed after performing of renal biopsies showed that the rate of perinephric hematoma to be as high as 90.8% [50]. This study, however, is now some 30 years old and did not employ modern techniques described earlier. More recent studies, where imaging was not obligatory but more symptom driven, have shown hematoma rates closer to 5% [45]. Following the procedure, bleeding complications may be minimized by laying supine to help with local compression of the biopsy site. Complications have been shown to largely occur early on, with 42% apparent by 4 h, 85% apparent by 12 h, and 89% apparent by 24 h [51]. At our institution, biopsies are performed under CT guidance and a post-biopsy scan is performed to assess for hematoma. Those patients who have either a visible hematoma on CT or gross hematuria are observed.

In addition to bleeding complications, there is the potential to injure intrarenal or perirenal vascular structures which may lead to pseudoaneurysm or arteriovenous fistula formation. Luckily, these complications are exceedingly rare with only one patient identified by Marconi et al. in their large meta-analysis [45]. Should this occur, treatment with embolization is typically warranted. A case of a post-biopsy arteriovenous fistula that was corrected by embolizastion of a segmental artery is illustrated in Fig. 5.2.

Injury to Surrounding Structures

Continuous attention and care must be paid to the fact that the kidneys have a number of closely associated structures, which may be at risk during renal mass biopsy. These structures include the pleura, colon, liver, spleen, stomach, and even pancreas.

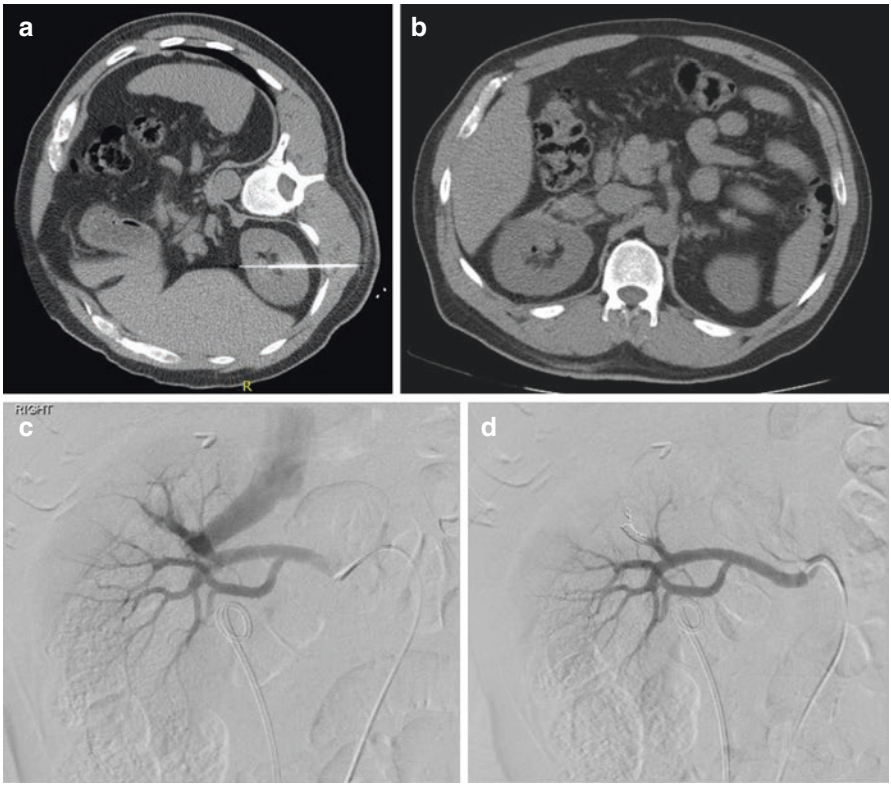

Fig. 5.2 (**a**) CT-guided right renal mass biopsy. (**b**) Post-procedure CT scan showing a very mild anterior subcapsular hematoma. (**c**) Early filling of the right renal vein on arteriogram suggestive of an arteriovenous fistula. (**d**) Successful fistula coil embolization

Luckily, with improved imaging and biopsy techniques, injury rates are minimal. Typically, upper pole lesions are the most technically demanding and often require a prone, intercostal approach. Stable respiration is essential, as biopsy under full inspiration will minimize risk to the organs but does lead to higher rates of pneumothorax [52]. Luckily, more recent studies seem to suggest that intercostal access is much safer than previously believed, with no pneumothoraces identified in one series [53].

Economic Implications

In the current healthcare environment, economic considerations must be taken into account when considering the role of renal mass biopsy. Two cost-effectiveness analyses have evaluated renal mass biopsy and demonstrated favorable economics associated with this procedure [54, 55]. Pandharipande and colleagues utilized a decision-analytic Markov model for patients with renal masses ≤4 cm and found that renal mass biopsy was economically superior to immediate intervention with a lifetime cost benefit of nearly $3500 [54]. Similarly, Heilbrun and colleagues found

that renal mass biopsy resulted in a cost of $33,840 for every quality-adjusted life-year gained, proving to be the most cost-effective diagnostic strategy [55].

Conclusions

Renal mass biopsy can help guide treatment recommendations in appropriately selected patients. Advances in imaging and biopsy techniques have led to a nondiagnostic rate consistently below 15%. Similarly, procedural safety has been greatly improved with minimal morbidity now commonplace. While further study and critical appraisal are needed, we feel that renal mass biopsy is, and will continue to be, a valuable adjunct in our care of patients with a renal mass.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30. Epub 2017/01/06
2. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. Rising incidence of renal cell cancer in the United States. JAMA. 1999;281(17):1628–31. Epub 1999/05/11
3. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst. 2006;98(18):1331–4. Epub 2006/09/21
4. Levi F, Ferlay J, Galeone C, Lucchini F, Negri E, Boyle P, et al. The changing pattern of kidney cancer incidence and mortality in Europe. BJU Int. 2008;101(8):949–58. Epub 2008/02/05
5. King SC, Pollack LA, Li J, King JB, Master VA. Continued increase in incidence of renal cell carcinoma, especially in young patients and high grade disease: United States 2001 to 2010. J Urol. 2014;191(6):1665–70. Epub 2014/01/16
6. O'Connor SD, Pickhardt PJ, Kim DH, Oliva MR, Silverman SG. Incidental finding of renal masses at unenhanced CT: prevalence and analysis of features for guiding management. AJR Am J Roentgenol. 2011;197(1):139–45. Epub 2011/06/28
7. Volpe A, Panzarella T, Rendon RA, Haider MA, Kondylis FI, Jewett MA. The natural history of incidentally detected small renal masses. Cancer. 2004;100(4):738–45. Epub 2004/02/11
8. Guethmundsson E, Hellborg H, Lundstam S, Erikson S, Ljungberg B. Metastatic potential in renal cell carcinomas </=7 cm: Swedish kidney cancer quality register data. Eur Urol. 2011;60(5):975–82. Epub 2011/07/12
9. Gill IS, Aron M, Gervais DA, Jewett MA. Clinical practice. Small renal mass. N Engl J Med. 2010;362(7):624–34. Epub 2010/02/19
10. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. J Urol. 2003;170(6 Pt 1):2217–20. Epub 2003/11/25
11. Johnson DC, Vukina J, Smith AB, Meyer AM, Wheeler SB, Kuo TM, et al. Preoperatively misclassified, surgically removed benign renal masses: a systematic review of surgical series and United States population level burden estimate. J Urol. 2015;193(1):30–5. Epub 2014/07/30
12. Leppert JT, Hanley J, Wagner TH, Chung BI, Srinivas S, Chertow GM, et al. Utilization of renal mass biopsy in patients with renal cell carcinoma. Urology. 2014;83(4):774–9. Epub 2014/02/18

13. Barwari K, de la Rosette JJ, Laguna MP. The penetration of renal mass biopsy in daily practice: a survey among urologists. J Endourol. 2012;26(6):737–47. Epub 2011/12/29
14. Silverman SG, Gan YU, Mortele KJ, Tuncali K, Cibas ES. Renal masses in the adult patient: the role of percutaneous biopsy. Radiology. 2006;240(1):6–22. Epub 2006/05/20
15. Rybicki FJ, Shu KM, Cibas ES, Fielding JR, vanSonnenberg E, Silverman SG. Percutaneous biopsy of renal masses: sensitivity and negative predictive value stratified by clinical setting and size of masses. AJR Am J Roentgenol. 2003;180(5):1281–7. Epub 2003/04/22
16. Rosenfield AT, Glickman MG, Taylor KJ, Crade M, Hodson J. Acute focal bacterial nephritis (acute lobar nephronia). Radiology. 1979;132(3):553–61. Epub 1979/09/01
17. Pierorazio PM, Johnson MH, Ball MW, Gorin MA, Trock BJ, Chang P, et al. Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. Eur Urol. 2015;68(3):408–15. Epub 2015/02/24
18. Capitanio U, Volpe A. Renal tumor biopsy: more dogma belied. Eur Urol. 2015;68(6):1014–5. Epub 2015/05/26
19. Kutikov A, Smaldone MC, Uzzo RG, Haifler M, Bratslavsky G, Leibovich BC. Renal mass biopsy: always, sometimes, or never? Eur Urol. 2016;70(3):403–6. Epub 2016/04/18
20. Parker PA, Alba F, Fellman B, Urbauer DL, Li Y, Karam JA, et al. Illness uncertainty and quality of life of patients with small renal tumors undergoing watchful waiting: a 2-year prospective study. Eur Urol. 2013;63(6):1122–7. Epub 2013/02/20
21. Kockelbergh R, Griffiths L. Renal tumour biopsy–a new standard of care? Eur Urol. 2016;69(4):674–5. Epub 2015/10/03
22. Rakowski SK, Winterkorn EB, Paul E, Steele DJ, Halpern EF, Thiele EA. Renal manifestations of tuberous sclerosis complex: incidence, prognosis, and predictive factors. Kidney Int. 2006;70(10):1777–82. Epub 2006/09/28
23. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA guideline. J Urol. 2017;198(3):520–9. Epub 2017/05/10
24. Motzer RJ, Jonasch E, Agarwal N, Bhayani S, Bro WP, Chang SS, et al. Kidney cancer, version 2.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2017;15(6):804–34. Epub 2017/06/10
25. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015;67(5):913–24. Epub 2015/01/27
26. Dave CN, Seifman B, Chennamsetty A, Frontera R, Faraj K, Nelson R, et al. Office-based ultrasound-guided renal core biopsy is safe and efficacious in the management of small renal masses. Urology. 2017;102:26–30. Epub 2016/12/28
27. Silverman SG, Collick BD, Figueira MR, Khorasani R, Adams DF, Newman RW, et al. Interactive MR-guided biopsy in an open-configuration MR imaging system. Radiology. 1995;197(1):175–81. Epub 1995/10/01
28. Uppot RN, Harisinghani MG, Gervais DA. Imaging-guided percutaneous renal biopsy: rationale and approach. AJR Am J Roentgenol. 2010;194(6):1443–9. Epub 2010/05/22
29. Breda A, Treat EG, Haft-Candell L, Leppert JT, Harper JD, Said J, et al. Comparison of accuracy of 14-, 18- and 20-G needles in ex-vivo renal mass biopsy: a prospective, blinded study. BJU Int. 2010;105(7):940–5. Epub 2009/11/06
30. Scanga LR, Maygarden SJ. Utility of fine-needle aspiration and core biopsy with touch preparation in the diagnosis of renal lesions. Cancer Cytopathol. 2014;122(3):182–90. Epub 2013/12/20
31. Yang CS, Choi E, Idrees MT, Chen S, Wu HH. Percutaneous biopsy of the renal mass: FNA or core needle biopsy? Cancer. 2017;125(6):407–15. Epub 2017/03/24
32. Barwari K, Kummerlin IP, ten Kate FJ, Algaba F, Trias I, Wijkstra H, et al. What is the added value of combined core biopsy and fine needle aspiration in the diagnostic process of renal tumours? World J Urol. 2013;31(4):823–7. Epub 2011/06/01
33. Babaei Jandaghi A, Lebady M, Zamani AA, Heidarzadeh A, Monfared A, Pourghorban R. A randomised clinical trial to compare coaxial and noncoaxial techniques in percutaneous core

needle biopsy of renal parenchyma. Cardiovasc Intervent Radiol. 2017;40(1):106–11. Epub 2016/10/04
34. Hobbs DJ, Zhou M, Campbell SC, Aydin H, Weight CJ, Lane BR. The impact of location and number of cores on the diagnostic accuracy of renal mass biopsy: an ex vivo study. World J Urol. 2013;31(5):1159–64. Epub 2012/04/25
35. Abel EJ, Heckman JE, Hinshaw L, Best S, Lubner M, Jarrard DF, et al. Multi-quadrant biopsy technique improves diagnostic ability in large heterogeneous renal masses. J Urol. 2015;194(4):886–91. Epub 2015/04/04
36. Patel HD, Johnson MH, Pierorazio PM, Sozio SM, Sharma R, Iyoha E, et al. Diagnostic accuracy and risks of biopsy in the diagnosis of a renal mass suspicious for localized renal cell carcinoma: systematic review of the literature. J Urol. 2016;195(5):1340–7. Epub 2016/02/24
37. Leveridge MJ, Finelli A, Kachura JR, Evans A, Chung H, Shiff DA, et al. Outcomes of small renal mass needle core biopsy, nondiagnostic percutaneous biopsy, and the role of repeat biopsy. Eur Urol. 2011;60(3):578–84. Epub 2011/06/28
38. Bernhard JC, Bigot P, Pignot G, Baumert H, Zini L, Lang H, et al. The accuracy of renal tumor biopsy: analysis from a national prospective study. World J Urol. 2015;33(8):1205–11. Epub 2014/11/07
39. Salem S, Ponsky LE, Abouassaly R, Cherullo EE, Isariyawongse JP, Maclennan GT, et al. Image-guided biopsy of small renal masses in the era of ablative therapies. Int J Urol. 2013;20(6):580–4. Epub 2012/11/30
40. Richard PO, Jewett MA, Bhatt JR, Kachura JR, Evans AJ, Zlotta AR, et al. Renal tumor biopsy for small renal masses: a single-center 13-year experience. Eur Urol. 2015;68(6):1007–13. Epub 2015/04/23
41. Lane BR, Samplaski MK, Herts BR, Zhou M, Novick AC, Campbell SC. Renal mass biopsy—a renaissance? J Urol. 2008;179(1):20–7.
42. Prince J, Bultman E, Hinshaw L, Drewry A, Blute M, Best S, et al. Patient and tumor characteristics can predict nondiagnostic renal mass biopsy findings. J Urol. 2015;193(6):1899–904. Epub 2014/12/17
43. Feldman AS, Deshmukh SM, Dhyani M, Barrisford G, Rodriguez D, McGovern FJ, et al. Proposal of an algorithm for utilization of percutaneous renal mass biopsy based on the results of 1000 case series. BJU Int. 2013;112:1–17.
44. Schmidbauer J, Remzi M, Memarsadeghi M, Haitel A, Klingler HC, Katzenbeisser D, et al. Diagnostic accuracy of computed tomography-guided percutaneous biopsy of renal masses. Eur Urol. 2008;53(5):1003–11. Epub 2007/12/07
45. Marconi L, Dabestani S, Lam TB, Hofmann F, Stewart F, Norrie J, et al. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. Eur Urol. 2016;69(4):660–73. Epub 2015/09/02
46. Lefaucheur C, Nochy D, Bariety J. Renal biopsy: procedures, contraindications, complications. Nephrol Ther. 2009;5(4):331–9. Epub 2009/04/07
47. Volpe A, Finelli A, Gill IS, Jewett MA, Martignoni G, Polascik TJ, et al. Rationale for percutaneous biopsy and histologic characterisation of renal tumours. Eur Urol. 2012;62(3):491–504. Epub 2012/05/29
48. Viswanathan A, Ingimarsson JP, Seigne JD, Schned AR. A single-centre experience with tumour tract seeding associated with needle manipulation of renal cell carcinomas. Can Urol Assoc J = Journal de l'Association des urologues du Canada. 2015;9(11–12):E890–3. Epub 2016/02/03
49. Corapi KM, Chen JL, Balk EM, Gordon CE. Bleeding complications of native kidney biopsy: a systematic review and meta-analysis. Am J Kidney Dis. 2012;60(1):62–73. Epub 2012/04/28
50. Ralls PW, Barakos JA, Kaptein EM, Friedman PE, Fouladian G, Boswell WD, et al. Renal biopsy-related hemorrhage: frequency and comparison of CT and sonography. J Comput Assist Tomogr. 1987;11(6):1031–4. Epub 1987/11/01
51. Whittier WL, Korbet SM. Timing of complications in percutaneous renal biopsy. J Am Soc Nephrol. 2004;15(1):142–7. Epub 2003/12/25

52. Hopper KD, Yakes WF. The posterior intercostal approach for percutaneous renal procedures: risk of puncturing the lung, spleen, and liver as determined by CT. AJR Am J Roentgenol. 1990;154(1):115–7. Epub 1990/01/01
53. Ajib KM, Matta IF, Zgheib JT, Jabbour ME. Non-angled intercostal percutaneous access under full expiration: safety is not an issue anymore. J Endourol. 2017. Epub 2017/05/26;31:736.
54. Pandharipande PV, Gervais DA, Hartman RI, Harisinghani MG, Feldman AS, Mueller PR, et al. Renal mass biopsy to guide treatment decisions for small incidental renal tumors: a cost-effectiveness analysis. Radiology. 2010;256(3):836–46. Epub 2010/08/20
55. Heilbrun ME, Yu J, Smith KJ, Dechet CB, Zagoria RJ, Roberts MS. The cost-effectiveness of immediate treatment, percutaneous biopsy and active surveillance for the diagnosis of the small solid renal mass: evidence from a Markov model. J Urol. 2012;187(1):39–43. Epub 2011/11/18

Chapter 6
Imaging-Based Scoring Systems for the Risk Stratification of Renal Tumors

Andrew G. McIntosh, Shreyas Joshi, Robert G. Uzzo, and Alexander Kutikov

Introduction

Patients presenting with a renal mass pose a unique and often complex set of challenges to the clinician. Individualizing an optimal treatment strategy requires the evaluation of a broad array of considerations and competing risks. Factors that can help match disease risk to treatment intensity can be patient-related and/or tumor-related. Patient-related risks such as age and comorbidity are well-established [1, 2], while tumor-related risks are the subject of ongoing clinical [3–5] and basic science research [6, 7]. To better describe and classify tumors, imaging-based scoring systems have been developed that can standardize reporting and guide management [8–14].

Higher utilization of cross-sectional imaging has led to an increase in identification of early stage renal masses [5]. In parallel, management strategies for renal masses have expanded from radical nephrectomy in all-comers to individualized application of nephron-sparing surgery, tumor ablation, and active surveillance [3, 15, 16]. To better objectify patient selection for these various management approaches, effective communication of tumor anatomic characteristics has become increasingly necessary. To this end, the first standardized system for objective reporting of renal mass anatomic complexity, the R.E.N.A.L. nephrometry score, was introduced in 2009 by Kutikov and Uzzo [8]. This scoring system allows for renal tumor size, location, and depth to be quantified in a standardized fashion. Subsequently, a variety of other scoring systems were developed to similarly

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standardize the assessment and reporting of renal masses. These include the PADUA [9], C-index [10], ABC [12], DAP [11], Zonal NePhRO [13], and CSA scores [14].

The value of renal scoring systems has been extensively evaluated in the literature, primarily using retrospective cohorts, to examine the utility and explore various applications of these scoring systems [17–20]. Initially described to standardize communication regarding choice of operative approach [21–23], association between renal scoring systems and intraoperative variables such as operative times [24] and warm ischemia time [17, 19, 25–30] has been extensively explored. Furthermore, R.E.N.A.L. nephrometry score appears to be associated with postoperative outcomes such as complications [18] and functional [28] and oncologic outcomes [31]. This chapter reviews the various renal scoring systems and highlights their utility for academic reporting and critical decision-making in clinical practice.

Renal Mass Anatomic Complexity Scoring Systems

A number of renal scoring systems have been introduced since 2009 [8]. Some, like the R.E.N.A.L. nephrometry score, have been comprehensively investigated and harnessed for reporting in the urologic literature, while others have seen more modest adoption and/or validation (Reviewed in [32]). The fundamental premise of all of the systems is to allow the clinician to objectively assign a reproducible alphanumeric metric to a renal mass's salient characteristics as they relate to anatomic location.

R.E.N.A.L. Nephrometry

The R.E.N.A.L. nephrometry scoring system was the first presented at the 2009 American Urological Meeting in Chicago, IL, and soon thereafter published in *The Journal of Urology* [8]. The premise was to introduce a "standardized descriptive construct" to communicate renal tumor anatomic complexity assessed from cross-sectional imaging. The score that was introduced is comprised of five components: tumor size (R), endo/exophycity (E), nearness to the renal sinus (N), anterior/posterior position (A), and location relative to the polar lines (L). Table 6.1 summarizes the components and the corresponding point values used to calculate the score. An additional modifier, "h," is added to the score if the mass is hilar in location and abuts the main renal artery or vein. These scores can be grouped into ranges that correspond to the complexity of the renal mass. Scores of 4–6 represent masses with relatively "simple complexity" (Fig. 6.1), scores of 7–9 are of "moderate complexity" (Fig. 6.2), and scores of 9–12 are of "high complexity" (Fig. 6.3).

Table 6.1 The R.E.N.A.L. nephrometry scoring system

	1 pt	2 pts	3 pts
(R)adius (maximal diameter in cm)	≤4	>4 but <7	≥7
(E)xophytic/endophytic properties	≥50%	<50%	100% endophytic
(N)earness of the tumor to the collecting system or sinus (in mm)	≥7	>4 but <7	≤4
(A)nterior/posterior	Mass assigned a, p, or x descriptor based on location relative to plane created by renal hilum. Those masses assigned x cross plane		
(L)ocation relative to the polar lines	Entirely above the upper or below the lower polar line	Lesion crosses polar line	>50% of mass is across polar line (a) *or* mass crosses the axial renal midline (b) *or* mass is entirely between the polar lines (c)
Suffix: (H)ilar	Assigned if the tumor touches the main renal artery or vein		

From Kutikov et al. [8], with permission of Elsevier

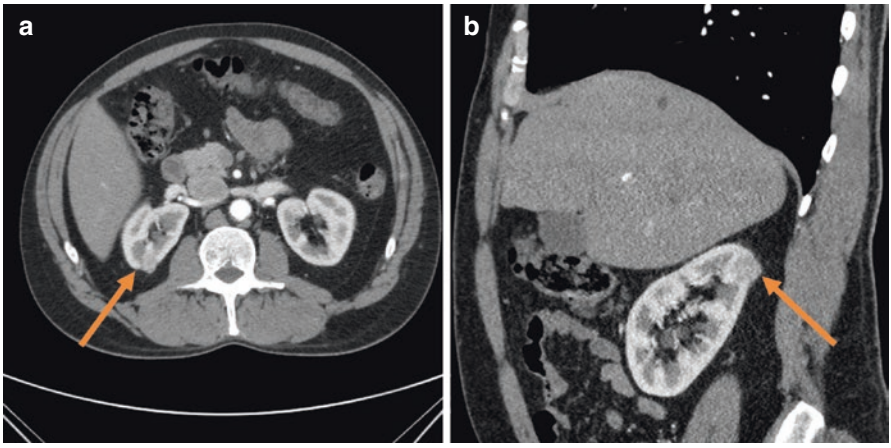

Fig. 6.1 (**a**) axial and (**b**) coronal computed tomography images of a "simple-complexity" lesion. R.E.N.A.L nephrometry score = 1 + 2 + 1 + *p* + 1 = 5*p*

A growing body of literature has evaluated the utility of the R.E.N.A.L. nephrometry scoring system in the management of renal masses and in prediction of clinical outcomes (Table 6.2). The R.E.N.A.L. nephrometry scoring system appears to have high intra- and interobserver reproducibility [29, 60], and clinicians across multiple levels of training can be readily taught to score the anatomic complexity of renal masses with a high level of fidelity [58].

A central feature of the R.E.N.A.L. nephrometry scoring system is its ability to stratify masses by complication risk following partial nephrectomy. In a seminal

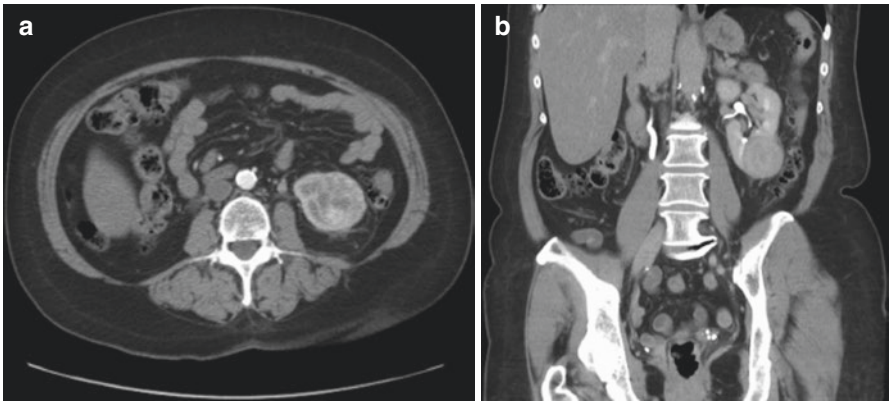

Fig. 6.2 (**a**) axial and (**b**) coronal computed tomography images of a "moderate-complexity" lesion. R.E.N.A.L. nephrometry score = 2 + 2 + 2 + *x* + 2 = 8*x*

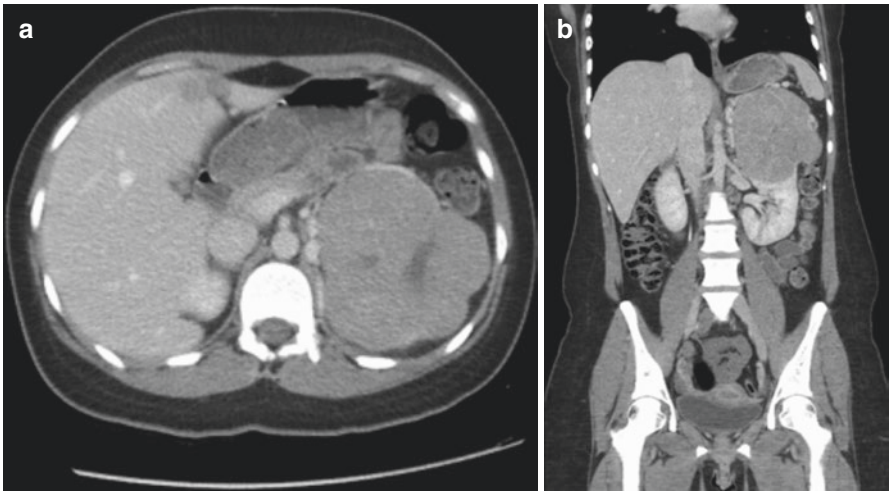

Fig. 6.3 (**a**) axial and (**b**) coronal computed tomography images of a "high-complexity" lesion. R.E.N.A.L. nephrometry score = 3 + 2 + 3 + *x* + 2*h* = 10*xh*

study, Simhan et al. [18] demonstrated that as tumor complexity increases, so do the rates of major complications following partial nephrectomy (6.4% vs. 11.1% vs. 21.9% for low, moderate, and high complexity score grouping, respectively, $p = 0.009$). Subsequent investigators have confirmed these findings in cohorts of patients undergoing both open and minimally invasive partial nephrectomy [22, 44]. Moreover, various reports have specifically investigated the correlation between tumor anatomic complexity, as objectified by the R.E.N.A.L. nephrometry scoring system, and postoperative urine leak [23, 30, 45]. For example, in a cohort of nearly 300 partial nephrectomies, Stroup et al. [23] found that higher R.E.N.A.L.

Table 6.2 Summary of studies evaluating the predictive utility of the R.E.N.A.L. nephrometry scoring system[a]

	References
Descriptive utility	
Correlation with treatment type and/or approach	Canter et al. [21] Broughton et al. [33] Rosevear et al. [22] Stroup et al. [23] Tobert et al. [34] Esen et al. [35] Tomaszewski et al. [36]
Correlation with operative and ischemia times	Okhunov et al. [29] Hayn et al. [17] Hew et al. [37] Mayer et al. [38] Bylund et al. [28] Kruck et al. [24] Ellison et al. [25] Lavallee et al. [39] Altunrende et al. [40] Liu et al. [41] Png et al. [26] Kobayashi et al. [42] Tomaszewski et al. [30] Borgmann et al. [43]
Correlation with complication rates	Simhan et al. [18] Rosevear et al. [22] Tanagho et al. [44] Borgmann et al. [43]
Complications after NSS (MIS or open)	Hayn et al. [17] Hew et al. [37] Liu et al. [41] Ellison et al. [25]
Urine leak	Bruner et al. [45] Stroup et al. [23] Tomaszewski et al. [46]
Hemorrhage	Kruck et al. [24] Jung et al. [47]
Conversion to nephrectomy	Kobayashi et al. [42]
Post-RFA complications	Schmit et al. [48] Reyes et al. [49] Chang et al. [50]
Post-cryotherapy complications	Okhunov et al. [51] Sisul et al. [52] Schmit et al. [48] Lagerveld et al. [53]
Predictive utility	
Length of stay	Kruck et al. [24] Ellison et al. [25]

(continued)

Table 6.2 (continued)

	References
Pathology	Kutikov et al. [54] Satasivam et al. [55] Wang et al. [56] Gorin et al. [57]
Surgical margins	Borgmann et al. [43]
Survival	Weight et al. [58] Kopp et al. [31]
Tumor growth rate	Matsumoto et al. [59]
Renal function	Bylund et al. [28] Kruck et al. [24]

Adapted from Joshi et al. [32]
NSS nephron-sparing surgery, *MIS* minimally invasive surgery, *RFA* radio-frequency ablation
[a]All cited studies are observational in nature (Grade C) and represent level 3 evidence

nephrometry score was associated with increased odds of urine leak (OR, 1.56; $p = 0.002$). In a smaller cohort, each point increase in the R.E.N.A.L. nephrometry score was associated with a 35% increased risk of urine leak [45]. Other authors have also identified an association between R.E.N.A.L. nephrometry score and perioperative blood loss, demonstrating a significantly higher bleeding risk for tumors with scores of greater than 7 [24]. Finally, the correlation between R.E.N.A.L. nephrometry score and warm ischemia time during nephron-sparing surgery is well documented. Tomaszewski et al., in a cohort of 375 patients undergoing robotic partial nephrectomy, observed that significant differences in ischemia time were noted between low, intermediate, and high complexity masses [30]. Other investigators have also noted a significant trend toward longer warm ischemia time in patients with higher-complexity tumors [40].

R.E.N.A.L. nephrometry score can be used to predict both postoperative renal functional decline [61] and progression-free/overall survival [31] following surgery. Kopp et al. observed that radical nephrectomy is independently associated with decreased renal function compared to partial nephrectomy for T2 renal masses with scores $\leq$10 but not for scores >10 [61]. Further, the authors noted an increasing decline in glomerular filtration rate for every point decrease in R.E.N.A.L. nephrometry score. These data suggest that this scoring system may help guide the decision to perform a radical nephrectomy in patients with large masses. In another study, the same investigators demonstrated improved progression-free survival for R.E.N.A.L. nephrometry scores <10 vs. $\geq$10 ($p < 0.001$) and that patients with a score of $\geq$10 were more likely to die of renal cell carcinoma ($p < 0.001$) or any cause ($p < 0.001$) [31]. Such findings are thought provoking and can help inform the decision-making process regarding surgical approach for complex renal masses [62].

As was demonstrated in the original manuscript, R.E.N.A.L. nephrometry score correlates with treatment type [1]. Anatomically complex masses, regardless of size, are more likely to be treated with radical nephrectomy or open partial nephrectomy than with minimally invasive nephron-sparing surgery [21]. Meanwhile, patients with masses placed on active surveillance were more likely to have lower individual R.E.N.A.L. component scores [36]. Indeed, it appears clinicians are more likely to

place low-complexity tumors on active surveillance, likely because these are felt to be less biologically aggressive [36]. R.E.N.A.L nephrometry score also appears to strongly correlate with case selection for both low- and high-volume surgeons in the community setting [34].

A number of investigators have explored the role of R.E.N.A.L nephrometry score for predicting surgical pathology [54–57]. Gorin et al. noted on multivariate analysis that higher scores were associated with tumor upstaging from cT1 to pT3a upon resection (OR 2.97, 95% CI 1.20–7.35, $p = 0.02$) [57]. Tumor anatomic complexity as captured by R.E.N.A.L. nephrometry score also appears to be predictive of tumor grade and histology [54]. A nomogram that demonstrated the predictive ability of anatomic complexity for pathologic assessment, albeit imperfect, has been subsequently validated in other cohorts [56]. Other investigators, nevertheless, reported that R.E.N.A.L. nephrometry score was suboptimal in distinguishing benign from malignant tumors [63] or in accurately predicting histology [64]. Table 6.2 summarizes publications analyzing the descriptive and predictive utility of the R.E.N.A.L. nephrometry score and their corresponding levels of evidence for its descriptive and predictive utility.

PADUA Score

Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) clasification system was introduced by Ficarra et al. soon after the publication of the R.E.N.A.L. nephrometry system and is similar in its descriptive characteristics [9]. The PADUA score also incorporates tumor size and includes the following anatomical elements: anterior or posterior face, longitudinal and rim tumor location, tumor relationships with the renal sinus or collecting system, and percentage of tumor deepening into the kidney. While the PADUA score similarly incorporates tumor radius and exo/endophycity, the two scores describe slightly different spatial relationships, such as the relation to polar lines or the renal rim.

The PADUA score has not been as widely utilized in the literature as the R.E.N.A.L. nephrometry score, although it appears to have similar utility in tumor risk stratification. Tyritzis et al. [65] found PADUA score to be an independent predictor of postoperative complications following partial nephrectomy. Other studies attempting to assess the utility of PADUA scores have confirmed its association with postoperative complications and have identified longer warm ischemia times with higher PADUA scores [19, 37].

Centrality Index (C-Index)

Introduced in 2010, the Centrality Index (C-index) utilizes the spatial relationship between the center of the tumor and the center of the kidney [10]. The C-index is the ratio of the calculated value "*c*" and the tumor radius. "*c*" represents the hypotenuse of

a right triangle with sides formed by two anatomical distance relationships ($x^2 + y^2 = c^2$). "x" is the "horizontal" (medial to lateral) distance from the renal hilum to the center of the tumor, and "y" is the "height" (cranio-caudal) in cm from hilar center to level of maximum tumor diameter. The C-index is unique in that it relies on objective measurements rather than incorporating points based on the qualitative components of the R.E.N.A.L. nephrometry and PADUA scores. A higher C-index score is indicative of a relatively lower level of mass complexity. For example, a C-index of "0" is indicative of a tumor that is concentric with the center of the kidney, while a C-index of >1 denotes a peripheral tumor increasingly distant from the kidney center.

The C-index has not been widely adopted and is less broadly validated in the literature. It may be that it is conceptually more complex than other descriptive scores, which may limit its clinical utility; however, high interobserver agreement between urologists (0.98) has been demonstrated [60]. Furthermore, the C-index has been associated with renal functional outcomes. A C-index of less than 2.5 correlated with a 2.2-fold increased risk of 30% loss of estimated glomerular filtration rate [20] and was significantly correlated with percent change in creatinine level ($p = -0.33$) [29] following laparoscopic partial nephrectomy. Additionally, C-index has been found to be associated with warm ischemia time [10, 28, 29], which is a surrogate for technical complexity.

DAP Score

The Diameter-Axial-Polar (DAP) scoring system was developed to simplify the previously developed R.E.N.A.L nephrometry and C-index scores by combining their optimized attributes [11]. As the name suggests, the score is tabulated utilizing three components: (1) the largest axial tumor diameter, (2) the axial distance between the edge of the tumor and center of the kidney, and (3) the distance from the tumor edge to the equatorial plane of the kidney.

The DAP score was conceived to combine established concepts into a relatively straightforward system, and the establishing authors demonstrated improved interobserver agreement relative to R.E.N.A.L. nephrometry and C-index scores [11]. Subsequent studies have shown DAP score to be a good predictor of warm ischemia time and renal functional decline following partial nephrectomy [27, 66]. More recent evidence, however, suggests that the R.E.N.A.L. nephrometry score may outperform the DAP score in predicting perioperative outcomes [43].

ABC Score

The Arterial Based Complexity (ABC) score was introduced in 2016 and was designed to assess the morbidity profile of partial nephrectomy [12]. The system analyzes renal masses by the branching order vessels that need to be transected during partial nephrectomy. Variable scores are assigned to each vessel category. Scores

of 1, 2, 3S, or 3H are assigned to interlobular or arcuate arteries, interlobar arteries, segmental arteries, or those in proximity to the renal hilum, respectively. Higher scores designate higher mass anatomic complexity.

External validation of this score is limited, but one study found association with the ABC score with on-clamp excision and opening of the collecting system on multivariate analysis [67]. Additionally, when modified to combine invasiveness and tumor diameter, it was an independent predictor of complications.

Zonal NePhRO Scoring System

The Zonal NePhRO scoring system was conceived to simplify the existing renal scoring systems into four anatomical components: nearness to collecting system, physical location of the tumor in the kidney, radius of the tumor, and organization of the tumor [13]. Each component receives a score of 1, 2, or 3, and these scores are added together to obtain a renal mass complexity score. Zonal NePhRO score has been found to have high interobserver reproducibility [60]. While the scoring system has shown promise in predicting perioperative renal functional decline, complications, and warm ischemia times [68], further validation is needed before this can be widely adopted.

Contact Surface Area

The main purpose for the development of the Contact Surface Area (CSA) score was to create a metric that best predicts perioperative nephron-sparing surgery outcomes [14]. CSA is calculated using image-rendering software that quantifies the CSA of the tumor with the surrounding renal parenchyma. A higher CSA corresponds to higher complexity, and investigators found CSA to be an independent predictor of operative time, complications, and renal functional outcomes. The requirement to utilize software-based computation is a major barrier to the widespread adoptability of CSA. However, a recent study demonstrated similar predictive value utilizing a computational formula rather than a software-based approach to calculate CSA [69]. Additionally, Haifler et al. validated this formula's utility for estimated CSA as an independent predictor of change in renal function following surgery [70].

Non-tumor Related Objective Scoring Systems

As the collective experience of using renal mass nephrometry continues to grow, efforts have been made to introduce scoring systems that objectify surgical anatomy not immediately related to the renal mass itself. The MAP score and renal pelvic score are two unique systems that have been introduced to describe some of these non-mass features.

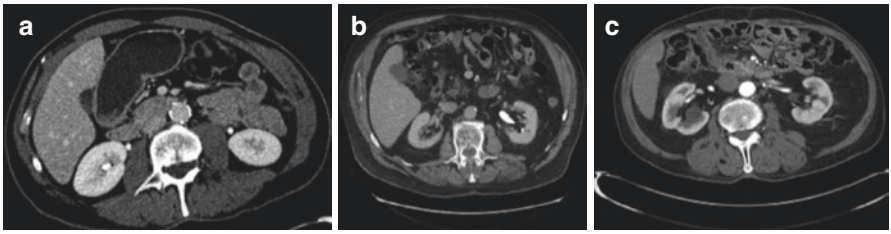

Fig. 6.4 Mayo Adhesive Probability (MAP) score grading perinephric stranding. (**a**) No stranding: 0 points. The tissue surrounding the kidney is uniformly black. (**b**) Type 1: 2 points. There is mild/moderate image-dense stranding, but no thick bars of inflamed tissue. (**c**) Type 2: 3 points. There is severe image-dense stranding with thick bars of inflammation

MAP Score

For many surgeons performing partial nephrectomy, the presence of abundant and adherent perinephric fat can be one of the most challenging aspects of this operation. This so-called "sticky" or "bad" perinephric fat often results in a tedious and time-consuming dissection.

The Mayo Adhesive Probability (MAP) score was developed to predict the presence of adherent perinephric fat [71]. The investigators evaluated axial imaging from 100 consecutive patients undergoing robot-assisted partial nephrectomy and demonstrated that perinephric fat thickness at the level of the renal vein along with grade of perinephric stranding (Fig. 6.4) accurately predicted the presence of adherent perinephric fat. A follow-up external validation study confirmed the predictive value of the MAP score [72]. Intriguingly, evidence also suggests that higher MAP scores may be associated with decreased progression-free survival following surgical treatment of clinically localized disease [73].

The Renal Pelvic Score

Relationship of the renal tumor to the renal collecting system, specifically whether a collecting system repair was performed, has been shown to predict urine leak [74] and appears to predict perioperative outcomes [38]. Recently, the renal pelvis anatomy itself has been shown as a possible independent predictor post-partial nephrectomy urine leak. The Renal Pelvic Score was conceived to evaluate whether renal pelvic anatomy could independently predict urine leak [46]. An objective method to classify renal pelvic anatomy was developed based on the percentage of renal pelvis contained within the renal parenchyma. Indeed, those patients with intraparenchymal renal pelvic anatomy were found to have a markedly increased risk for urine leak, prolonged duration of leak, and need for intervention to stop the leak. This novel tool can help with case selection, inform decisions to take extra intraoperative precaution, such as ureteral stenting, and direct patient counseling.

Comparisons of Renal Scoring Systems

Systematic comparisons of the various renal scoring systems are somewhat limited. In one study, R.E.N.A.L. nephrometry and PADUA scores were found to have similarly high intra- and interobserver reproducibility [37]. Additionally, these scoring systems were found to have comparable ability to predict perioperative complications. Another study found that R.E.N.A.L. nephrometry, PADUA, and C-index scores all had a significant correlation with ischemia time ($p < 0.001$), with C-index having the strongest correlation [28]. The authors also observed that all three scoring systems outperformed simply measuring tumor size and location.

Esen et al. [35] investigated the association of the R.E.N.A.L., PADUA, and C-index scores with surgical case selection and approach. The authors observed that both R.E.N.A.L. nephrometry and PADUA scores were associated with treatment choice, surgical approach, and open conversion. R.E.N.A.L. nephrometry score appeared to outperform the others in this analysis. Investigators have commonly noted R.E.N.A.L. nephrometry and PADUA scores to be useful in predicting perioperative outcomes [42].

Kriegmair et al. reported on 305 patients with renal masses whose tumors were prospectively evaluated using the R.E.N.A.L., PADUA, C-index, and NePhRO scores [60]. High interobserver agreement was noted for all scoring systems. Moreover, all of the scoring correlated well with surgical outcomes. The C-index, however, appeared to have less fidelity relative to R.E.N.A.L. nephrometry, PADUA, and NePhRO scores. Specifically, all scores but C-index were independent predictors of severe complications.

In another recent analysis, investigators retrospectively evaluated the cross-sectional imaging of 188 patients undergoing nephron-sparing surgery and indexed anatomic complexity using the R.E.N.A.L., PADUA, C-index, and DAP scores [43]. The study evaluated quantitative perioperative outcomes (operative time, estimated blood loss, warm ischemia time, and hospital stay) in addition to tumor margin status and complications. R.E.N.A.L. nephrometry score was found to correlate best with margin, ischemia, and complications (MIC) score optimization and quantitative perioperative outcomes. In general, although further prospective systematic comparison of various scores would be revealing, R.E.N.A.L. nephrometry score – and to a lesser degree PADUA – appears to be reproducible, widely adopted, and clinically useful.

Conclusions

The appropriate management of patients presenting with a renal mass pivots on taking into account both patient and tumor-related factors. Since 2009, investigators have used a variety of strategies to objectify reporting of radiographic features of renal masses along with variations in renal anatomy. These conceptual constructs now provide objective and reproducible tools for communication of patient selection and afford meaningful comparisons of outcomes and risks.

References

1. Kutikov A, Egleston BL, Wong YN, Uzzo RG. 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):311–7.
2. Lane BR, Babineau D, Kattan MW, Novick AC, Gill IS, Zhou M, et al. A preoperative prognostic nomogram for solid enhancing renal tumors 7 cm or less amenable to partial nephrectomy. J Urol. 2007;178(2):429–34.
3. Ristau BT, Correa AF, Uzzo RG, Smaldone MC. Active surveillance for the small renal mass: growth kinetics and oncologic outcomes. Urol Clin North Am. 2017;44(2):213–22.
4. Lane BR, Kattan MW. Prognostic models and algorithms in renal cell carcinoma. Urol Clin North Am. 2008;35(4):613–25. vii
5. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst. 2006;98(18):1331–4.
6. Tang J, Qin Z, Li X, Han P, Wang F, Yang C, et al. Association between vascular endothelial growth factor gene polymorphisms and the risk and prognosis of renal cell carcinoma: a systematic review and meta-analysis. Oncotarget. 2017;8(30):50034–50.
7. Rabjerg M. Identification and validation of novel prognostic markers in renal cell carcinoma. Dan Med J. 2017;64(10):B5339.
8. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol. 2009;182(3):844–53.
9. Ficarra V, Novara G, Secco S, Macchi V, Porzionato A, De Caro R, et al. Preoperative aspects and dimensions used for an anatomical (PADUA) classification of renal tumours in patients who are candidates for nephron-sparing surgery. Eur Urol. 2009;56(5):786–93.
10. Simmons MN, Ching CB, Samplaski MK, Park CH, Gill IS. Kidney tumor location measurement using the C index method. J Urol. 2010;183(5):1708–13.
11. Simmons MN, Hillyer SP, Lee BH, Fergany AF, Kaouk J, Campbell SC. Diameter-axial-polar nephrometry: integration and optimization of R.E.N.A.L. and centrality index scoring systems. J Urol. 2012;188(2):384–90.
12. Spaliviero M, Poon BY, Karlo CA, Guglielmetti GB, Di Paolo PL, Beluco Corradi R, et al. An Arterial Based Complexity (ABC) scoring system to assess the morbidity profile of partial nephrectomy. Eur Urol. 2016;69(1):72–9.
13. Hakky TS, Baumgarten AS, Allen B, Lin HY, Ercole CE, Sexton WJ, et al. Zonal NePhRO scoring system: a superior renal tumor complexity classification model. Clin Genitourin Cancer. 2014;12(1):e13–8.
14. Leslie S, Gill IS, de Castro Abreu AL, Rahmanuddin S, Gill KS, Nguyen M, et al. Renal tumor contact surface area: a novel parameter for predicting complexity and outcomes of partial nephrectomy. Eur Urol. 2014;66(5):884–93.
15. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA guideline. J Urol. 2017;198(3):520–9.
16. Withington J, Neves JB, Barod R. Surgical and minimally invasive therapies for the management of the small renal mass. Curr Urol Rep. 2017;18(8):61.
17. Hayn MH, Schwaab T, Underwood W, Kim HL. RENAL nephrometry score predicts surgical outcomes of laparoscopic partial nephrectomy. BJU Int. 2011;108(6):876–81.
18. Simhan J, Smaldone MC, Tsai KJ, Canter DJ, Li T, Kutikov A, et al. Objective measures of renal mass anatomic complexity predict rates of major complications following partial nephrectomy. Eur Urol. 2011;60(4):724–30.
19. Waldert M, Waalkes S, Klatte T, Kuczyk MA, Weibl P, Schuller G, et al. External validation of the preoperative anatomical classification for prediction of complications related to nephron-sparing surgery. World J Urol. 2010;28(4):531–5.
20. Samplaski MK, Hernandez A, Gill IS, Simmons MN. C-index is associated with functional outcomes after laparoscopic partial nephrectomy. J Urol. 2010;184(6):2259–63.

21. Canter D, Kutikov A, Manley B, Egleston B, Simhan J, Smaldone M, et al. Utility of the R.E.N.A.L. nephrometry scoring system in objectifying treatment decision-making of the enhancing renal mass. Urology. 2011;78(5):1089–94.
22. Rosevear HM, Gellhaus PT, Lightfoot AJ, Kresowik TP, Joudi FN, Tracy CR. Utility of the RENAL nephrometry scoring system in the real world: predicting surgeon operative preference and complication risk. BJU Int. 2012;109(5):700–5.
23. Stroup SP, Palazzi K, Kopp RP, Mehrazin R, Santomauro M, Cohen SA, et al. RENAL nephrometry score is associated with operative approach for partial nephrectomy and urine leak. Urology. 2012;80(1):151–6.
24. Kruck S, Anastasiadis AG, Walcher U, Stenzl A, Herrmann TR, Nagele U. Laparoscopic partial nephrectomy: risk stratification according to patient and tumor characteristics. World J Urol. 2012;30(5):639–46.
25. Ellison JS, Montgomery JS, Hafez KS, Miller DC, He C, Wolf JS Jr, et al. Association of RENAL nephrometry score with outcomes of minimally invasive partial nephrectomy. Int J Urol. 2013;20(6):564–70.
26. Png KS, Bahler CD, Milgrom DP, Lucas SM, Sundaram CP. The role of R.E.N.A.L. nephrometry score in the era of robot-assisted partial nephrectomy. J Endourol. 2013;27(3):304–8.
27. Li M, Gao Y, Cheng J, Qu L, Chen J, Cai C, et al. Diameter-axial-polar nephrometry is predictive of surgical outcomes following partial nephrectomy. Medicine (Baltimore). 2015;94(30):e1228.
28. Bylund JR, Gayheart D, Fleming T, Venkatesh R, Preston DM, Strup SE, et al. Association of tumor size, location, R.E.N.A.L., PADUA and centrality index score with perioperative outcomes and postoperative renal function. J Urol. 2012;188(5):1684–9.
29. Okhunov Z, Rais-Bahrami S, George AK, Waingankar N, Duty B, Montag S, et al. The comparison of three renal tumor scoring systems: C-index, P.A.D.U.A., and R.E.N.A.L. nephrometry scores. J Endourol. 2011;25(12):1921–4.
30. Tomaszewski JJ, Smaldone MC, Mehrazin R, Kocher N, Ito T, Abbosh P, et al. Anatomic complexity quantitated by nephrometry score is associated with prolonged warm ischemia time during robotic partial nephrectomy. Urology. 2014;84(2):340–4.
31. Kopp RP, Mehrazin R, Palazzi KL, Liss MA, Jabaji R, Mirheydar HS, et al. Survival outcomes after radical and partial nephrectomy for clinical T2 renal tumours categorised by R.E.N.A.L. nephrometry score. BJU Int. 2014;114(5):708–18.
32. Joshi SS, Uzzo RG. Renal tumor anatomic complexity: clinical implications for urologists. Urol Clin North Am. 2017;44(2):179–87.
33. Broughton GJ, Clark PE, Barocas DA, Cookson MS, Smith JA Jr, Herrell SD, et al. Tumour size, tumour complexity, and surgical approach are associated with nephrectomy type in small renal cortical tumours treated electively. BJU Int. 2012;109(11):1607–13.
34. Tobert CM, Kahnoski RJ, Thompson DE, Anema JG, Kuntzman RS, Lane BR. RENAL nephrometry score predicts surgery type independent of individual surgeon's use of nephron-sparing surgery. Urology. 2012;80(1):157–61.
35. Esen T, Acar O, Musaoglu A, Vural M. Morphometric profile of the localised renal tumors managed either by open or robot-assisted nephron-sparing surgery: the impact of scoring systems on the decision making process. BMC Urol. 2013;13:63.
36. Tomaszewski JJ, Uzzo RG, Kocher N, Li T, Manley B, Mehrazin R, et al. Patients with anatomically "simple" renal masses are more likely to be placed on active surveillance than those with anatomically "complex" lesions. Urol Oncol. 2014;32(8):1267–71.
37. Hew MN, Baseskioglu B, Barwari K, Axwijk PH, Can C, Horenblas S, et al. Critical appraisal of the PADUA classification and assessment of the R.E.N.A.L. nephrometry score in patients undergoing partial nephrectomy. J Urol. 2011;186(1):42–6.
38. Mayer WA, Godoy G, Choi JM, Goh AC, Bian SX, Link RE. Higher RENAL nephrometry score is predictive of longer warm ischemia time and collecting system entry during laparoscopic and robotic-assisted partial nephrectomy. Urology. 2012;79(5):1052–6.

39. Lavallee LT, Desantis D, Kamal F, Blew B, Watterson J, Mallick R, et al. The association between renal tumour scoring systems and ischemia time during open partial nephrectomy. Can Urol Assoc J. 2013;7(3–4):E207–14.
40. Altunrende F, Laydner H, Hernandez AV, Autorino R, Khanna R, White MA, et al. Correlation of the RENAL nephrometry score with warm ischemia time after robotic partial nephrectomy. World J Urol. 2013;31(5):1165–9.
41. Liu ZW, Olweny EO, Yin G, Faddegon S, Tan YK, Han WK, et al. Prediction of perioperative outcomes following minimally invasive partial nephrectomy: role of the R.E.N.A.L nephrometry score. World J Urol. 2013;31(5):1183–9.
42. Kobayashi K, Saito T, Kitamura Y, Nobushita T, Kawasaki T, Hara N, et al. The RENAL nephrometry score and the PADUA classification for the prediction of perioperative outcomes in patients receiving nephron-sparing surgery: feasible tools to predict intraoperative conversion to nephrectomy. Urol Int. 2013;91(3):261–8.
43. Borgmann H, Reiss AK, Kurosch M, Filmann N, Frees S, Mager R, et al. R.E.N.A.L. score outperforms PADUA score, C-index and DAP score for outcome prediction of nephron sparing surgery in a selected cohort. J Urol. 2016;196(3):664–71.
44. Tanagho YS, Kaouk JH, Allaf ME, Rogers CG, Stifelman MD, Kaczmarek BF, et al. Perioperative complications of robot-assisted partial nephrectomy: analysis of 886 patients at 5 United States centers. Urology. 2013;81(3):573–9.
45. Bruner B, Breau RH, Lohse CM, Leibovich BC, Blute ML. Renal nephrometry score is associated with urine leak after partial nephrectomy. BJU Int. 2011;108(1):67–72.
46. Tomaszewski JJ, Cung B, Smaldone MC, Mehrazin R, Kutikov A, Viterbo R, et al. Renal pelvic anatomy is associated with incidence, grade, and need for intervention for urine leak following partial nephrectomy. Eur Urol. 2014;66(5):949–55.
47. Jung S, Min GE, Chung BI, Jeon SH. Risk factors for postoperative hemorrhage after partial nephrectomy. Korean J Urol. 2014;55(1):17–22.
48. Schmit GD, Thompson RH, Kurup AN, Weisbrod AJ, Boorjian SA, Carter RE, et al. Usefulness of R.E.N.A.L. nephrometry scoring system for predicting outcomes and complications of percutaneous ablation of 751 renal tumors. J Urol. 2013;189(1):30–5.
49. Reyes J, Canter D, Putnam S, Simhan J, Smaldone MC, Kutikov A, et al. Thermal ablation of the small renal mass: case selection using the R.E.N.A.L.-Nephrometry score. Urol Oncol. 2013;31(7):1292–7.
50. Chang X, Ji C, Zhao X, Zhang F, Lian H, Zhang S, et al. The application of R.E.N.A.L. nephrometry scoring system in predicting the complications after laparoscopic renal radiofrequency ablation. J Endourol. 2014;28(4):424–9.
51. Okhunov Z, Shapiro EY, Moreira DM, Lipsky MJ, Hillelsohn J, Badani K, et al. R.E.N.A.L. nephrometry score accurately predicts complications following laparoscopic renal cryoablation. J Urol. 2012;188(5):1796–800.
52. Sisul DM, Liss MA, Palazzi KL, Briles K, Mehrazin R, Gold RE, et al. RENAL nephrometry score is associated with complications after renal cryoablation: a multicenter analysis. Urology. 2013;81(4):775–80.
53. Lagerveld BW, Brenninkmeijer M, van der Zee JA, van Haarst EP. Can RENAL and PADUA nephrometry indices predict complications of laparoscopic cryoablation for clinical stage T1 renal tumors? J Endourol. 2014;28(4):464–71.
54. Kutikov A, Smaldone MC, Egleston BL, Manley BJ, Canter DJ, Simhan J, et al. Anatomic features of enhancing renal masses predict malignant and high-grade pathology: a preoperative nomogram using the RENAL nephrometry score. Eur Urol. 2011;60(2):241–8.
55. Satasivam P, Sengupta S, Rajarubendra N, Chia PH, Munshey A, Bolton D. Renal lesions with low R.E.N.A.L nephrometry score are associated with more indolent renal cell carcinomas (RCCs) or benign histology: findings in an Australian cohort. BJU Int. 2012;109(Suppl 3):44–7.
56. Wang HK, Zhu Y, Yao XD, Zhang SL, Dai B, Zhang HL, et al. External validation of a nomogram using RENAL nephrometry score to predict high grade renal cell carcinoma. J Urol. 2012;187(5):1555–60.
57. Gorin MA, Ball MW, Pierorazio PM, Tanagho YS, Bhayani SB, Kaouk JH, et al. Outcomes and predictors of clinical T1 to pathological T3a tumor up-staging after robotic partial nephrectomy: a multi-institutional analysis. J Urol. 2013;190(5):1907–11.

58. Weight CJ, Atwell TD, Fazzio RT, Kim SP, Kenny M, Lohse CM, et al. A multidisciplinary evaluation of inter-reviewer agreement of the nephrometry score and the prediction of long-term outcomes. J Urol. 2011;186(4):1223–8.
59. Matsumoto R, Abe T, Shinohara N, Murai S, Maruyama S, Tsuchiya K, et al. RENAL nephrometry score is a predictive factor for the annual growth rate of renal mass. Int J Urol. 2014;21(6):549–52.
60. Kriegmair MC, Mandel P, Moses A, Lenk J, Rothamel M, Budjan J, et al. Defining renal masses: comprehensive comparison of RENAL, PADUA, NePhRO, and C-index score. Clin Genitourin Cancer. 2016;15(2):248–55.
61. Kopp RP, Liss MA, Mehrazin R, Wang S, Lee HJ, Jabaji R, et al. Analysis of renal functional outcomes after radical or partial nephrectomy for renal masses >/=7 cm using the RENAL score. Urology. 2015;86(2):312–9.
62. Kim SP, Campbell SC, Gill I, Lane BR, Van Poppel H, Smaldone MC, et al. Collaborative review of risk benefit trade-offs between partial and radical nephrectomy in the management of anatomically complex renal masses. Eur Urol. 2017;72(1):64–75.
63. Bagrodia A, Harrow B, Liu ZW, Olweny EO, Faddegon S, Yin G, et al. Evaluation of anatomic and morphologic nomogram to predict malignant and high-grade disease in a cohort of patients with small renal masses. Urol Oncol. 2014;32(1):37.e17–23.
64. Antonelli A, Furlan M, Sandri M, Minervini A, Cindolo L, Parma P, et al. The R.E.N.A.L. nephrometric nomogram cannot accurately predict malignancy or aggressiveness of small renal masses amenable to partial nephrectomy. Clin Genitourin Cancer. 2014;12(5):366–72.
65. Tyritzis SI, Papadoukakis S, Katafigiotis I, Adamakis I, Anastasiou I, Stravodimos KG, et al. Implementation and external validation of Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score for predicting complications in 74 consecutive partial nephrectomies. BJU Int. 2012;109(12):1813–8.
66. Wang L, Li M, Chen W, Wu Z, Cai C, Xiang C, et al. Is diameter-axial-polar scoring predictive of renal functional damage in patients undergoing partial nephrectomy? An evaluation using technetium Tc 99m ((9)(9)Tcm) diethylene-triamine-penta-acetic acid (DTPA) glomerular filtration rate. BJU Int. 2013;111(8):1191–8.
67. Kriegmair MC, Hetjens S, Mandel P, Wadle J, Budjan J, Michel MS, et al. Tumor size and invasiveness matters for partial nephrectomy: external validation and modification of the arterial based complexity score. J Surg Oncol. 2017;115:768–74.
68. Kriegmair MC, Mandel P, Moses A, Bolenz C, Michel MS, Pfalzgraf D. Zonal NephRo score: external validation for predicting complications after open partial nephrectomy. World J Urol. 2016;34(4):545–51.
69. Hsieh PF, Wang YD, Huang CP, Wu HC, Yang CR, Chen GH, et al. A mathematical method to calculate tumor contact surface area: an effective parameter to predict renal function after partial nephrectomy. J Urol. 2016;196(1):33–40.
70. Haifler M, Higgins A, Ristau BT, Smaldone MC, Kutikov A, Zisman A, et al. External validation of contact surface area as a predictor of post-operative renal function in patients undergoing partial nephrectomy. In: Center FCC, editor. In peer review; 2017.
71. Davidiuk AJ, Parker AS, Thomas CS, Leibovich BC, Castle EP, Heckman MG, et al. Mayo adhesive probability score: an accurate image-based scoring system to predict adherent perinephric fat in partial nephrectomy. Eur Urol. 2014;66(6):1165–71.
72. Martin L, Rouviere O, Bezza R, Bailleux J, Abbas F, Schott-Pethelaz AM, et al. Mayo adhesive probability score is an independent computed tomography scan predictor of adherent perinephric fat in open partial nephrectomy. Urology. 2017;103:124–8.
73. Thiel DD, Davidiuk AJ, Meschia C, Serie D, Custer K, Petrou SP, et al. Mayo adhesive probability score is associated with localized renal cell carcinoma progression-free survival. Urology. 2016;89:54–60.
74. Meeks JJ, Zhao LC, Navai N, Perry KT Jr, Nadler RB, Smith ND. Risk factors and management of urine leaks after partial nephrectomy. J Urol. 2008;180(6):2375–8.

Chapter 7
Active Surveillance of Renal Tumors

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Abbreviations

CT	Computed tomography
DISSRM	Delayed intervention and surveillance for small renal masses
ECOG	Eastern Cooperative Oncology Group performance status
MRI	Magnetic resonance imaging
SRM	Small renal mass

Introduction

Solid renal tumors have been increasingly diagnosed in recent decades, largely attributable to incidental findings on cross-sectional imaging [1–5]. The growing incidence has led to stage migration where newly diagnosed tumors are more often asymptomatic and almost 50% are localized small renal masses (SRMs) ≤4 cm in size (clinical stage T1a) [1–5]. A significant proportion of these lesions may have low metastatic potential with about 20–30% of localized tumors found to have benign pathology after surgery [6]. Given concerns about potential overtreatment of patients that may not benefit from intervention, active surveillance has emerged as a management option for well-selected patients based on risk stratification and shared decision-making [7]. Recent evidence has demonstrated favorable outcomes in both retrospective and prospective cohorts for patients with localized renal tumors placed on active surveillance that minimizes risk of metastatic progression and

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death due to kidney cancer. While the 2014 update of the European Association of Urology Guidelines [2] recommends active surveillance as an option only for elderly or comorbid patients with cT1a tumors, the 2017 American Urological Association Guidelines [3] indicate that it may be considered as an initial management option for any patient with a localized SRM based on the growing body of evidence.

The intent of active surveillance is twofold. First, it aims to avoid the morbidity of intervention, in the form of surgery or ablation, for localized renal tumors that would otherwise remain localized and asymptomatic during the remainder of a patient's life span. Second, for patients exhibiting signs for potential progression of disease, it aims to provide a window of opportunity for prompt intervention. While the first goal tries to reduce overtreatment by initial patient selection, the second goal attempts to reduce risks of under treatment with triggers for intervention. Appropriate time intervals for follow-up, methods of imaging and diagnostics, and absolute triggers for intervention remain points of debate.

Epidemiology

It is estimated that a total of 64,000 newly diagnosed cases and over 14,000 deaths due to kidney or renal pelvic cancer were expected in 2017 with a twofold greater incidence for men than women [8]. The incidence has more than doubled in the last 20 years, largely due to incidental diagnoses, but the overall death rate remains unchanged from 1980 to 2014 at 4.6 deaths per 100,000 of the United States population [9]. In contrast, prostate cancer mortality decreased by 21.7% during the same time frame.

The paradoxical observation that death rates have not improved despite increasing diagnosis of early stage renal tumors has a few potential explanations. One interpretation is that the increased incidence is truly due to increased development of kidney cancer in the United States rather than greater detection of incidental tumors, with stable outcomes after available management options (no improvement or detriment to survival over time). However, a more likely explanation is that the increase is due to incidental diagnoses of tumors with low metastatic potential that would have minimally contributed to the death rate had they remained undiagnosed.

While radical nephrectomy is the traditional gold standard for the management of localized kidney cancer, nephron-sparing surgery in the form of partial nephrectomy or ablation has increasingly been utilized for SRMs and has outpaced the use of radical nephrectomy, partially attributable to increased utilization of robotic assistance for laparoscopic surgery [10–12]. The prevalence of the use of active surveillance for localized renal tumors is uncertain, but data from the Surveillance, Epidemiology, and End Results Program suggests up to 10% of patients with SRMs do not undergo intervention for at least 6 months after diagnosis [10, 11]. The proportion of these patients followed on a regimented active surveillance protocol, rather than watchful waiting or no follow-up, is unknown.

Natural History

Active surveillance for renal tumors is inherently tied to the expected natural history of kidney cancer including development and progression of disease. The proportion of SRMs found to be benign after surgical resection is inversely related to tumor diameter [6]. Prognostic nomograms generally suggest >90% probability of freedom from metastasis for incidentally diagnosed SRMs (>98% for tumors ≤2 cm) at up to 12 years follow-up after surgical resection [13]. Importantly, for all patients with clinically localized disease, deaths from competing comorbidities outweigh the number of deaths from kidney cancer when stratified by tumor size, treatment strategy, age, or comorbidity status [14, 15]. However, all available nomograms, regardless of whether they utilize preoperative or postoperative characteristics, can only predict outcomes after surgery [13, 16]. No currently available nomograms provide a prognosis in the setting of active surveillance.

Tumor volume and growth is often used as a marker of aggressiveness for various cancers. However, renal tumors can include a heterogeneous mix of benign and malignant histologies without a definitive diagnosis until surgical resection. A number of reports and pooled analyses have suggested SRMs have a linear growth rate of about 0.3 cm/year, which includes a proportion of tumors that may remain completely static [17–19]. For tumors with known histologies, one review suggested that the mean linear growth rate for benign (0.3 cm/year) and malignant (0.35 cm/year) renal tumors were similar and unable to aid in differentiation [17]. While the overall rates may be similar, another analysis comprised of 18 surveillance series noted that the minority of patients progressing to metastasis (2% at 3–4 years) generally had a higher linear growth rate (0.8 cm/year vs. 0.3 cm/year) compared to patients who did not progress [18].

Patient Selection

Patient selection is the first of two critical components of active surveillance, with the second being appropriate triggers for intervention. Appropriate risk stratification will select out patients who may benefit most from immediate intervention and optimize outcomes for those electing to pursue active surveillance. While traditional "hard" outcomes include metastasis and cancer-specific survival, it is also important to consider decisions at the patient-level with an additional focus on shared decision-making and quality of life. No set objective criteria exist for selection, but general considerations include increased age, number of comorbidities and life expectancy, and tumor characteristics.

Age and Comorbidities

Increased patient age is often cited as an important criterion for active surveillance but also serves as a surrogate for other selection criteria. Older age is associated with decreased performance status, which may be measured on a number of scales

including the Eastern Cooperative Oncology Group (ECOG) performance [20] status or Karnofsky Performance Scale [21]. The elderly may also experience a greater number of chronic, comorbid conditions. Most elderly patients, despite an increased comorbidity burden, can safely undergo surgical intervention with partial or radical nephrectomy. The available literature suggests a somewhat increased but acceptable rate of postoperative complications [22, 23]. Therefore, active surveillance with the option for delayed intervention is often a feasible option for many elderly patients with SRMs. Patients that are not candidates for surgery may still be candidates for active surveillance if they can receive renal mass ablation as a delayed intervention. Otherwise, watchful waiting may be the most appropriate management strategy for patients that are not candidates for an intervention.

Patients with multiple comorbidities may have significant competing risk of death that outweighs the risk imparted by a localized renal tumor. Cardiovascular disease is the leading cause of death in the world and slightly outpaces malignancies in the United States [24, 25]. Specific comorbidities have been suggested as selection criteria for active surveillance with a focus on cardiovascular comorbidities for both selection and potential postoperative risks given its relationship to renal function [15, 26]. Patients with cardiovascular risk factors who deferred surgery were found to have similar cancer survival to those undergoing partial or radical nephrectomy [15]. Furthermore, a cardiovascular index specific to the SRM population, incorporating both congestive heart failure and chronic kidney disease, was shown to risk-stratify patients as well or better than the Charlson comorbidity index [14]. Notably, patients with chronic kidney disease or a solitary kidney may deserve special consideration for active surveillance as it provides a management strategy that maximizes renal preservation.

Patient age and comorbidity burden may most effectively be considered in concert, through a composite score or calculation, to better estimate the trade-off between life expectancy and risk of cancer progression. Comorbidity-adjusted life expectancy, although intended to assist with decision about cancer screening, could also be used in the context of shared decision-making [27]. The prospective delayed intervention and surveillance for small renal masses (DISSRM) registry includes objective criteria such as age, ECOG performance status, and a modified cardiovascular index to develop a score specific to patients on active surveillance and may assist with selection if validated [28].

Tumor Characteristics Based on Imaging

Active surveillance is most often considered for SRMs, although some patients with limited life expectancies may be offered surveillance for larger tumors. Accurate tumor characterization on imaging is necessary to assign a patient's clinical stage. Computed tomography (CT) scan with intravenous contrast remains the mainstay for diagnosis and differentiates the clinical stage of localized tumors by determining

tumor size and helps identify potential venous or perinephric extension suggesting higher-risk disease not suitable for active surveillance [1–3]. While both CT and magnetic resonance imaging (MRI) have high sensitivity in identifying venous invasion, they are more limited in identifying perinephric fat invasion with 45–50% sensitivity for CT and up to 60–70% for MRI [29]. For localized tumors, absolute size, and hence clinical stage, may be the most important parameter as it is associated with increased risk of metastatic progression [18]. Larger tumors have also been shown to exhibit greater potential for growth [19].

Several methods to measure tumor complexitybeyond tumor size have been used clinically including the R.E.N.A.L. nephrometry score [30]. While nephrometry score may be a reasonable measure of tumor complexity, based on associations with perioperative outcomes and postoperative complications, it has not been proven to aid in differentiating benign from malignant lesions or predict outcomes on active surveillance [31–33]. One analysis demonstrated the association of tumor complexity and growth rate, a potential surrogate for progression and aggressiveness, but the magnitude of the association was small [32]. A systematic review of the literature indicated only increasing tumor size and male sex were predictive of malignancy for localized renal tumors based on the available evidence base [33]. Because of this, active surveillance is mostly limited to patients with SRMs in modern series, and patients with larger tumors require the presence of other strong selection factors or patient preference to consider surveillance.

Tumor Characteristics Based on Renal Mass Biopsy

Renal mass sampling, via fine needle aspiration or core biopsy, is not routinely employed for most patients with newly diagnosed renal tumors or those comfortable with the decision to pursue active surveillance [34]. However, renal mass biopsy has the potential to alter management decisions in some situations. Younger patients hesitant about pursuing surgical intervention may be comfortable pursuing active surveillance if a biopsy reveals benign or favorable pathology. Additionally, women may be more likely to have benign tumors [33]. Biopsy has the potential to provide adjunct data for risk stratification, and some groups have suggested incorporating it into management algorithms [35].

While a biopsy positive for malignancy has a >99% positive predictive value, the negative predictive value appears to be on the order of 65–70% [36]. Therefore, a negative biopsy result or findings of a low grade or chromophobe renal cell carcinoma on biopsy can increase confidence in placing a patient on active surveillance. Still, the possibility of a false-negative result and the potential for grade discordance [37] suggests continued follow-up on an active surveillance protocol is prudent. In general, the use of renal mass biopsy for patient selection into active surveillance remains a decision through shared decision-making.

Outcomes for Active Surveillance and Delayed Intervention

While active surveillance has become more widely practiced and incorporated into updated guidelines statements [2, 3] as an option for small solid or complex cystic renal masses, no randomized data has compared it to other management options [1–3, 7]. Randomized data may be difficult to obtain, as selection is a core component with surveillance often reserved for elderly or sick patients. Enrolling a sufficient number of patients meeting inclusion criteria for randomization and obtaining sufficient follow-up presents a challenge. Fortunately, a number of retrospective series have been reported in the past 15 years, and two prospective experiences have recently matured, providing insight on patient outcomes and indications for crossover to delayed intervention.

Early and Retrospective Experiences

A review of the literature identified a number of retrospective series reporting outcomes for active surveillance of renal masses [38]. Notably, among identified series, 11 reported no metastases for any patients on surveillance during follow-up and 8 reported variable but generally low rates. The highest rates, as may be expected, are from the smallest and oldest series. One series of 13 patients with mean tumor size of 5 cm and no set inclusion criteria, allowing inclusion of patients unfit for surgery along with T2 and T3 disease, reported 1 (7.7%) patient with metastasis [39]. Another series of 35 patients retrospectively assembled during a 14-year period (with 4-year mean follow-up) reported 2 (5.7%) metastases [40]. However, one of these patients was lost to follow-up for a period of 40 months where a 2.7 cm mass grew to 5.8 cm when he returned with a diagnosis of spinal cord compression from metastasis. The second patient, diagnosed with a 2.7 cm mass, elected to continue surveillance despite an elevated growth rate but ultimately agreed to radical nephrectomy after 26 months and developed lung metastasis 3 months after surgery.

More recent reports have included larger cohorts with greater attention to growth rates, albeit in the absence of a regimented active surveillance protocol. Currently, the largest retrospective series included 223 lesions in 212 patients and reported a total of 4 (1.9%) metastatic events, 1 death from renal cell carcinoma (0.5%), and 11 (5.2%) patients undergoing delayed intervention at a median follow-up of 35 months [41]. They included all patients who deferred surgery with a wide range of tumor sizes (up to 13.7 cm). Patients progressing to metastasis had a median growth rate >1 cm/year, and the patient dying of cancer had 3 cm of tumor growth over 13 months. When limited to patients with SRMs, 2 (1.2%) of 173 patients experienced metastasis. Another large series of 173 tumors in 154 patients reported 2 (1.3%) patients with metastatic disease and 39% of tumors eventually receiving treatment at a median of 24 months [42]. Retrospective experiences have suggested acceptable outcomes for patients placed on active surveillance for renal tumors, but

the absence of set selection criteria and variable triggers to consider intervention make them difficult to compare head to head.

Renal Cell Carcinoma Consortium of Canada

The first regimented, prospective active surveillance protocol was initiated at eight centers comprising the Renal Cell Carcinoma Consortium of Canada, enrolling 178 patients with 209 SRMs between 2004 and 2009 [43]. This phase 2 clinical trial included a single-arm cohort of patients with SRMs deemed to be "unfit for surgery due to advanced age, comorbidity, or refusal of other treatment" with exclusion of patients with less than 2 years of life expectancy. Tumor progression was defined as growth to 4 cm or larger diameter, doubled tumor volume, or metastatic disease. A total of 27 (15.2%) patients progressed, 33 (18.5%) electively withdrew within 48 months, and 2 (1.1%) experienced metastases leading to 1 (0.6%) kidney cancer death. For patients that were on active surveillance for at least 12 months, growth rates were similar for malignant and benign tumors based on biopsy pathology at a mean of 28 months.

The Canadian experience verified several important principles of active surveillance for renal tumors in a prospective setting but also raised a few pertinent questions. It confirmed that appropriately surveyed SRMs with serial imaging and a definition for progression leading to consideration of intervention had a low rate of metastasis in the short term. Absolute growth rate did not differentiate malignant and benign tumors determined by biopsy, and a follow-up analysis noted no statistically significant predictors among the limited variables they captured [44]. Additionally, for patients opting for renal mass biopsy at trial entry, the nondiagnostic rate was found to be 33%. The rate is over twice the modern tabulated estimates for all localized renal tumors and likely driven by the relative predominance of small SRMs [36]. With limited follow-up, the management and decision-making implications for biopsy pathology at enrollment are not yet clear. Longer follow-up is necessary, and the ability to evaluate additional selection criteria (e.g., tumor complexity, patient comorbidities) and outcomes (e.g., quality of life, renal function) has been suggested.

Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry

Beginning in 2009, the DISSRM registry was initiated as a multi-institutional prospective, non-inferiority trial to evaluate selection criteria, predictors of progression, and outcomes of active surveillance relative to a contemporaneous cohort of patients receiving primary intervention [45]. Intervention was recommended for

renal tumors progressing to greater than 4 cm or growth rate >0.5 cm/year; metastasis or delayed intervention also counted toward an a priori definition for progression. Recently updated results have reported on >600 patients with a median follow-up of 3 years [46–48]. Of 317 patients on active surveillance, 45 (14.2%) underwent delayed intervention, the majority being elective, with no metastatic events or kidney cancer deaths in the cohort. Importantly, overall survival, as expected, was worse for active surveillance compared to primary intervention with surgery or ablation, but cancer outcomes were not significantly different; 2 (0.7%) of 298 patients receiving primary intervention died due to kidney cancer. The 45 patients under going delayed intervention experienced similar pathologic and recurrence-free survival as patients receiving primary intervention.

The DISSRM registry verified prior retrospective series and the Canadian experience while comparing surveillance patients to a modern cohort of treated patients. The similar distribution of surgical pathologies for patients undergoing delayed or primary intervention is an important observation. While risk stratification and renal mass biopsy may have helped enrich the active surveillance cohort for benign and low-risk pathologies, this data is not available for most patients and may not be necessary given the favorable outcomes. Delayed intervention for patients followed on the DISSRM protocol did not compromise outcomes. Notably, grade on biopsy was only concordant with surgical pathology in 52% of cases found to have renal cell carcinoma, suggesting renal mass biopsy may only be helpful in determining whether a patient harbors a malignancy rather than knowing the exact tumor grade. Active surveillance for patients with negative biopsies is still necessary given the reported negative predictive value of 68.8%.

While continued follow-up will be enlightening, early results suggest mental quality of life is not adversely affected for patients receiving surveillance compared to primary intervention [49]. Renal function has also been shown to be similar for active surveillance, partial nephrectomy, and ablation but decreased for patients receiving radical nephrectomy [50, 51]. Despite the favorable outcomes thus far, active surveillance remains a calculated risk requiring appropriate risk stratification. The goal may not be to prevent all cancer deaths, as two deaths were observed even in the primary intervention cohort but to balance the advantages and risks of surveillance through shared decision-making for appropriately selected patients with set thresholds to recommend intervention.

Triggers for Intervention

A growing body of literature has suggested several selection criteria for patients considering active surveillance, but less data are available on appropriate triggers for intervention. Both prospective experiences [43, 45] have utilized absolute size as an indication of progression because size is a known predictor of cancer outcomes for renal tumors [18]. The benefit of including size is that it allows an objective assessment that can be tracked over time with serial imaging, and intervention can

be recommended, while disease remains clinically localized. However, it provides minimal space for growth or variability in measurements for tumors that are already near 4 cm in size. Repeat imaging is generally recommended within 6 months of initial diagnosis and at least annually thereafter, although prospective protocols have performed more frequent imaging for the first few years [52]. Overall, absolute size may be one of the most valid measures of progression as it is related to both cancer prognosis and likelihood of harboring malignancy with the caveat that inclusion criteria would be limited to SRMs [33].

As previously discussed, growth rate measured by linear or volumetric rate of change in observational series is not associated with likelihood of malignancy and has a slight, but small, association with progression to metastasis [18]. The association has not been confirmed in prospective cohorts, but this may be due to prevention of some events by early recommended intervention and a low overall rate of metastasis. Tumor growth rate is commonly associated with prognosis for various cancers, and it is likely to remain a consideration for SRMs on active surveillance [53]. The question remains as to what threshold for growth should be used, possibly relative to absolute tumor size, as growth kinetics can be highly variable early on before stabilizing [54]. Renal mass biopsy should be a consideration to aid management decisions for patients with elevated growth rates. Development of metastatic disease is an appropriate criterion for progression and need for therapy, but the ideal triggers for intervention would occur, while the tumor remains localized. Some emerging modalities and recommendations to address research gaps in the diagnosis and management of localized renal tumors may improve outcomes for patients on active surveillance and safely reduce overtreatment [55].

Emerging Modalities

Improvements in renal mass biopsy as well as emerging biomarkers and imaging techniques could help improve selection and monitoring for patients with renal tumors on active surveillance. Currently, a number of serum markers have been explored, but none are able to accurately diagnose renal cell carcinoma [56]. Two urinary markers that may hold the greatest promise currently are aquaporin-1 and perilipin-2, which have been shown to be associated with renal cell carcinoma, not affected by common kidney diseases, and to increase with tumor size [56–58]. A validated urinary marker may help distinguish benign and malignant lesions without requiring renal mass biopsy and can be repeated noninvasively over time. No association with prognosis has been established, and one potential limitation may be that the markers do not measure progression to distant metastasis if dependent on glomerular filtration from local tumor shedding.

A recent evaluation of ^{99m}Tc-sestamibi SPECT/CT demonstrated high sensitivity and specificity in differentiating tumors with low likelihood of metastasis such as renal oncocytomas and hybrid oncocytic/chromophobe tumors from renal cell carcinoma [59]. A noninvasive imaging modality identifying oncocytic neoplasms

could provide reassurance for some patients to pursue active surveillance, especially given that the only false positives were chromophobe renal cell carcinoma, which are recommended for active surveillance by biopsy-based algorithms [35]. One small external validation study has confirmed similar performance characteristics [60]. While direct comparisons to renal mass biopsy are lacking, ^{99m}Tc-sestamibi SPECT/CT may be able to serve as an adjunct or replacement to biopsy in some cases if validated in further studies.

Conclusions

Solid renal tumors have been increasingly diagnosed with stage migration increasing the proportion of asymptomatic and localized SRMs with low metastatic potential. Active surveillance has emerged as a management option for well-selected patients with a number of studies supporting acceptable rates of metastasis for elderly patients with competing risks of death. Prospective cohorts with defined inclusion criteria and triggers to consider delayed intervention have shown SRMs can be safely managed on active surveillance based on survival outcomes, renal function, and quality of life compared to primary intervention. Expanding inclusion criteria for active surveillance will depend on better initial risk stratification, based on tumor and patient characteristics, emerging diagnostic modalities, and shared decision-making with patients showing signs of progression. Active surveillance may currently be underutilized, but long-term follow-up will solidify its role in the management of renal tumors.

References

1. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, et al. Guideline for management of the clinical T1 renal mass. J Urol. 2009;182(4):1271–9.
2. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015;67(5):913–24.
3. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA guideline. J Urol. 2017;198(3):520–9.
4. Nguyen MM, Gill IS, Ellison LM. The evolving presentation of renal carcinoma in the United States: trends from the surveillance, epidemiology, and end results program. J Urol. 2006;176(6 Pt 1):2397–400. discussion 2400
5. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. Cancer. 2008;113(1):78–83. https://doi.org/10.1002/cncr.23518.
6. Johnson DC, Vukina J, Smith AB, Meyer AM, Wheeler SB, Kuo TM, et al. Preoperatively misclassified, surgically removed benign renal masses: a systematic review of surgical series and United States population level burden estimate. J Urol. 2015;193(1):30–5.
7. Pierorazio PM, Johnson MH, Patel HD, Sozio SM, Sharma R, Iyoha E, et al. Management of renal masses and localized renal cancer: systematic review and meta-analysis. J Urol. 2016;196(4):989–99.

8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
9. Mokdad AH, Dwyer-Lindgren L, Fitzmaurice C, Stubbs RW, Bertozzi-Villa A, Morozoff C, et al. Trends and patterns of disparities in cancer mortality among US counties, 1980–2014. JAMA. 2017;317(4):388–406.
10. Huang WC, Atoria CL, Bjurlin M, Pinheiro LC, Russo P, Lowrance WT, et al. Management of small kidney cancers in the new millennium: contemporary trends and outcomes in a population-based cohort. JAMA Surg. 2015;150(7):664–72.
11. Patel HD, Kates M, Pierorazio PM, Hyams ES, Gorin MA, Ball MW, et al. Survival after diagnosis of localized T1a kidney cancer: current population-based practice of surgery and nonsurgical management. Urology. 2014;83(1):126–32.
12. Patel HD, Mullins JK, Pierorazio PM, Jayram G, Cohen JE, Matlaga BR, et al. Trends in renal surgery: robotic technology is associated with increased use of partial nephrectomy. J Urol. 2013;189(4):1229–35.
13. Raj GV, Thompson RH, Leibovich BC, Blute ML, Russo P, Kattan MW. Preoperative nomogram predicting 12-year probability of metastatic renal cancer. J Urol. 2008;179(6):2146–51. discussion 2151
14. Patel HD, Kates M, Pierorazio PM, Gorin MA, Jayram G, Ball MW, et al. Comorbidities and causes of death in the management of localized T1a kidney cancer. Int J Urol. 2014;21(11):1086–92.
15. Patel HD, Kates M, Pierorazio PM, Allaf ME. Balancing cardiovascular (CV) and cancer death among patients with small renal masses: modification by CV risk. BJU Int. 2015;115(1):58–64.
16. Karakiewicz PI, Briganti A, Chun FK, Trinh QD, Perrotte P, Ficarra V, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. J Clin Oncol. 2007;25(11):1316–22.
17. Nayyar M, Cheng P, Desai B, Cen S, Desai M, Gill I, et al. Active surveillance of small renal masses: a review on the role of imaging with a focus on growth rate. J Comput Assist Tomogr. 2016;40(4):517–23.
18. Smaldone MC, Kutikov A, Egleston BL, Canter DJ, Viterbo R, Chen DY, et al. Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. Cancer. 2012;118(4):997–1006.
19. Mason RJ, Abdolell M, Trottier G, Pringle C, Lawen JG, Bell DG, et al. Growth kinetics of renal masses: analysis of a prospective cohort of patients undergoing active surveillance. Eur Urol. 2011;59(5):863–7.
20. Zubrod CG, Schneiderman M, Frei E III, Brindley C, Gold GL, Shnider B, et al. Appraisal of methods for the study of chemotherapy in man: comparative therapeutic trial of nitrogen mustard and thiophosphoramide. J Chronic Dis. 1960;11(1):7–33.
21. Karnofsky D, Burchenal J. The clinical evaluation of chemotherapeutic agents in cancer. In: MacLeod C, editor. Evaluation of chemotherapeutic agents. New York: Columbia University Press; 1949. p. 191–205.
22. Lowrance WT, Yee DS, Savage C, Cronin AM, O'Brien MF, Donat SM, et al. Complications after radical and partial nephrectomy as a function of age. J Urol. 2010;183(5):1725–30.
23. Patel HD, Ball MW, Cohen JE, Kates M, Pierorazio PM, Allaf ME. Morbidity of urologic surgical procedures: an analysis of rates, risk factors, and outcomes. Urology. 2015;85(3):552–9.
24. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459–544.
25. Health, United States, 2015. With special feature on racial and ethnic health disparities. Hyattsville: National Center for Health Statistics; 2016.
26. Huang WC, Elkin EB, Levey AS, Jang TL, Russo P. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors--is there a difference in mortality and cardiovascular outcomes? J Urol. 2009;181(1):55–61. discussion 61-2

27. Cho H, Klabunde CN, Yabroff KR, Wang Z, Meekins A, Lansdorp-Vogelaar I, et al. Comorbidity-adjusted life expectancy: a new tool to inform recommendations for optimal screening strategies. Ann Intern Med. 2013;159(10):667–76.
28. Pierorazio PM, Hyams ES, Mullins JK, Allaf ME. Active surveillance for small renal masses. Rev Urol. 2012;14(1–2):13–9.
29. Reznek RH. CT/MRI in staging renal cell carcinoma. Cancer Imaging. 2004;4(Spec No A):S25–32.
30. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. J Urol. 2009;182(3):844–53.
31. Rosevear HM, Gellhaus PT, Lightfoot AJ, Kresowik TP, Joudi FN, Tracy CR. Utility of the RENAL nephrometry scoring system in the real world: predicting surgeon operative preference and complication risk. BJU Int. 2012;109(5):700–5.
32. Mehrazin R, Smaldone MC, Egleston B, Tomaszewski JJ, Concodora CW, Ito TK, et al. Is anatomic complexity associated with renal tumor growth kinetics under active surveillance? Urol Oncol. 2015;33(4):167.e7–12.
33. Pierorazio PM, Patel HD, Johnson MH, Sozio SM, Sharma R, Iyoha E, et al. Distinguishing malignant and benign renal masses with composite models and nomograms: a systematic review and meta-analysis of clinically localized renal masses suspicious for malignancy. Cancer. 2016;122(21):3267–76.
34. Patel HD, Pierorazio PM. Kidney cancer: undertreatment of small renal masses by overuse of biopsy. Nat Rev Urol. 2016;13(12):701–3.
35. Halverson SJ, Kunju LP, Bhalla R, Gadzinski AJ, Alderman M, Miller DC, et al. Accuracy of determining small renal mass management with risk stratified biopsies: confirmation by final pathology. J Urol. 2013;189(2):441–6.
36. Patel HD, Johnson MH, Pierorazio PM, Sozio SM, Sharma R, Iyoha E, et al. Diagnostic accuracy and risks of biopsy in the diagnosis of a renal mass suspicious for localized renal cell carcinoma: systematic review of the literature. J Urol. 2016;195(5):1340–7.
37. Ball MW, Bezerra SM, Gorin MA, Cowan M, Pavlovich CP, Pierorazio PM, et al. Grade heterogeneity in small renal masses: potential implications for renal mass biopsy. J Urol. 2015;193(1):36–40.
38. Smaldone MC, Corcoran AT, Uzzo RG. Active surveillance of small renal masses. Nat Rev Urol. 2013;10(5):266–74.
39. Fernando HS, Duvuru S, Hawkyard SJ. Conservative management of renal masses in the elderly: our experience. Int Urol Nephrol. 2007;39(1):203–7.
40. Abou Youssif T, Kassouf W, Steinberg J, Aprikian AG, Laplante MP, Tanguay S. Active surveillance for selected patients with renal masses: updated results with long-term follow-up. Cancer. 2007;110(5):1010–4.
41. Rosales JC, Haramis G, Moreno J, Badani K, Benson MC, McKiernan J, et al. Active surveillance for renal cortical neoplasms. J Urol. 2010;183(5):1698–702.
42. Crispen PL, Viterbo R, Boorjian SA, Greenberg RE, Chen DY, Uzzo RG. Natural history, growth kinetics, and outcomes of untreated clinically localized renal tumors under active surveillance. Cancer. 2009;115(13):2844–52.
43. Jewett MA, Mattar K, Basiuk J, Morash CG, Pautler SE, Siemens DR, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol. 2011;60(1):39–44.
44. Organ M, Jewett M, Basiuk J, Morash C, Pautler S, Siemens DR, et al. Growth kinetics of small renal masses: a prospective analysis from the renal cell carcinoma consortium of Canada. Can Urol Assoc J. 2014;8(1–2):24–7.
45. Pierorazio PM, Johnson MH, Ball MW, Gorin MA, Trock BJ, Chang P, et al. Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. Eur Urol. 2015;68(3):408–15.
46. Pierorazio PM, Alam R, Patel HD, Gorin MA, Johnson MH, Gausepohl H, et al. Active surveillance is safe for patients with solid, small renal masses: intermediate results of the DISSRM registry. Eur Urol. 2015;68(3):408–15.

47. Alam R, Patel HD, Osumah T, Srivastava A, Gorin MA, Johnson MH, et al. Comparative effectiveness of management options for patients with small renal masses:a Prospective Cohort Study. BJU Int
48. Alam R, Patel HD, Riffon MF, Trock BJ, Uzosike A, Chang P, et al. Intermediate-term outcomes from the DISSRM registry: a prospective analysis of active surveillance in patients with small renal masses. J Clin Oncol. 2017;35(6_suppl):430–430
49. Patel HD, Riffon MF, Joice GA, Johnson MH, Chang P, Wagner AA, et al. A prospective, comparative study of quality of life among patients with small renal masses choosing active surveillance and primary intervention. J Urol. 2016;196(5):1356–62.
50. Danzig MR, Ghandour RA, Chang P, Wagner AA, Pierorazio PM, Allaf ME, et al. Active surveillance is superior to radical nephrectomy and equivalent to partial nephrectomy for preserving renal function in patients with small renal masses: results from the DISSRM registry. J Urol. 2015;194(4):903–9.
51. Patel HD, Pierorazio PM, Johnson MH, Sharma R, Iyoha E, Allaf ME, et al. Renal functional outcomes after surgery, ablation, and active surveillance of localized renal tumors: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2017;12(7):1057–69.
52. Donat SM, Diaz M, Bishoff JT, Coleman JA, Dahm P, Derweesh IH, et al. Follow-up for clinically localized renal neoplasms: AUA guideline. J Urol. 2013;190(2):407–16.
53. Mehrara E, Forssell-Aronsson E, Ahlman H, Bernhardt P. Specific growth rate versus doubling time for quantitative characterization of tumor growth rate. Cancer Res. 2007;67(8):3970–5.
54. Uzosike AC, Patel HD, Alam R, Schwen ZR, Gupta M, Gorin MA, et al. Growth kinetics of small renal masses on active surveillance: variability and results from the DISSRM registry. J Urol. 2018;199(3):641–8.
55. Patel HD, Iyoha E, Pierorazio PM, Sozio SM, Johnson MH, Sharma R, et al. A systematic review of research gaps in the evaluation and management of localized renal masses. Urology. 2016;98:14–20.
56. Pastore AL, Palleschi G, Silvestri L, Moschese D, Ricci S, Petrozza V, et al. Serum and urine biomarkers for human renal cell carcinoma. Dis Markers. 2015;2015:251403.
57. Morrissey JJ, Mellnick VM, Luo J, Siegel MJ, Figenshau RS, Bhayani S, et al. Evaluation of urine Aquaporin-1 and Perilipin-2 concentrations as biomarkers to screen for renal cell carcinoma: a prospective cohort study. JAMA Oncol. 2015;1(2):204–12.
58. Morrissey JJ, Mobley J, Song J, Vetter J, Luo J, Bhayani S, et al. Urinary concentrations of aquaporin-1 and perilipin-2 in patients with renal cell carcinoma correlate with tumor size and stage but not grade. Urology. 2014;83(1):256.e9–14.
59. Gorin MA, Rowe SP, Baras AS, Solnes LB, Ball MW, Pierorazio PM, et al. Prospective evaluation of (99m)Tc-sestamibi SPECT/CT for the diagnosis of renal oncocytomas and hybrid oncocytic/chromophobe tumors. Eur Urol. 2016;69(3):413–6.
60. Tzortzakakis A, Gustafsson O, Karlsson M, Ekström-Ehn L, Ghaffarpour R, Axelsson R. Visual evaluation and differentiation of renal oncocytomas from renal cell carcinomas by means of 99mTc-sestamibi SPECT/CT. EJNMMI Res. 2017;7(1):29.

Chapter 8
Contemporary Surgical Approaches for Small Renal Tumors

Pascal Mouracade, Juan Garisto, and Jihad Kaouk

Introduction

Current guidelines on the management of renal tumors recommend the use of nephron-sparing approaches, such as thermoablation and partial nephrectomy, for patients presenting with a small renal tumor in need of treatment [1, 2]. These guidelines aim to avoid the sequelae of surgically induced chronic kidney disease, the risk of which is directly related to the amount of resected or treated normal renal parenchyma [3–5]. The most definitive method of nephron-sparing surgery is partial nephrectomy. First described using an open approach [6, 7], partial nephrectomy for small renal tumors is now most commonly performed by minimally invasive techniques including laparoscopic and robotic surgery [8]. When compared to the conventional open surgical technique, minimally invasive partial nephrectomy has resulted in significantly less postoperative pain, shorter hospital stays, earlier return to work and daily activities, and a more favorable cosmetic result [9, 10]. Additionally, oncologic outcomes appear to be equivalent to that of open surgery [11–13].

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Laparoscopic Partial Nephrectomy

The first reports on the feasibility of laparoscopic renal surgery were published in the 1990s [14, 15]. Laparoscopic partial nephrectomy is now commonly performed worldwide. Two basic approaches for laparoscopic partial nephrectomy have been described: transperitoneal and retroperitoneal approach.

Transperitoneal Approach When performing transperitoneal laparoscopic partial nephrectomy, the patient is typically placed in modified flank position with 60° of flexion (Fig. 8.1). A four- or five-port approach may be used. A primary port 10 or 12 mm is placed lateral to the rectus muscle at the level of the umbilicus. The next port is placed lateral to the rectus muscle and just inferior to the costochondral margin, and the other port is inserted at the midaxillary line near the tip of the 11th rib. A 5-mm trocar is placed between the two working trocars in the posterior axillary line for the assistant. For right-sided procedures, a 5-mm trocar is often placed in the upper midline near the xiphoid process to accommodate a traumatic locking grasper forceps that can grasp the diaphragm and hold the liver up exposing the upper pole of the kidney. After obtaining pneumoperitoneum, the pressure is maintained at 15–20 mmHg.

Once the colon is mobilized, the ureter and gonadal vein are identified. On the left side, the ureter and the gonadal vein are retracted laterally. While on the right side, the gonadal vein is kept medially, and only the ureter is retracted laterally. The dissection is carried cephalad along the psoas muscle, and the renal hilum is dissected. The renal artery and vein are dissected to facilitate further application of laparoscopic bulldog clamps to each vessel (Fig. 8.2). Prior to incising beyond the

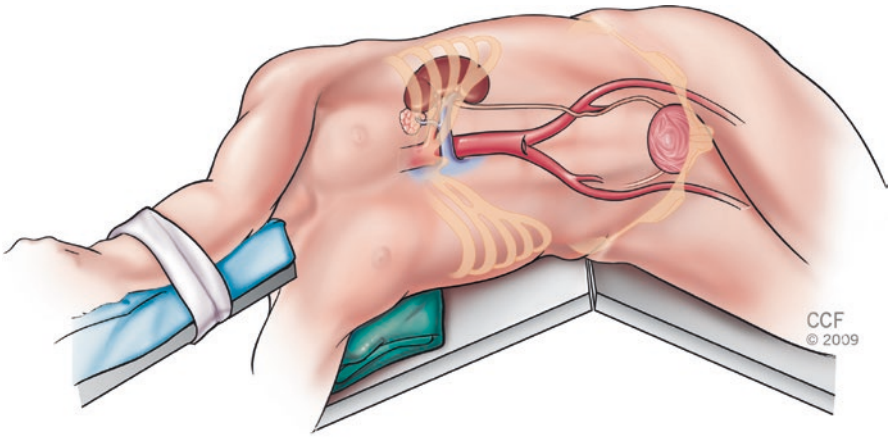

Fig. 8.1 Patient positioning for the transperitoneal approach to minimally invasive partial nephrectomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

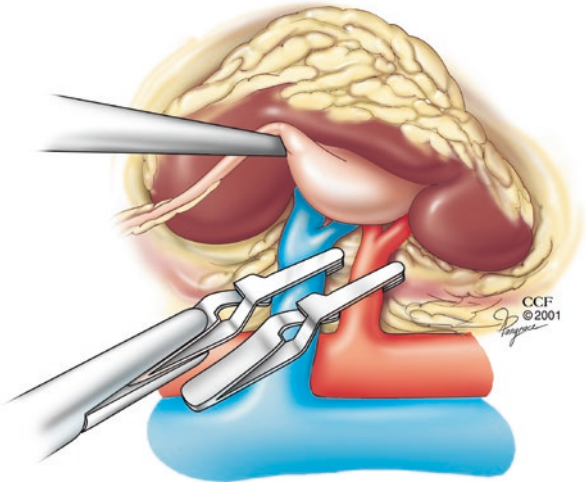

Fig. 8.2 Clamping of the renal hilum during minimally invasive partial nephrectomy using bulldog clamps. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

renal capsule, all necessary materials, including sutures and instruments, should be confirmed to be at hand before proceeding.

Gerota's fascia is dissected off the kidney, preserving the perirenal fat in contact with the tumor. Intraoperatively, a flexible laparoscopic color Doppler ultrasound probe can be introduced through a 10- or 12-mm port and positioned in direct contact with the surface of the kidney. Information regarding tumor size, depth of intraparenchymal extension, and distance from the collecting system is obtained. The renal capsule is scored circumferentially with monopolar scissors. Regional hypothermia may be employed with ice slush only when prolonged ischemic times are anticipated (technique below). Bulldog clamps are then inserted. The renal artery, and if necessary the vein, is then clamped in the event that both vessels require clamping. The renal artery is clamped prior to the vein. The tumor is then excised with cold scissors, and the resection is carried deep to the tumor so that an adequate resection margin is achieved. This commonly requires entry into the renal collecting system.

The closure of the renal defect proceeds in two layers. The first layer includes the tumor bed and, if opened, the collected system. A single running suture is used for this deep layer and secured on both ends by Hem-O-Lock clip (Teleflex, Wayne, PA). The second suture layer includes the remaining kidney parenchyma. For this layer we use the sliding-clip technique [16]. A 0 or number 1-polyglactin suture is prepared on the back table by cutting to a length of 15 cm. A knot is tied at the end of the suture, and a Hem-O-Lock clip is placed proximal to the knot so that the clip will not slide off of the suture when pulled tight. The capsular stitches are then placed, after which the assistant places a Hem-O-Lock clip on the loose end, a few centimeters from the capsule. The Hem-O-Lock clip is then slid into place using the needle driver, providing tension that is under complete control of the surgeon. Once the defect is closed, the bulldog clamps are released. The defect can be covered with oxidized cellulose (Surgicel, Ethicon Inc., Somerville, NJ, USA) and/or a fibrin

sealant (Evicel, Ethicon, Inc., or Vitagel, Orthovita, Malvern, PA, USA). Gerota's fascia may be closed by using Hem-o-Lok clips.

The specimen is next removed with the aid of a laparoscopic entrapment sac that is introduced by the assistant. Care must be taken to make the extraction incision large enough to avoid fracturing the specimen, possibly preventing accurate histopathologic examination for margin status and staging. All 12-mm incisions are closed with 0-Vicryl suture by using the Carter-Thomason device (Inlet Medical Inc., Eden Prairie, MN, USA). Finally, a surgical drain may be placed at the discretion for the surgeon. We find a drain is helpful for screening for a urine leak, a complication that is known to occur in 1% to 3% of minimally invasive partial nephrectomies [17, 18].

Retroperitoneal Approach Surgical approach (transperitoneal or retroperitoneal) is determined by surgical goals, patient medical and surgical history, and surgeon experience. In performing the retroperitoneal approach, a major benefit is avoidance of intra-abdominal organs and adhesions. An understanding of the retroperitoneal anatomy is crucial when attempting this surgical approach, since the retroperitoneal space provides fewer landmarks than the intraperitoneal space. This approach can be particularly convenient for perihilar and posterior upper pole tumors. It had been associated with reduction in operative time and hospital stay [19].

With the retroperitoneal approach, the patient is placed in a full flank position (Fig. 8.3). The flank should be directly over the table break. The table is flexed adequately to open the space between the 12th rib and the iliac crest. The retroperitoneum is then balloon dilated (Fig. 8.4), and three 12-mm ports are placed (Fig. 8.5). The renal artery and vein are dissected to facilitate application of laparoscopic bulldog clamps to each vessel. Similar to the transperitoneal approach, the tumor is excised and the renal parenchyma is repaired.

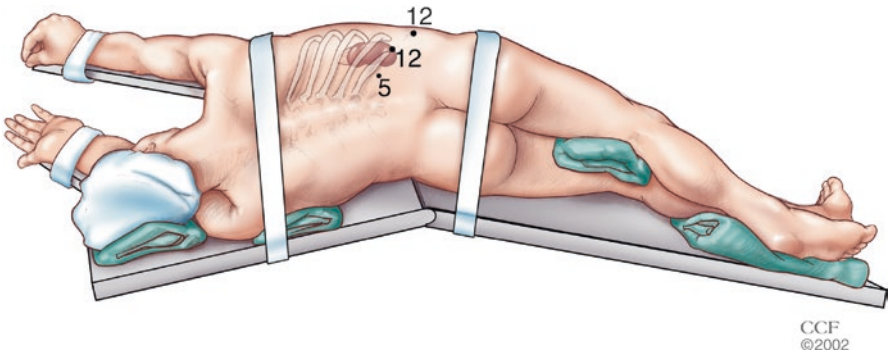

Fig. 8.3 Patient positioning for the retroperitoneal approach to minimally invasive partial nephrectomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

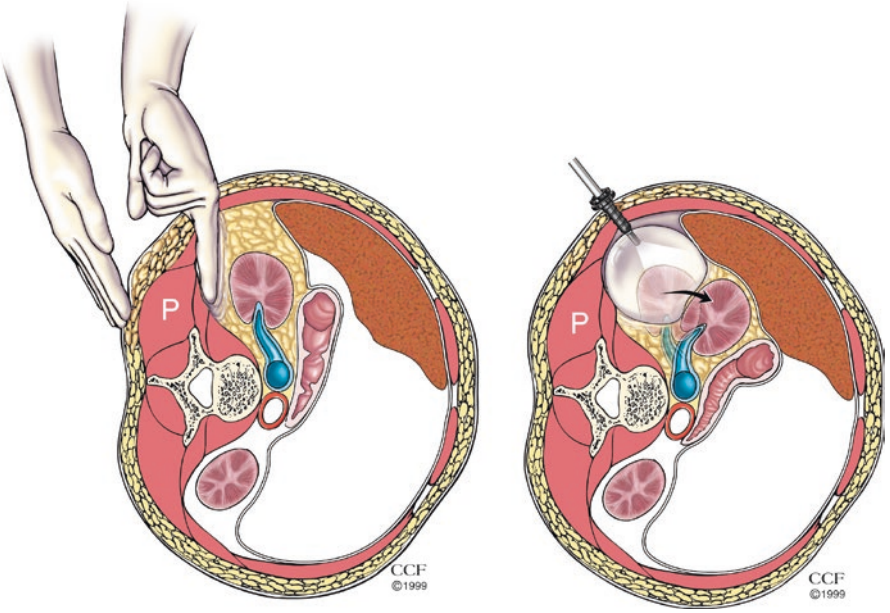

Fig. 8.4 Blunt and balloon dissection of the retroperitoneal space. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

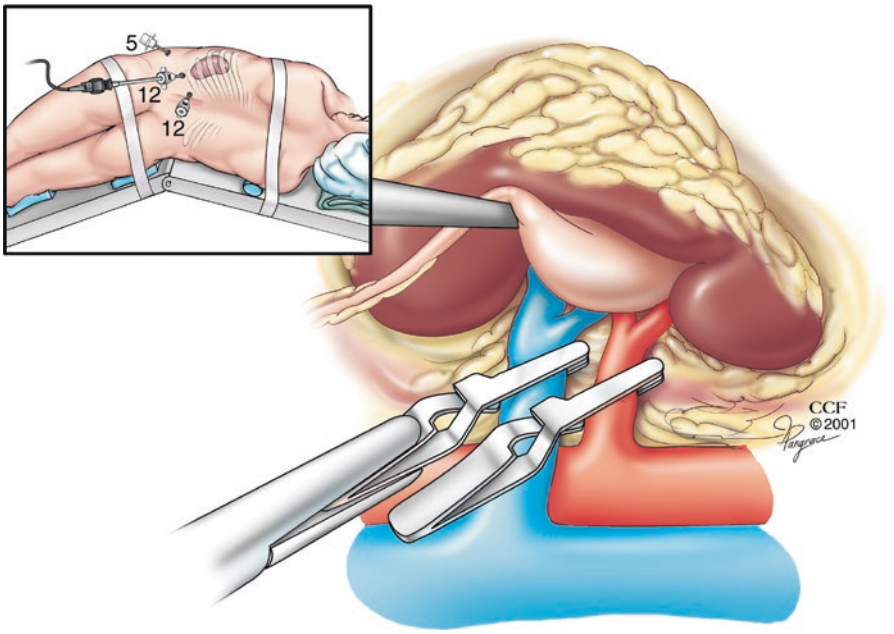

Fig. 8.5 Trocar position and bulldog clamp placement during laparoscopic retroperitoneal partial nephrectomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

Robotic-Assisted Laparoscopic Partial Nephrectomy

Robotic-assisted laparoscopic partial nephrectomy was initially reported by Gettman et al. in 2004 [20]. The robot offers two main advantages over conventional laparoscopy. First, the binocular camera allows for a three-dimensional view of the operating field leading to improved depth perception by the surgeon. Second, the "wrist" of the robotic arms has 7 degrees of freedom, which allows the surgeon improved control over certain aspects of the operation, most importantly precise suturing with minimal tissue manipulation. The technological advantages of robotic-assisted partial nephrectomy over conventional laparoscopy have allowed a shorter learning curve [21–24] and have in turn led to the wider use of partial nephrectomy for the treatment of renal tumors [8]. As with laparoscopy, robotic partial nephrectomy can be performed with either a transperitoneal or retroperitoneal approach. Regardless of surgical approach, the procedure is commonly performed using a three-arm configuration with a 30° down scope, ProGrasp forceps, hot monopolar curved scissors, hook cautery, and large needle drivers.

Concerning differences between surgical platforms (da vinci Si vs Xi from Intuitive Surgical Inc., Sunnyvale, CA, USA), there is no evidence to suggest the superiority of one system over the other. Kallingal et al. were the first to describe their operative technique with the newer Xi system [25]. They found that the procedure with the Xi system could be safely performed with acceptable perioperative and pathologic outcomes. Abdel Raheem et al. compared the Si and Xi surgical platforms [26]. The authors observed shorter docking times with the Xi robot but no differences in terms of significant intraoperative advantage, perioperative complications, or short-term functional outcomes between the two robotic systems. From the oncological and renal function point of view, all tumors were excised successfully with negative surgical margins.

Transperitoneal Approach The patient is positioned in a modified flank position at approximately 60°. Pressure points are carefully padded with pillows and foam pads, and the patient is secured to the table with tape. The surgical table is mildly flexed and positioned in slight Trendelenburg position.

A similar port configuration is used for both right and left sides, as illustrated in Fig. 8.1. The abdomen is insufflated to 15 mmHg with a Veress needle at the lateral border of the rectus muscle across from the 12th rib. This serves later as the site for a 12-mm port through which the robot scope is inserted. An 8-mm robot port is placed at the lateral border of the ipsilateral rectus muscle, about 3 cm below the costal margin. A second 8-mm robot port is placed approximately 5–7 cm cephalad to the anterior superior iliac spine. An assistant 12-mm port is placed along the lateral border of the rectus muscle in the lower abdominal quadrant. On the right side, an additional 5-mm port is placed in the subxiphoid area to retract the liver (Fig. 8.6). Port configuration can vary based on tumor location to optimize the working angles. For upper pole tumors, all the ports can be shifted 1–2 cm cephalad. Moreover, an extra 5-mm assistant port between the camera and the right robot port can be placed to allow the assistant better access to the operative field. For posterior tumors, all the ports can be shifted medially, as the kidney needs to be mobilized to allow access to its posterior aspect. The robot is positioned over the patient's shoulder so that its

axis makes an obtuse angle in relation to the patient's axis to have the camera oriented in line with the kidney (Fig. 8.7). The bedside assistant stands next to the abdomen.

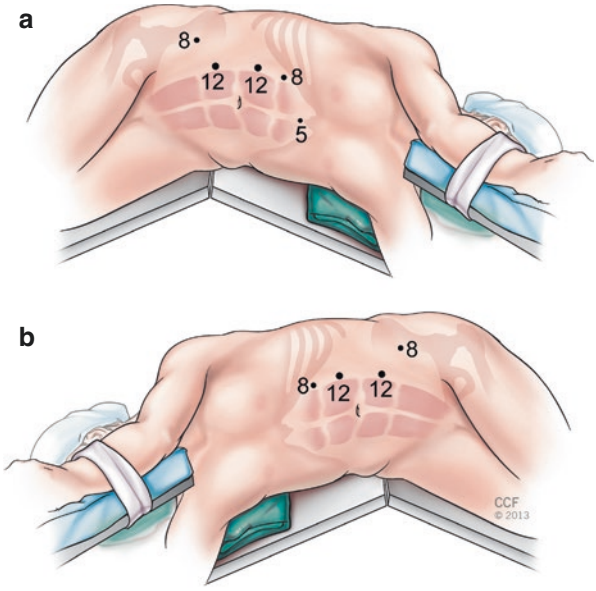

Fig. 8.6 Port configuration used during robot-assisted laparoscopic partial nephrectomy. (**a**) Right-side port placement. (**b**) Left-side port placement. 12-mm port for the robotic scope, 8-mm ports for the robotic instruments, 12-mm port for the assistant, and 5-mm port for liver retraction. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

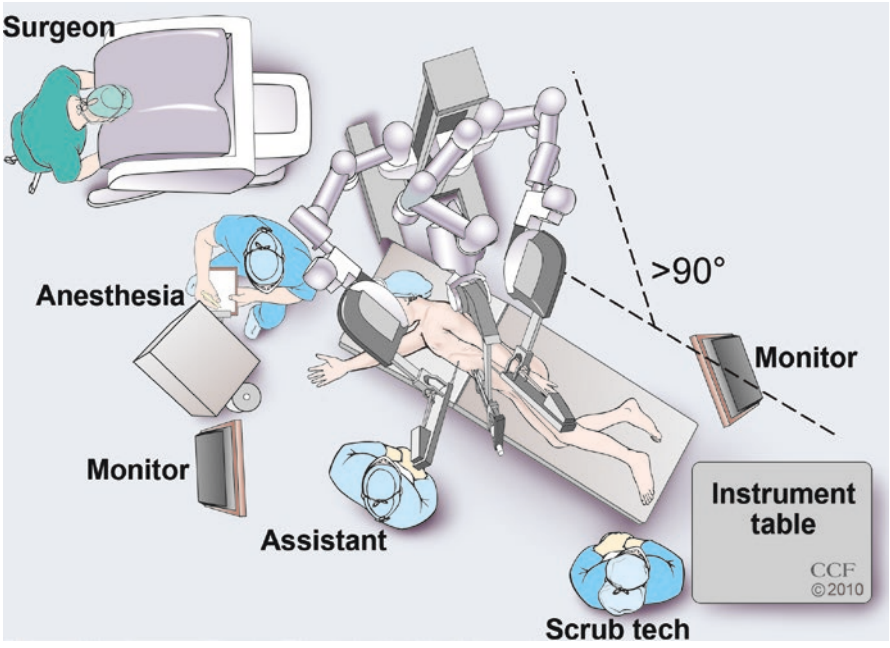

Fig. 8.7 Operating room setup and robot docking for transperitoneal partial nephrectomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

On the right side, liver retraction is achieved by introducing a locking Allis clamp through the 5-mm subxiphoid port. With a monopolar curved scissors in the surgeons' right hand and a ProGrasp forceps in the left hand, the peritoneum is sharply incised along with the white line of Toldt. The bowel is mobilized medially, developing a plane anterior to Gerota's fascia and posterior to the mesocolon by using both sharp and blunt dissection. Attachments to the spleen or liver are released as necessary. It is important to remain outside Gerota's fascia during bowel mobilization. On the right side, there is no need for extensive mobilization of the bowel to expose the renal hilum. During the mobilization of the duodenum medially, the use of cautery is minimized. The gonadal vein is an important anatomic landmark when proceeding toward the renal hilum. On the right side, the gonadal vein is kept medially toward the vena cava, whereas on the left side, the gonadal vein is lifted along with the left ureter to expose the lower margin of the left renal hilum.

Dissection proceeds along the psoas muscle with anterior elevation of the ureter and/or gonadal vein to identify the renal hilum (Fig. 8.8). The renal vein can be identified by tracing the gonadal vein proximally to its insertion in the renal vein on the left side or to its insertion in the inferior vena cava just caudal to the hilum on the right side. A flexible robotic Doppler probe (Vascular Technology Inc., Nashua, NH, USA) can be used to identify hilar vessels before clamping, especially in cases involving

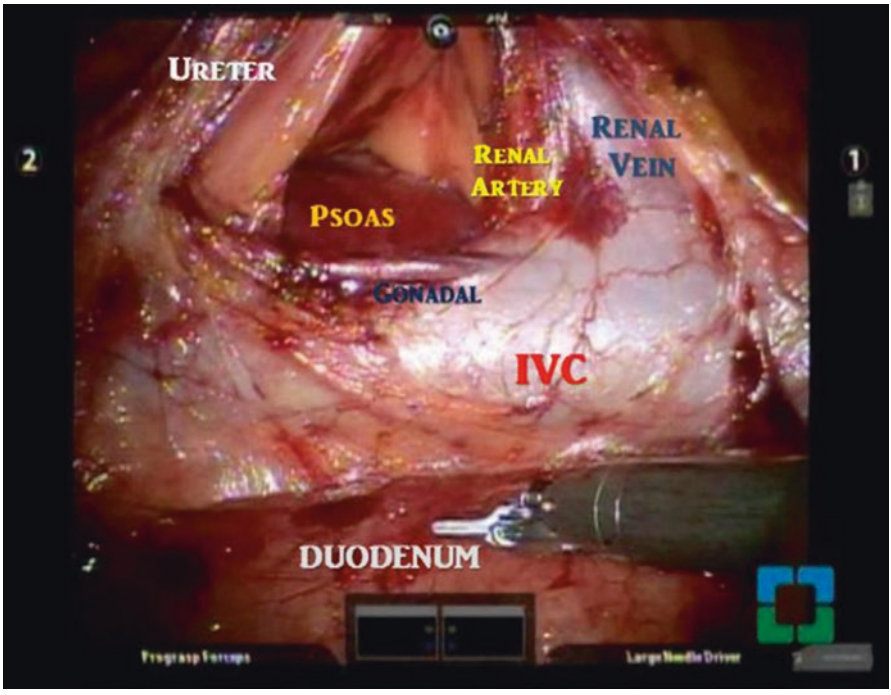

Fig. 8.8 Surgical landmarks during transperitoneal robot-assisted partial nephrectomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

multiple renal arteries or early branching. The main hilar vessels are circumferentially dissected to allow adequate placement of bulldog clamps. It is important not to miss early arterial branching that is more common on the right side, especially if occlusion of the renal vein is planned, as this may lead to kidney congestion and may result in more bleeding. Once the main landmarks are identified, manipulation of the ureter should be avoided to minimize risk of injury or devascularization. If an early branching or bifurcation is suggested by the CT scan, the dissection should be carried medially. While dissecting the hilum, the assistant can provide countertraction by using suction. In our experience, we have found the hook cautery to be particularly useful at this step of the operation and can be used according to the surgeon's preference.

Once the hilum is dissected, Gerota's fascia is opened in an area far from the tumor to find the capsule, and dissection is performed along the renal capsule until the mass is exposed. A clue that one is approaching the tumor area is the presence of adhesions. The fat is then cleared circumferentially around the mass, allowing for visualization of 1–2 cm of normal parenchyma for future renal reconstruction. Gerota's fascia atop the mass should be preserved to assist in histopathologic staging and also to use as a handle for retraction. A laparoscopic ultrasound probe is used to plan the excision margins by allowing accurate identification of the location, depth, and borders of the tumor (Fig. 8.9). A recently introduced, drop-in, flexible, ultrasound probe (ProART

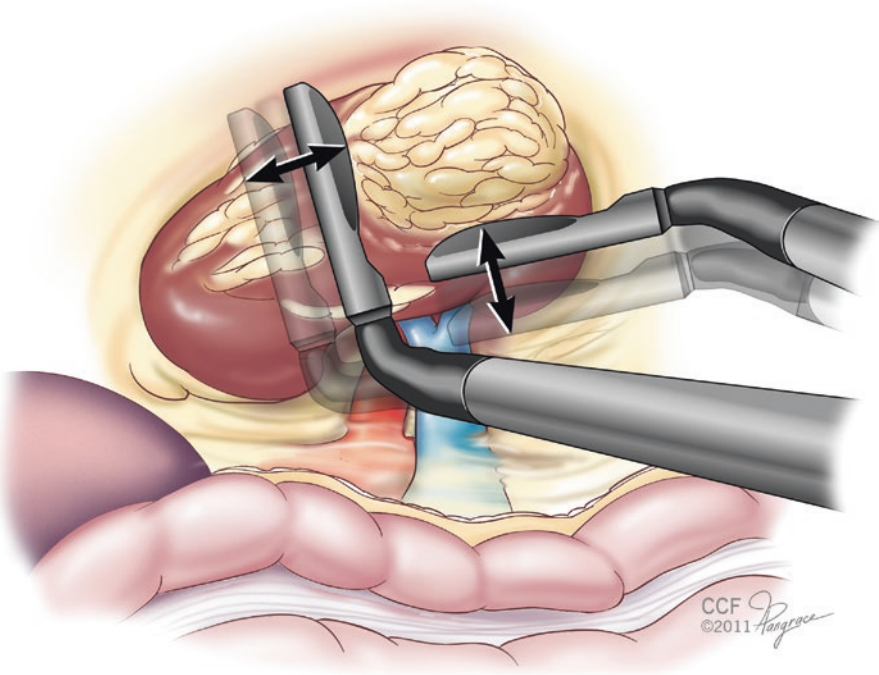

Fig. 8.9 Flexible ultrasound probe being used during robotic partial nephrectomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

Robotic Drop-In Transducer 8826; BK Medical, Peabody, MA, USA) was specifically developed for robotic surgery and can be directly controlled by the console surgeon by grasping a notch on its ventral aspect. Live intraoperative images are shown as a picture on picture display on the console screen using the TilePro functionality of the da vinci surgical system. To define the border of the tumor, the ultrasound probe is oriented parallel to the tumor border. Margins of resection of the renal capsule are scored with cautery to delineate the resection boundaries.

Renal vasculature clamping is achieved using bulldog clamps. In selected cases, resection may be performed by clamping the renal artery only. Recently, robotic bulldog clamps (Scanlan International, St. Paul, MN, USA), applied by the console surgeon using the robotic ProGrasp, have also become available. As with the laparoscopic approach, the renal hilum is clamped and the tumor resected along the previously scored margin using cold scissors (Fig. 8.10). The bedside assistant can use suction to clear the resection bed, enabling improved visualization while applying slight counter retraction, as needed.

Renorrhaphy is performed in two layers with robotic needle drivers and the sliding-clip technique [16]. A 20-cm 2-0 Vicryl suture on an SH-1 needle (Ethicon Endo-Surgery, Somerville, NJ, USA) with a knot and Hem-o-Lok clip applied to the free end is used as a running suture of the tumor excision bed to oversew larger vessels and entries into the collecting system. The suture is brought through the renal capsule with the final throw and secured with two sliding Hem-o-Lok clips. The renal capsule is reapproximated using a continuous, horizontal mattress 0-Vicryl suture on a CT-1 needle with a sliding Hem-o-Lok clip placed after each suture is passed through the capsule (Fig. 8.11). After completion of the renorrhaphy, the hilum is unclamped, and the resection bed is inspected for hemostasis with pneumoperitoneum pressure lowered to 6 mm Hg. Hem-o-Lok clips may be cinched down further to secure hemostasis. Whenever possible, the hilum is unclamped before capsular suturing in an early unclamping technique to minimize warm ischemia time. Further steps for specimen retrieval, Gerota's fascia approximation, Jackson-Pratt placement, and incision closure are similar to the techniques described in the laparoscopic section above.

Retroperitoneal Approach The patient is placed in the full flank position and the table fully flexed to increase the space between the 12th rib and iliac crest. Low-profile supports, e.g., rolled blankets, are preferred to bulky padding to avoid clashing with the robotic arms. The spine and hip must be positioned in a straight line and the spine fully exposed to allow space for placement of the lateral robotic arm. The dependent arm is padded and secured to an arm board, which is tilted toward the head as much as possible. After positioning, the table is rotated, so that the patient side-cart can be docked straight over the patient's head. The patient is then draped and the bed-side assistant stands beside the abdomen.

A 12- to 15-mm length incision for the camera port is made in the midaxillary line, 2 cm above the iliac crest. The external oblique muscles are separated using retractors to expose the lumbodorsal fascia. Access to the retroperitoneum is gained by perforating the dorsal lumbar fascia. Blunt finger dissection is useful to create

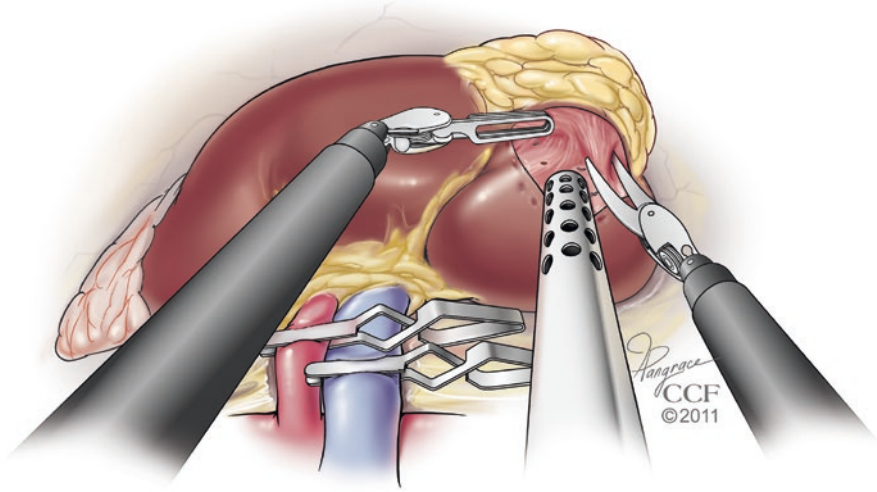

Fig. 8.10 Resection of the tumor during robotic partial nephrectomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

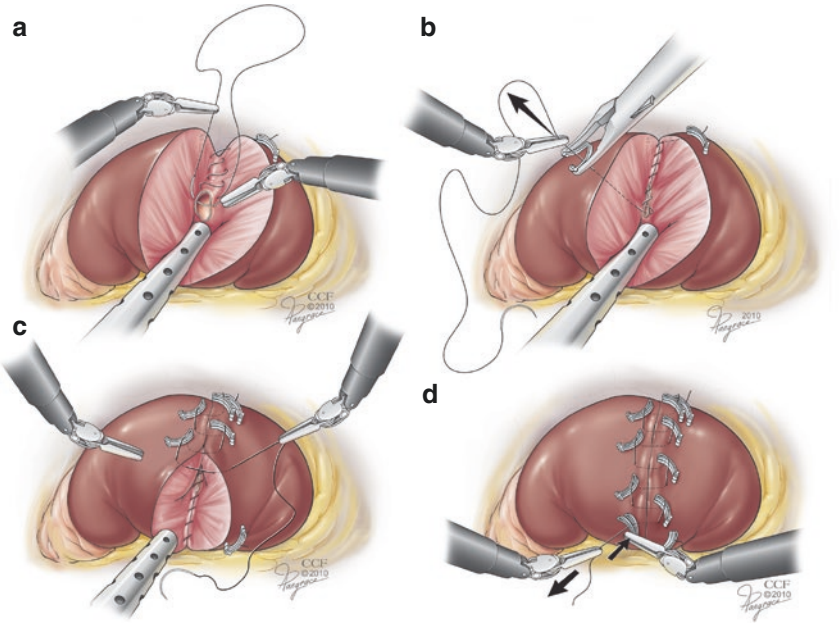

Fig. 8.11 Renorrhaphy following tumor excision during robotic partial nephrectomy. The reconstruction is performed in two layers using the sliding-clip technique. **a**) 2-0 Vicryl 6-inches suture on a SH-1 needle with a knot and Hem-o-Lok clip applied to the free end is used as a running suture to oversew the collecting system as well larger vessels from the tumor excision bed; **b**) sutures are brought through the renal capsule with the final throw and secured with two sliding Hem-o-Lok clips; **c** and **d**) a continuos horizontal mattreess is used for reapproximation the renal capsule with a 0-Vicryl suture on a CT-1 needle and a sliding Hem-o-Lok clip placed after each suture is passed through the capsule. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

the working space anterior to the psoas. Caution is taken to avoid entry to the peritoneal cavity. The operative space in the retroperitoneum is then developed with a balloon dilator (Fig. 8.4). By generating this space, intraperitoneal structures such as liver, spleen, and colon are deflected medially. The camera is then placed to inspect the retroperitoneal space. Two 8-mm incisions for the robotic working arms are made medial (along the lateral border of the paraspinous muscle) and lateral (inferior to the 11th rib), to the camera port. In case of obese patients, ports need to be shifted laterally and cephalad. The assistant 12-mm trocar is placed inferior and medially to the anterior robotic port and should be no closer than 6 cm to avoid conflict with the anterior robotic arm (Fig. 8.12). The robot is docked directly over the patient's head parallel to the spine.

The first step in exposing the kidney is the management of paranephric fat. This fat is carefully dissected off of Gerota's fascia and placed in the lower retroperitoneum. Care is taken medially and anteriorly where the peritoneum can be easily entered. Great attention must be taken to identify the peritoneal reflection anteriorly to avoid blind trocar passage into the peritoneal cavity. Next, Gerota's fascia is incised just above the psoas muscle exposing the perinephric fat and kidney. Dissection is then carried along the psoas muscle elevating the kidney and perinephric fat. The ureter is typically encountered first medial to the incision in Gerota's

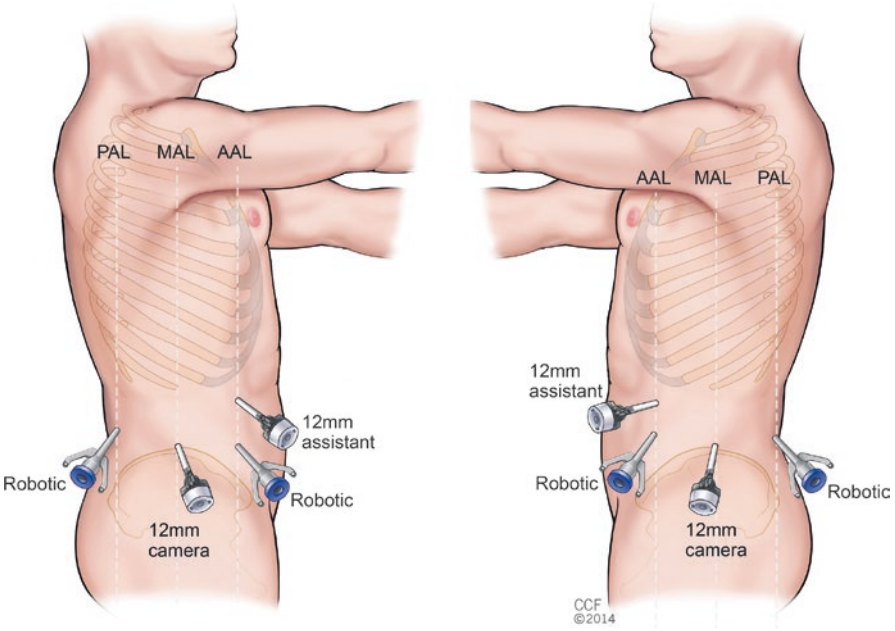

Fig. 8.12 Positioning and trocar placement for retroperitoneal robotic partial nephrectomy. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

fascia and then followed up toward the hilum. The renal artery is typically encountered first, unlike the transperitoneal approach.

Next, the renal artery is exposed to allow a bulldog clamp on the artery. The renal vein is rarely clamped and only if the tumor is large or centrally located. A 5-mm margin is then scored circumferentially around the tumor. The tumor is excised under warm ischemic conditions, and judicious suctioning is used to maintain a clear operative field allowing the identification of tumor if encountered. Aggressive suctioning in the retroperitoneal space can lead to rapid desufflation and should be avoided. The renal defect is reconstructed in two layers as described above.

Modifications to Robotic Partial Nephrectomy

Robotic Partial Nephrectomy with Intracorporeal Renal Hypothermia There is general consensus in the literature that when performing a partial nephrectomy, warm ischemia time should be limited to 20–25 min [27, 28]. When a longer ischemia time is expected, the use of renal cooling is encouraged as it is known to improve renal tolerance for ischemia up to 45 min [29]. It has been shown that cold ischemia decreases oxidative harm to the kidney secondary to direct hypoxia and subsequent reperfusion [30–32]. During open surgery, ice slush cooling is routinely used. However, renal cooling during minimally invasive partial nephrectomy is more challenging. Different techniques such as endoscopic retrograde ureteric cooling [33], arterial infusion [34], and cooling via renal surface irrigation [35] have been described. The use of intracorporeal ice slush to obtain renal hypothermia during robotic partial nephrectomy was first described by Rogers and colleague with direct instillation of ice slush onto the surface of the kidney [36]. Thereafter, Kaouk and coworkers described a simplified modification of that technique that will be detailed below [37, 38].

Patient positioning, port placement, and docking of the robot are similar to the previously described technique for transperitoneal partial nephrectomy. An additional 12-mm laparoscopic port is placed along the midaxillary line and the costal margin. This port is used for introduction of the temperature probe and ice slush during cooling phase of the procedure.

Sterile ice slush is created in an ice slush machine (Hush Slush System; Ecolab Inc., St. Paul, MN) and constantly stirred manually to keep ice consistency uniform. Five 20- or 30-mL syringes are modified by cutting off the nozzle ends of the barrels with a scalpel. The rubber on the ends of the plungers are also removed. The modified syringes are then prefilled with ice slush in preparation for instillation. A lateral 12-mm accessory port is placed directly above the kidney. The port is removed, and the needle temperature thermocouple (Mon-a-Therm; Covidien, Mansfield, MA) is introduced via the port site using a laparoscopic grasper and placed in the renal parenchyma away from area of planned excision. The 12-mm accessory port is reintroduced alongside the thermocouple wire following the positioning of the

thermocouple. Renal and core body temperatures (via esophageal probe) are monitored during the procedure. A 4- × 18-cm laparoscopic sponge is then placed surrounding the kidney, creating a barrier between the kidneys and neighboring bowel. The mobilized kidney is overturned medially, and ice slush is introduced through the 12-mm port posterior to the kidney and packed on top of the psoas muscle and on the renal parenchyma (Fig. 8.13). The kidney is allowed to cool for several minutes before clamping the renal hilum. The hilum is clamped with bulldog clamps placed on the renal artery and vein sequentially. More ice slush is introduced, and the kidney is allowed to cool further, until parenchymal temperatures are <20 °C. Of note, it is imperative to clamp both the artery and the vein to achieve renal parenchymal cooling (Fig. 8.14).

Using a suction or irrigation device, ice slush is then cleared from the renal tumor and surrounding renal capsule. The tumor is then resected along the previously scored margin using cold scissors. Renorrhaphy is performed as previously described. The renal parenchymal temperature is monitored in real time, and further ice slush is introduced as needed to keep kidney temperature under 20 °C and to provide a constant coverage of ice over the kidney beyond area of resection. The

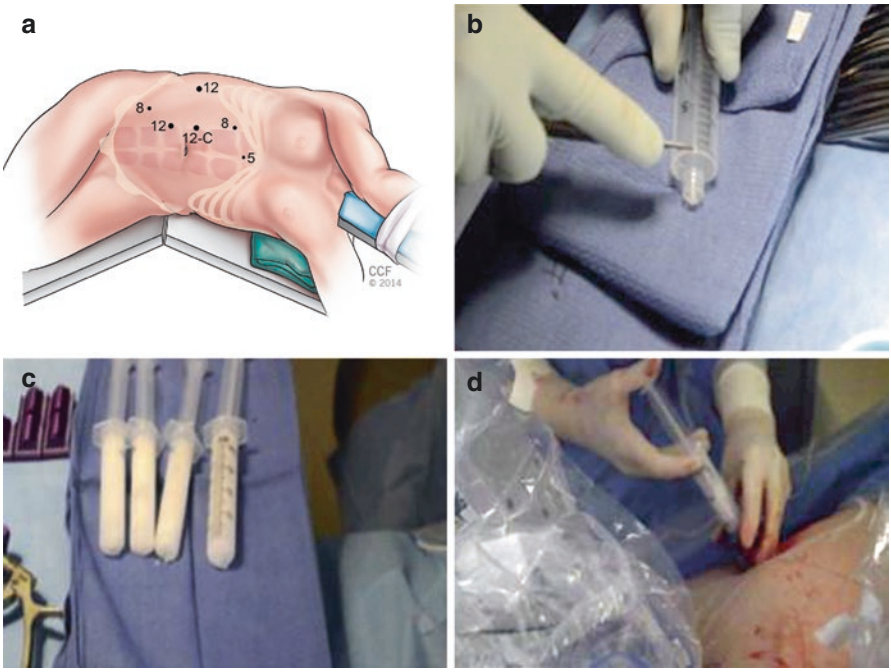

Fig. 8.13 (**a**) Patient positioning and port placement for intracorporeal hypothermia during minimally invasive partial nephrectomy. (**b**) A 20- or 30-mL syringe is modified by cutting off the nozzle end of the barrel with scalpel. (**c**) The modified syringes are then prefilled with ice slush in preparation for instillation. (**d**) The ice is instilled through the accessory 12-mm port. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

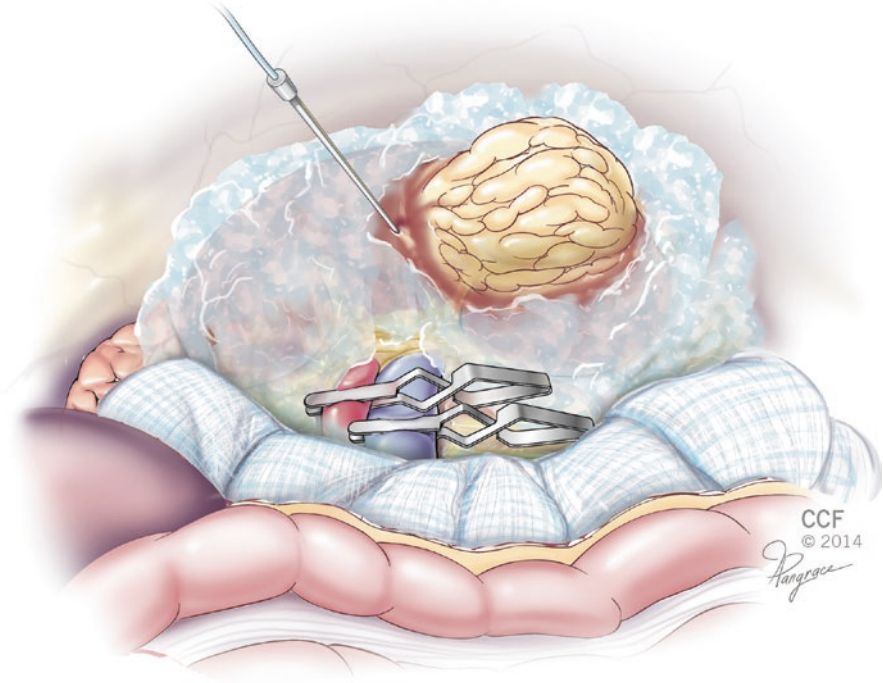

Fig. 8.14 Illustration of a kidney following placement of ice slush just prior to tumor resection. A thermocouple is used to measure the temperature of the renal parenchyma. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

hilum is unclamped and the renorrhaphy is inspected for hemostasis. Any additional remaining ice can be removed by suction or by transfer into the entrapment sac. A Jackson-Pratt drain is placed through a lower lateral port to also aid with the evacuation of melted ice slush.

Fluorescence Image-Guided Robotic Surgery Robotic surgery utilizing near-infrared fluorescence imaging is a technology with emerging applications in urologic surgery [39]. During partial nephrectomy this technology has the potential to enhance discrimination between normal renal parenchyma and tumor allowing for a more accurate dissection. Furthermore, this technology has the potential to aid in the visualization of the renal vasculature allowing for selective arterial clamping [40].

Injected indocyanine green (ICG, Akorn, Lake Forest, IL) is a fluorescent tricarbocyanine dye that emits light in the near-infrared wavelength (700–850 nm) after activation by a light-emitting diode [41]. ICG binds to albumin when intravenously injected and therefore remains primarily in the vasculature. The light emitted is not visible to the human eye and requires use of a charge-coupled device camera which has been integrated into the da vinci surgical system. Using what is known as the

Firefly imaging system, the surgeon can switch between standard (white) light and fluorescence-enhanced views in real time [42].

ICG is diluted to a 2.5-mg/mL solution immediately before each case and administered in discrete boluses intravenously by the anesthesia team as directed by the surgeon. After scoring of the parenchyma surrounding the tumor, ICG is administered at a dose of 5–10 mg intravenously. The maximum dosage is 2 mg/kg, and it must be given within 6 h of reconstitution. The intravenous injection is given immediately before clamping the renal artery. The initial pass of the dye is seen as fluorescence of the artery and then the renal vein, followed by the renal parenchyma. The tumor generally has a lower level of fluorescence than the normal surrounding kidney tissue. Tumor excision is started along the prescored area on the kidney surface and deepened down into the renal parenchyma. The console view can be switched between the standard white light vision and near-infrared vision at the discretion of the operating surgeon to confirm the plane of excision between tumor and parenchyma to avoid entry into the tumor [43].

Near-infrared fluorescence imaging with ICG can also be used to facilitate selective arterial clamping. In this setting, local ischemia to the tumor and immediate surrounding renal segment is induced by applying mini-bulldog clamps (Scanlan International, St. Paul, MN, USA) to secondary-, tertiary-, or quaternary-level arterial branches. Well-perfused renal parenchyma appears fluorescent green under near-infrared fluorescence imaging. Ischemic tissue will not fluoresce, verifying the correct arterial branch has been controlled. If peritumoral arterial flow continues despite selective arterial clamping, either additional arterial branches may be sought and selectively clamped or complete arterial clamping may be utilized.

Robotic Laparoendoscopic Single-Site Partial Nephrectomy Laparoendoscopic single-site surgery (LESS) has been developed to further minimize the morbidity associated with multiport minimally invasive surgery. The single-site approach to LESS surgery requires only one entry point to the body. By reducing the number and length of skin and fascial incisions, it is hypothesized that patients will experience less pain, faster convalescence, and improved cosmesis following surgery [44–47]. In recent years, the advantages offered by robotic technology have been combined with those of LESS (Fig. 8.15). The majority of surgical steps for preforming partial nephrectomy with robotic LESS are similar to what has been described earlier. However, several modifications are required in order to accommodate the limited available working space of LESS.

Subtle differences exist when comparing traditional robotic docking with docking used for robotic LESS procedures. In regard to the robotic platform, the da vinci Si or Xi models are preferred over the S model secondary to enhanced visualization, improved ergonomic control at the surgeon console, and, most importantly, a more-compact, sleeker bedside profile which assists with minimizing external clashing of the robotic arms [48, 49]. For robotic LESS procedures, typically only two robotic instrument arms are used due to limited working space.

A number of technical modifications have been described in order to minimize external clashing of instrument arms during LESS. For example, the “chopstick”

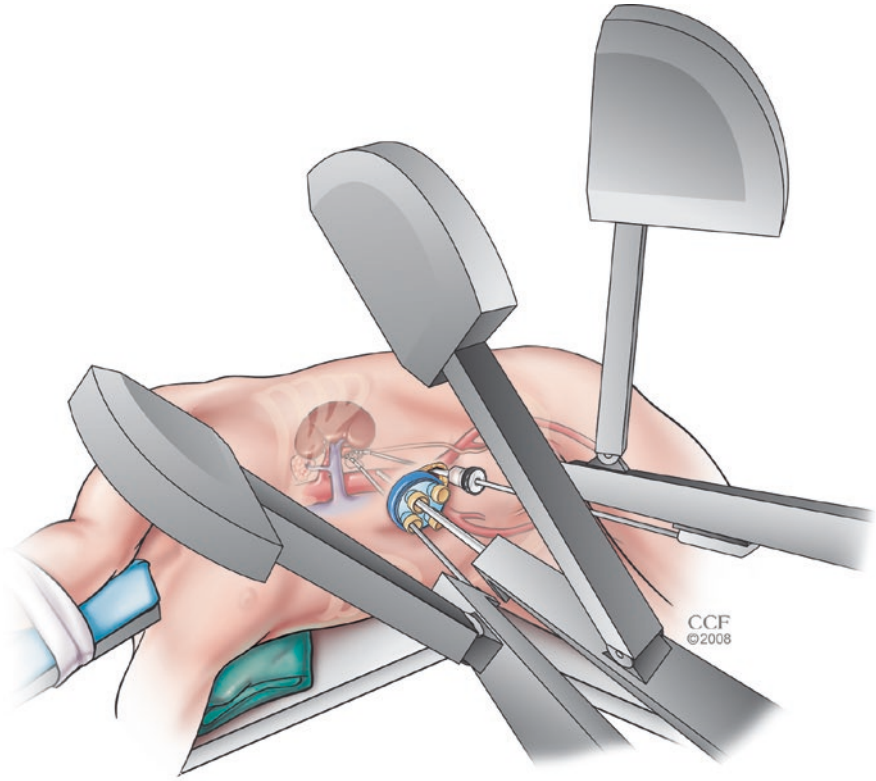

Fig. 8.15 Robotic laparoendoscopic single-site surgery. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

technique popularized by Joseph et al. minimizes external instrument clashing by crossing the instruments at the level of the fascia in order to create more space between the robotic arms outside of the body [50]. This technique was previously employed during traditional LESS but has proven to be very challenging secondary to the crossing of instruments resulting in "reverse handedness." This benefit of using the robotic platform is that the robotic instruments are controlled electronically, allowing the left and right hand joystick hand effectors to be interchanged, thus removing this challenge (Fig. 8.16).

In addition to these technical modifications, a variety of multichannel access ports have been described for use during robotic LESS [51]. Additionally, an innovative device precisely designed for robotic LESS has been developed by da vinci surgical, known as the SP999 single-port system [52]. This system uses the same base of the patient side cart as the da vinci Xi robotic system and has been adopted for use with a single arm that controls an articulating endoscopic camera and three double-jointed articulating endoscopic instruments which enter the patient through a multichannel robotic port (25-mm cannula) (Fig. 8.17).

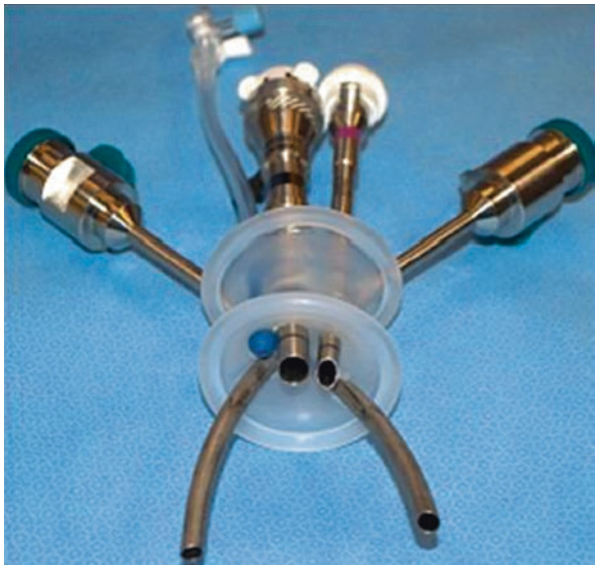

Fig. 8.16 da vinci curved cannula system for robotic laparoendoscopic single-site surgery. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

A newer da vinci single-port surgical system has recently been developed (SP1098) and includes upgraded technology designed specifically for extraperitoneal single-site surgery [53–56]. Similar to the SP999, the SP1098 consists of three main components: a surgeon console, a patient side cart, and a vision cart. As before, four robotic manipulators, or instrument drives, that control the camera and instruments are mounted on an instrument arm that is attached to the patient side cart. The surgeon console is identical to the second-generation robotic system (SP999) with a foot pedal that allows control of the instrument arm. Unique to this robotic system is the ability to clutch and pivot the instrument arm about its remote center without moving each individual instrument. In effect, an instrument can be stationed at one location in the surgical field (e.g., for retraction), while the instrument arm is clutched and reoriented to a separate site, where the remaining instruments can be deployed without disturbing the stationary instrument. This improvement overcomes the constraint of multiple instruments entering the body through a fixed point, effectively expanding the workspace and improving maneuverability. The new vision cart is similar to the previous generation with upgraded resolution to accommodate the improved camera optics (Fig. 8.18).

These new single-port robotic technologies represent a step forward in minimally invasive surgery. It is unique as it allows for intracorporeal triangulation while eliminating instrument clashing seen with other methods of performing single-site surgery.

Because of space limitations and the size of the robot at the patient side, the standard approach to robotic kidney and adrenal surgery has been transperitoneal. However, posteriorly located kidney tumors are sometimes difficult to approach transperitoneally and require the kidney to be completely mobilized and flipped medially. The retroperitoneal approach has emerged as an alternative to

Fig. 8.17 The da vinci SP999 single-port platform. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

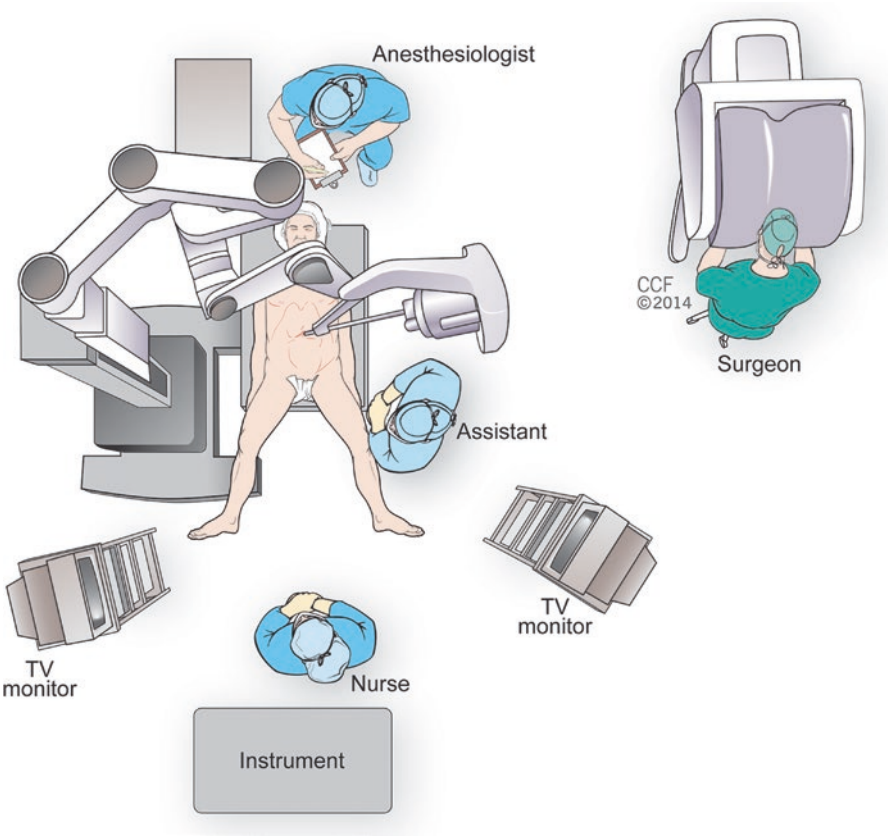

Fig. 8.18 Operating room setup and robot docking for laparoendoscopic single-site renal surgery. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

transabdominal robotic adrenal and kidney surgery for posterior tumors. With the SP1098 system, approaching posterior and anterior tumors is feasible using a retroperitoneal access [56].

For transperitoneal renal surgery using the da vinci single-port system, the patient is positioned in a modified flank position at approximately 60°. A transumbilical incision or pararectal incision is made to allow the insertion of the 2.5-cm robotic port (Fig. 8.19). One 12-mm assistant port is placed through the same skin incision alongside the single robotic port.

For the retroperitoneal approach, the patient is placed in the full flank position and the table fully flexed to increase the space between the 12th rib and iliac crest. The port is placed at any point between the anterior axillary line and the paraspinous muscle (according to the location of the tumor, anterior or posterior), 2 cm above the iliac crest. The dissection and exposure are also the same for standard robotic partial nephrectomy.

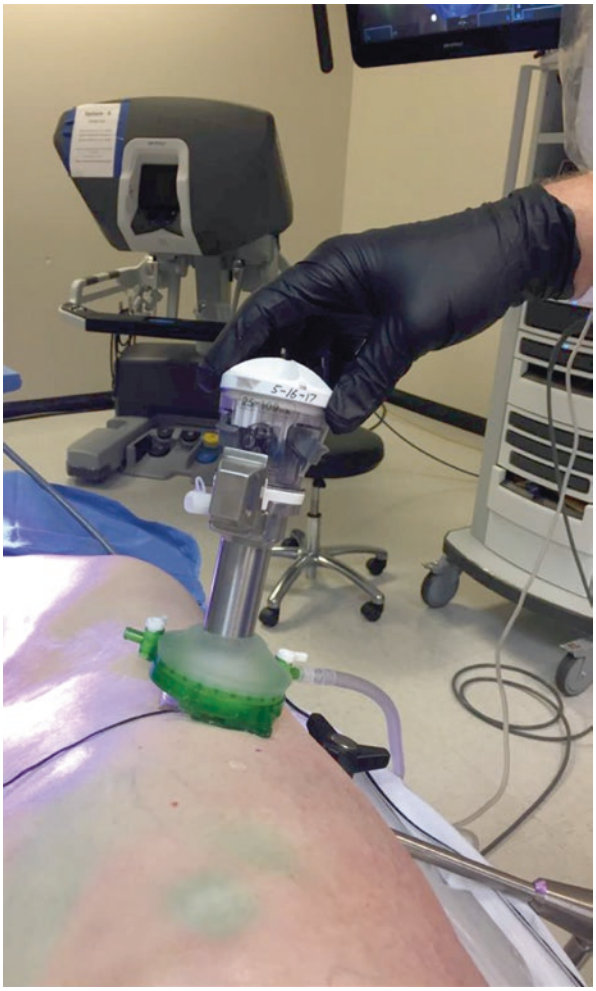

Fig. 8.19 The da vinci SP1098 single-port cannula. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 1999–2018. All Rights Reserved)

Conclusion

With the advancement of new technologies, the surgical management of small renal masses has dramatically changed over the last several decades. Minimally invasive partial nephrectomy is now the standard of care and is most commonly performed using a robotic approach. Recent technological advancements aim to further improve visualization, decrease the impact of renal surgery on kidney function, and minimize the size and number of surgical incisions. There is no doubt that in the coming years, technical advancements will continue to improve the care and outcomes of patients presenting with a renal mass in need of surgical extirpation.

References

1. Ljunberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma. Eur Urol. 2015;67(5):913–24.
2. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA guideline. J Urol. 2017;198(3):520–9.
3. Mir MC, Ercole C, Takagi C, Zhang Z, Velet L, Remer EM, et al. Decline in renal function after partial nephrectomy: etiology and prevention. J Urol. 2015;193(6):1889–98.
4. Mir MC, Campbell RA, Sharma N, Remer EM, Simmon MN, Li J, et al. Parenchymal volume preservation and ischemia during partial nephrectomy: functional and volumetric analysis. Urology. 2013;82:263.
5. Simmons MN, Hillyer SP, Lee BH, Fergany AF, Kaouk J, Campbell S. Functional recovery after partial nephrectomy: effects of volume loss and ischemic injury. J Urol. 2012;187:1667.
6. Herr HW. A history of partial nephrectomy for renal tumros. J Urol. 2005;173(3):705–8.
7. Herr HW. Surgical management of renal tumors: a historical perspective. Urol Clin North Am. 2008;35(4):543–9.
8. Patel SG, Penson DF, Pabla B, Clark PE, Cookson MS, Chang SS, et al. National trends in the use of partial nephrectomy: a rising tide that has not lifted all boats. J Urol. 2012;187(3):816–21.
9. Peyronnet B, Selsen T, Oger E, Vaessen C, Grassano Y, Benoit T, et al. Comparison of 1800 robotic and open partial nephrectomies for renal tumors. Ann Surg Oncol. 2016;23(13):4277–83.
10. Wang Y, Shao J, Ma X, Du Q, Gong H, Zhang X. Robotic and open partial nephrectomy for complex renal tumors: a matched-pair comparison with a long-term follow up. World J Urol. 2017;35(1):72–80.
11. Boy A, Hein J, Bollow M, Lazica D, Roosen A, Ubrig B. Minimally invasive vs open partial nephrectomy: perioperative success and complications rates. Urologe A. 2018. https://doi.org/10.1007/S00120-018-0646.
12. Malkoc E, Ramirez D, Kara O, Maurice MJ, Nelson RJ, Caputo PA, et al. Robotic and open partial nephrectomy for localized renal tumors larger than 7cm: a single center experience. World J Urol. 2017;35(5):781–7.
13. Kara O, Maurice MJ, Malkoc E, Ramirez D, Nelson RJ, Caputo PA, et al. Comparison of robot-assisted and open partial nephrectomy for completely endophytic renal tumours: a single centre experience. BJU Int. 2016;118(6):946–51.
14. Clayman RV, Kavoussi LR, Soper NJ, et al. Laparoscopic nephrectomy: initial case report. J Urol. 1991;146:278.
15. Jordan GH, Winslow BH. Laparoendoscopic upper pole partial nephrectomy with ureterectomy. J Urol. 1993;150(3):940–3.
16. Benway RM, Wang AJ, Cabello JM, Bhayani SB. Robotic partial nephrectomy with sliding-clip renorrhaphy: techniques and outcomes. Eur Urol. 2009;55(3):592–9.
17. Spana G, Haber GP, Dulabon LM, Petros F, et al. Complications after robotic partial nephrectomy at centers of excellence: multi-institutional analysis of 450 cases. J Urol. 2011;186(2):417–21.
18. Wheat JC, Roberts WW, Hollenbeck, et al. Complications of laparoscopic partial nephrectomy. Urol Oncol. 2013;31(1):57–62.
19. Pavan N, Derweesh IH, Hamplton L, White W, Porter JR, Challacombe B, et al. Retroperitoneal robotic partial nephrectomy: systematic review and cumulative analysis of comparative outcomes. J Endourol. 2018. https://doi.org/10.1089/en.d2018.0211.
20. Gettman MT, Blute ML, Chow GK, Neururer R, Bartsch G, Peschel R. Robotiic-assisted laparoscopic partial nephrectomy: technique and initial experience with DaVinci robotic system. Urology. 2004;64(5):914–8.
21. Mottrie A, De Naeyer G, Schatteman P, Carpentier P, Sangalli M, Ficarra V. Impact of the learning curve on perioperative outcomes in patients who underwent robotic partial nephrectomy for parenchymal renal tumours. Eur Urol. 2010;58(1):127–32.

22. Ficarra V, Bhayani S, Porter J, Buffi N, Lee R, Cestari A, Mottrie A. Predictors of warm ischemia time and perioperative complications in a multicenter, international series of robot-assisted partial nephrectomy. Eur Urol. 2012;61(2):395–402.
23. Krane LS, Manny TB, Mufarrij PW, et al. Does experience creating a robot-assisted partial nephrectomy (RAPN) programme in an academic entre impact outcomes or complication rate? BJU Int. 2013;112:207.
24. Lavery HJ, Small AC, Samadi DB, Palese MA. Transition from laparoscopic to robotic partial nephrectomy: the learning curve for an experienced laparoscopic surgeon. JSLS. 2011;15:291–7.
25. Kallingal G, Swain S, Darwiche F, Punnen S, Manoharan M, Gonzalgo ML, Parekh DJ. Robotic partial nephrectomy with the da Vinci Xi. Adv Urol. 2016;2016:9675095. https://doi.org/10.1155/2016/9675095.
26. Abdel Raheem A, Sheikh A, Kim DK, Alatawi A, Alabdulaali I, Han WK, Choi YD, Rha KH. Da Vinci Xi and Si platforms have equivalent perioperative outcomes during robot-assisted partial nephrectomy: preliminary experience. J Robot Surg. 2017;11(1):53–61.
27. Volpe A, Blute ML, Ficarra V, Gill IS, Kutikov A, Porpiglia F, et al. Renal ischemia and function after partial nephrectomy: a collaborative review of the literature. Eur Urol. 2015;68(1):61–74.
28. Porpiglia F, Fiori C, Bertolo R, Angusti T, Piccoli GB, Podio V, et al. The effects of warm ischaemia time on renal function after laparoscopic partial nephrectomy in patients with normal contralateral kidney. World J Urol. 2012;30(2):257–63.
29. Russo P. Partial nephrectomy for renal cancer (part II): the impact of renal ischaemia, patient preparation, surgical approaches, management of complications and utilization. BJU Int. 2010;105(11):1494–507.
30. Becker F, Van Poppel H, Hakenberg OW, et al. Assessing the impact of ischemia time during partial nephrectomy. Eur Urol. 2009;56:624–35.
31. Simmons MN, Liser GC, Fergany AF, et al. Association between warm ischemia time and renal parenchymal atrophy after partial nephrectomy. J Urol. 2013;189:1638–42.
32. Stubenitsky BM, Ametani M, Danielewicz R, et al. Regeneration of ATP in kidney slices after warm ischemia and hypothermic preservation. Transpl Int. 1995;8:293–7.
33. Saitz TR, Dorsey PJ, Colli J, Lee BR. Induction of cold ischemia in patients with solitary kidney using retrograde intrarenal cooling: 2-year functional outcomes. Int Urol Nephrol. 2013;45:313–20.
34. Schoeppler GM, Klippstein E, Hell J, et al. Prolonged cold ischemia time for laparoscopic partial nephrectomy with a new cooling material: Freka-Gelice – a comparison of four cooling methods. J Endourol. 2003;170:52–6.
35. Kijvikai K, Viprakasit DP, Milhoua P, et al. A simple, effective method to create laparoscopic renal protective hypothermia with cold saline surface irrigation: clinical application and assessment. J Urol. 2010;184:1861–6.
36. Rogers CG, Ghani KR, Kumar RK, et al. Robotic partial nephrectomy with cold ischemia and on-clamp tumor extraction: recapitulating the open approach. Eur Urol. 2013;63:573–8.
37. Kaouk JH, Samarasekera D, Krishnan J, et al. Robotic partial nephrectomy with intracorporeal renal hypothermia using ice slush. Urology. 2014;84:712–8.
38. Ramirez D, Caputo PA, Krishnan J, Zargar H, Kaouk JH. Robot-assisted partial nephrectomy with intracorporeal renal hypothermia using ice slush: step-by-step and matched comparison with warm ischemia. BJU Int. 2016;117(3):531–6.
39. Van den Berg NS, van Leeuwen FW, van der Poel HG. Fluorescence guidance in urologic surgery. Curr Opin Urol. 2012;22:109–20.
40. McClintock TR, Bjurlin MA, Wysock JS, Borofsky MS, Marien TP, Okoro C, et al. Can selective arterial clamping with fluorescence imaging preserver kidney function during robotic partial nephrectomy? Urology. 2014;84(2):327–34.
41. Marano A, Priora F, Lenti LM. Application of fluorescence in robotic general surgery: review of the literature and state of the art. World J Surg. 2013;37:2800–11.

42. Tobis S, Knopf J, Silver C, Yao J, Rashid H, Wu G, et al. Near infrared fluorescence imaging with robotic assisted laparoscopic partial nephrectomy: initial experience for renal cortical tumors. J Urol. 2011;186(1):47–52.
43. Bjurlin MA, McClintock TR, Stifelman MD. Near-infrared fluorescence imaging with intraoperative administration of indocyanine green for robotic partial nephrectomy. Curr Urol Rep. 2015;16(4):20.
44. Raman JD, Bensalah K, Stern JM, Cadeddu JA. Laboratory and clinical development of single keyhole umbilical nephrectomy. Urology. 2007;70(6):1039–42.
45. Rane A, Rao P, Bonadio F. Single port laparoscopic nephrectomy using a novel laparoscopic port (R-port) and evolution of single laparoscopic port procedure (SLIPP). J Endourol. 2007;21:A287.
46. Desai MM, Raoo PP, Aron M, Pascal-Haber G, Desai MR, Mishra S, et al. Scarless single port transumbilical nephrectomy and pyeloplasty: first clinical report. BJU Int. 2008;101:83–8.
47. Kaouk JH, Goel RK, Haber GP, Crouzet S, Stein RJ. Robotic single-port transumbilical surgery in humans: initial report. BJU Int. 2008;103:366–9.
48. White MA, Autorino R, Spana G, Hillyer S, Stein RJ, Kaouk JH. Robotic laparoendoscopic single site urological surgery: analysis of 50 consecutive cases. J Urol. 2012;187:1696–701.
49. Seidman CA, Yong KT, Faddegon S, et al. Robot-assisted laparoendoscopic single-site pyeloplasty: technique using the da Vinci Si robotic platform. J Endourol. 2012;26:971–4.
50. Joseph RA, Goh AC, Cuevas SP, et al. Chopstick surgery: a novel technique improves surgeon performance and eliminates arm collision in robotic- single incision laparoscopic surgery. Surg Endosc. 2010;24:13331–5.
51. White MA, Autorino R, Spana G, Laydner H, Hillyer SP, Khanna R, Yang B, Alunrende F, Isac W, Stein RJ, Haber GP, Kaouk JH. Robotic laparoendoscopic single-site radical nephrectomy: surgical technique and comparative outcomes. Eur Urol. 2011;59(5):815–22.
52. Kaouk JH, Haber GP, Autorino R, Crouzet S, Ouzzane A, Flamand V, Villers A. A novel robotic system for single-port urologic surgery: first clinical investigation. Eur Urol. 2014;66:1033–43.
53. Maurice MJ, Kaouk JH. Robotic radical perineal cystectomy and extended pelvic lymphadenectomy: initial investigations using a purpose-built single-port robotic system. BJU Int. 2017;120(6):881–4.
54. Kaouk J, Sagalovich D, Garisto J. Robotic Transvesical Partial prostatectomy using a purpose built single port robotic system. BJU Int. 2018. https://doi.org/10.1111/bju.14194.
55. Ramirez D, Maurice MJ, Kaouk JH. Robotic perineal radical prostatectomy and pelvic lymph node dissection using a purpose-built single-port robotic platform. BJU Int. 2016;118(5):829–33. https://doi.org/10.1111/bju.13581. Epub 2016 Sep 3
56. Maurice MJ, Ramirez D, Kaouk JH. Robotic laparoendoscopic single-site retroperitoneal renal surgery: initial investigation of a purpose-built single-port surgical system. Eur Urol. 2017;71(4):663–4.

Chapter 9
Approach to the Management of Large and Advanced Renal Tumors

Bimal Bhindi and Bradley C. Leibovich

Introduction

Since the 1990s, the increasing use of abdominal imaging has led to a stage migration, with a marked rise in the incidental detection of small renal masses [1–6]. However, approximately 30% of renal cell carcinomas (RCCs) are still diagnosed as stage II (organ confined larger than 7 cm in size) or stage III (tumor extends into major veins or perinephric tissues and/or regional lymph node involvement), and approximately 10% are still diagnosed at stage IV (adjacent organ invasion or distant metastatic disease) [6].

The oncologic outcomes for large and advanced RCC are very different from pT1a tumors, where the 10-year cancer-specific survival is 90–96% [7, 8]. The 10-year cancer-specific survival for large organ-confined tumors decreases gradually with increasing tumor size and ranges from 85% for 4–5 cm tumors to 49% for >15 cm tumors [9]. Meanwhile, the 10-year cancer-specific survival among those treated for pT3a, pT3b, pT3c, and pT4 RCC is 36%, 26%, 25%, and 12% at 5 years, respectively.

There are many facets that warrant attention in the surgical management of large and advanced renal tumors. In this chapter, we describe the anatomic considerations, preoperative evaluation and preparation, perioperative considerations, surgical principles, and outcomes of the surgical management of large and advanced renal tumors.

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Anatomic Considerations

Surgeons who operate on large and advanced renal tumors must be well-versed in retroperitoneal anatomy. While this is not meant to be a comprehensive description of surgical anatomy, several key points are highlighted.

Anatomic Relationships

The kidneys are retroperitoneal structures with their hila at the level of the L1 vertebral body and are surrounded by Gerota's fascia. They are related posteriorly to the diaphragm, quadratus lumborum, and psoas muscles. The left kidney is typically positioned slightly more cranially and is bordered by the spleen superolaterally, the adrenal gland superomedially, and the tail of the pancreas anteriorly. The left colonic flexure, descending colon, and the colonic mesentery are in turn anterior to the lower pole of the left kidney and the tail of the pancreas. The right kidney is usually slightly more inferior compared to the left and is bordered superiorly by the liver, superomedially by the adrenal gland, and medially by the duodenum. The ascending colon, right colonic flexure, and the colonic mesentery are in turn anterior to the lower pole of the right kidney and duodenum. These anatomic relationships must be considered, especially when normal anatomy is distorted by large renal tumors.

Vascular Anatomy and Variants

The renal artery is normally positioned posterior to the vein and is anterior to the renal pelvis. The right renal artery courses posterior to the inferior vena cava (IVC). Understanding the path of the right renal artery can be valuable when a locally advanced right renal tumor renders the approach to the right renal hilum difficult. An often preferable and easier option is identification and ligation at its origin in the interaortocaval space. The left renal vein crosses anterior to the aorta, inferior to the superior mesenteric artery, and posterior to the small bowel mesentery. On the left, the adrenal and gonadal veins drain into the left renal vein, while on the right, these veins each drain directly into the IVC. The other branches of the abdominal aorta include the paired inferior phrenic branches, the celiac trunk, the paired adrenal arteries, the superior mesenteric artery, the paired gonadal arteries, the inferior mesenteric artery, the paired common iliac arteries, and the paired lumbar arteries. Additional arterial supply to the adrenal can be provided via the inferior phrenic and renal arteries. The second, third, and fourth paired lumbar arteries are infrarenal and somewhat variable in position. The additional tributaries of the abdominal IVC include the hepatic veins, the minor hepatic veins, the right inferior phrenic vein, the right adrenal vein, the right gonadal vein, the paired common iliac veins, and the

lumbar veins. In the setting of an IVC thrombus, the azygos and hemiazygos venous systems may provide collateral drainage. The identification of relevant venous branches is essential to ensure a bloodless field at the time of cavotomy during IVC tumor thrombectomy (Fig. 9.1).

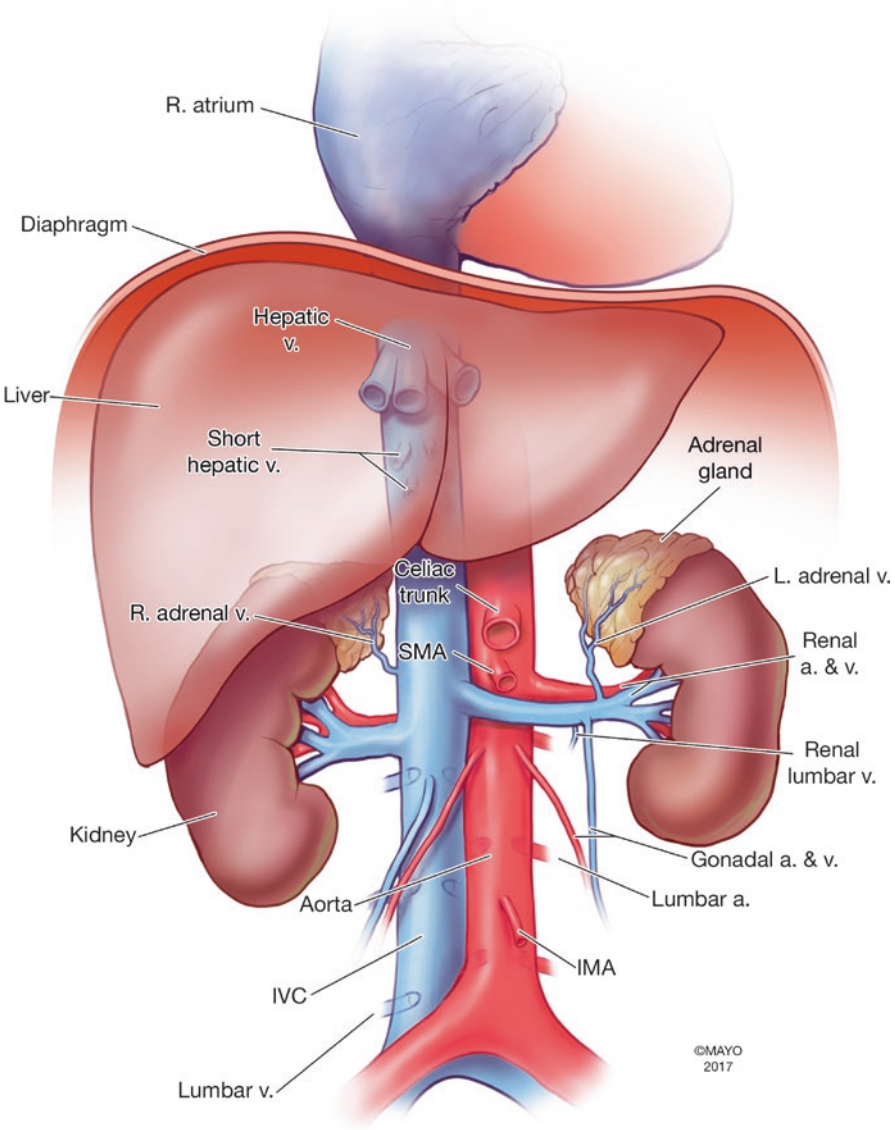

Fig. 9.1 Relevant vascular anatomy of the retroperitoneum. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

Arterial anatomic variants are not uncommon. In cadaver studies, approximately 80% of kidneys have a single artery [10]. In contrast, the reported probabilities of a single renal artery are higher in studies relying solely on imaging (88–95%). This suggests that preoperative imaging may not detect all clinically relevant accessory vessels and intraoperative vigilance is necessary. Accessory upper or lower pole renal arteries can arise from the aorta or branch early off the main renal artery.

Venous anatomic variants also warrant attention. For example, a lumbar vein drains into the left renal vein in approximately 40% of individuals [11]. Persistence of the left supracardinal vein can lead to a left-sided IVC, which crosses at the level of the renal vein and returns to the right side once suprarenal. Persistence of both supracardinal veins can lead to a duplicated IVC. It is possible to have multiple renal veins, most commonly on the right. A retroaortic left renal vein is present in 3% of individuals [12]. A circumaortic left renal vein is also possible. Persistence of the posterior cardinal vein can lead to a retrocaval right ureter [12]. These must be recognized in order to avoid intraoperative vascular disasters.

Preoperative Evaluation and Preparation

Basic Evaluation

For patients presenting with a renal mass, a focused history and physical exam should routinely be performed regardless of the presentation and radiographic findings. While most small renal masses are asymptomatic, large and locally advanced renal tumors may present with gross hematuria, flank pain, or palpable mass or may even present with a spontaneous retroperitoneal bleed [13–15]. Signs and symptoms indicating the presence of a paraneoplastic syndrome should be noted. Resting blood pressure should be measured. Symptoms and signs of distant disease, such as pulmonary symptoms, bone pain, constitutional symptoms, weight loss, and cervical adenopathy, should be fully evaluated. Potential symptoms and signs of IVC obstruction from thrombus, such as bilateral leg swelling, weight gain, caput medusa, and nonreducing or right-sided varicocele, should not be missed. Although rare, symptoms and signs of hepatic vein obstruction (Budd-Chiari syndrome) may also be present [16]. Finally, a family history of renal tumor syndromes and personal history of associated findings of these syndromes should be considered, as these may warrant referral for genetic counselling [17–19].

Laboratory evaluation should be tailored to the history and physical exam and should generally include, at a minimum, a complete blood count, serum electrolytes, serum creatinine, coagulation profile, serum calcium (with correction for hypoalbuminemia as needed), liver enzymes, and urinalysis [20].

Cross-sectional imaging is central in the evaluation of a renal mass [21]. As it pertains to large and advanced renal tumors, the images should be personally reviewed by the surgeon to anticipate intraoperative challenges. The number and position of renal vessels should be confirmed. The relationship of the tumor to adja-

cent structures should be assessed and potential for local invasion considered. Neovascularity and aberrant parasitic vessels should be noted. The renal vein and IVC should be inspected for the presence of tumor thrombus, and attempts should be made to differentiate tumor and bland thrombus. Retroperitoneal lymphadenopathy should be noted, and other intra-abdominal organs should be assessed for potential metastases. The contralateral kidney and adrenal gland should be inspected.

For staging, a chest X-ray should be performed at minimum. A CT scan of the chest may be worth considering in patients with high-risk tumors. For example, in a large study of patients undergoing nephrectomy who had a CT scan of the chest, a strategy of performing a CT scan of the chest for ≥cT1b, cN1, systemic symptoms, or anemia and thrombocytopenia would spare 37% of patients from this test while missing only 0.2% of intrathoracic metastases [22]. A bone scan or brain imaging should be performed as indicated based on symptoms, signs, and extent of disease on other imaging studies. Additionally, brain imaging may be worth considering if perioperative systemic anticoagulation is being considered in the setting of venous tumor thrombus (VTT) to avert potentially catastrophic intracranial bleeding related to an occult metastasis. If present, hematuria should be evaluated via cystourethroscopy and urine cytology, along with upper tract imaging to rule out a concurrent urothelial tumor.

Renal Mass Biopsy

In contrast to small renal masses, the role of renal mass biopsy is limited in the setting of a large or locally advanced nonmetastatic renal tumor and should only be performed if it will alter clinical management [23]. For example, renal mass biopsy may be considered if the tumor is central in location or if other features lead to the suspicion of urothelial carcinoma, as this will alter operative approach. Biopsy may also be helpful in establishing a tissue diagnosis for unresectable tumors prior to initiation of systemic therapy. Otherwise, for patients with large and locally advanced tumors destined for surgery, the risk of malignant histology [24] and cancer-specific mortality [9] is sufficiently high that biopsy will not alter management and will only delay definitive therapy.

Imaging for Venous Tumor Thrombus

Multiple VTT classification systems have been described (Table 9.1) [30]. In this chapter we use the Neves and Zincke classification [26], since it offers the greatest degree of granularity, which in turn directly relates to management.

VTT can present with a wide array of symptoms, while approximately 19% are found incidentally on imaging [31]. Cephalad extension of the tumor thrombus between the time of imaging and operative date can radically change the operative

Table 9.1 VTT classification systems

Landmark	Staging classification				
	AJCC-TNM [25]	Neves and Zincke 1987 [26]	Novick et al. 1989 [27]	Hinman 1998 [28]	Robson 1982 [29]
Renal vein	T3a	0	I	I	IIIa
IVC <2 cm from renal vein ostium	T3b	I	II		
IVC >2 cm from renal vein ostium		II			
IVC at/above major hepatic veins		III	III	II	
Above diaphragm	T3c	IV	IV	III	

Summary of surgical and prognostic VTT classifications for renal cell carcinoma. Adapted from Pouliot et al. [30]

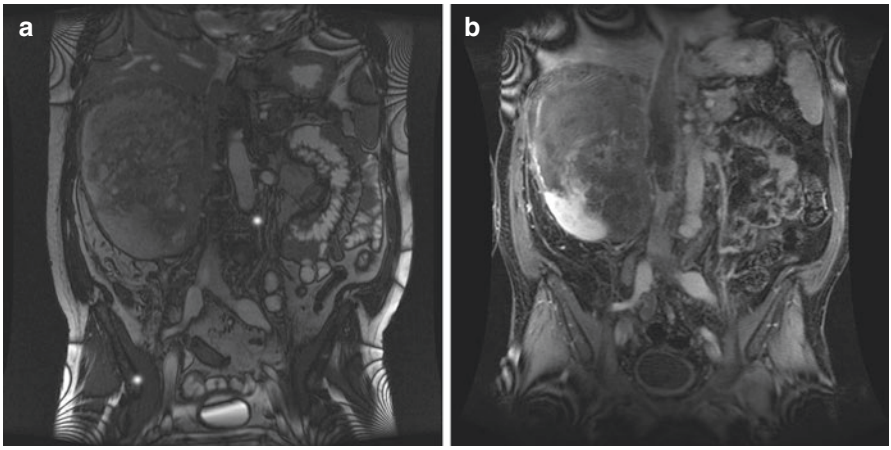

Fig. 9.2 Potential for rapid venous tumor thrombus progression. Images (**a**) and (**b**) were taken 20 days apart in a patient with a right renal mass and venous tumor thrombus prior to surgery. A contrast-enhanced MRI is recommended within 7–10 days of surgery. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

approach (Fig. 9.2). Contrast-enhanced magnetic resonance imaging (MRI) is the preferred modality to characterize an IVC tumor thrombus, and this should ideally be performed within 7–10 days of the surgical date [32–34]. Although multidetector CT scan will identify 79–100% of venous tumor thrombi, MRI appears to be superior in delineating the cephalad extent of the thrombus, in identifying whether there is flow around the thrombus, and in differentiating bland (non-enhancing) and tumor thrombus (enhancing) [32, 35–37] (Fig. 9.3).

The possibility of IVC wall invasion and the potential need for vascular resection must be considered preoperatively. One study considered several clinical and radiologic variables and developed a parsimonious multivariable model to predict

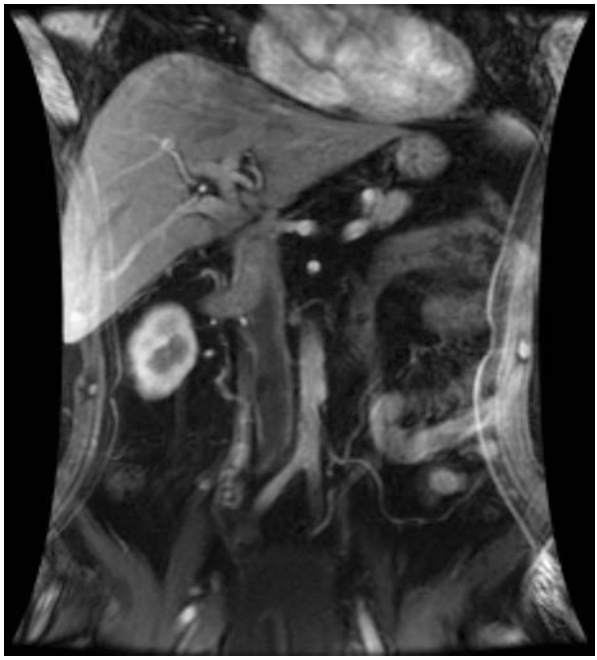

Fig. 9.3 MRI differentiation of bland and tumor thrombus. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

the need for vascular resection in patients with an IVC tumor thrombus [14]. The authors found that right-sided tumor location (OR = 3.30; 95%CI 1.24–8.81), anterior-posterior diameter of the IVC ≥24 mm at the renal vein ostium (OR = 4.35; 95%CI 1.31–14.53), and radiographic identification of complete occlusion of the IVC at the level of the renal vein ostium (defined by the absence of contrast passing around the thrombus within the IVC on preoperative MRI; OR = 4.90; 95%CI 1.96–12.26) were the most important predictors of needing vascular reconstruction at the time of tumor thrombectomy (*c*-index = 0.81).

Assessment of Retroperitoneal Lymph Nodes

In patients with advanced renal tumors, it is important to consider the potential for retroperitoneal lymph node metastasis. Several predictors of lymph node involvement have been described [38–42]. One study found that the two most important radiographic predictors of pN1 disease are the maximum short axis diameter and perinephric/sinus fat invasion [38]. The probabilities of pN1 disease are 28.9%, 66.1%, and 90.4%, for lymph nodes measuring 10, 20, and 30 mm on short axis, respectively. Pathologic features associated with nodal involvement include high nucleolar grade (grades 3 and 4), pT3–4 tumor stage, tumor size ≥10 cm, histologic tumor necrosis, and sarcomatoid component [39]. There is a progressive increase in the risk of pathologic nodal involvement with increasing number of these features.

With 0–1, 2–4, and 5 of these features, the risk of pathologic node positivity was 0.6%, 10%, and 53%, respectively. However, it should be noted that in order to apply this risk stratification scheme, intraoperative pathologic assessment is required [40]. One group reported a preoperative nomogram to predict the probability of nodal metastasis using age, presence of symptoms, and tumor size (AUC = 0.784) [41]. Similarly, Capitanio et al. reported a prediction model for pathologic nodal involvement with an AUC of 0.869, using clinical T-stage, clinical node status (cN1 versus cN0), metastases at diagnosis, and tumor size [42].

Preoperative Consultations

Preoperative cardiology evaluation may be warranted if considering cardiopulmonary bypass for a level III–IV IVC tumor thrombus in order to assess coronary risk and the need for coronary angiography. If significant coronary artery disease is present, performance of concurrent coronary artery bypass grafting at the time of radical nephrectomy may be considered [30].

Preoperative cardiothoracic surgery consultation should be considered if cardiopulmonary bypass is potentially necessary. Hepatobiliary surgeon involvement may be helpful if liver mobilization is needed, particularly in patients with liver congestion secondary to IVC obstruction. Additionally, involvement by a vascular surgeon may be helpful if IVC graft reconstruction is necessary. All efforts should be made to ensure the appropriate personnel are available for the critical stages of the procedure.

Perioperative Considerations

Preoperative Angioembolization

There is insufficient evidence to support the routine use of preoperative arterial embolization (PAE). PAE using absolute ethanol, polyvinyl alcohol particles, acrylic microspheres, or water-insoluble gelatin is considered by some surgeons for patients with large renal tumors and/or VTT [43]. PAE can provide arterial control in instances when intraoperative arterial identification is anticipated to be challenging, such as a bulky hilum, and may allow for the vein to be addressed directly. It may also be associated with reduced blood loss and transfusion requirement [44, 45]. Following PAE, a postinfarction syndrome is anticipated, which includes flank pain, nausea, and fever [46].

The utility of PAE, however, has been contested. In most cases, early arterial control can be achieved intraoperatively, which will reduce the size and turgor of the primary tumor, and even of the tumor thrombus, if present, in the same way as PAE. Second, a survival benefit of PAE has not been demonstrated in the literature

[45, 47]. In fact, one large institutional series evaluating PAE in patients with IVC tumor thrombi found no associated benefit in complication risk or length of hospital stay and even found an associated increased risk of perioperative mortality on multivariable analysis (OR = 5.5, 95%CI 1.2–25.6; $p = 0.029$) [47]. While unmeasured selection bias and confounding cannot be ruled out, these data certainly urge for caution in the liberal use of PAE.

Perioperative Management of Venous Thromboembolic Risk

Although there is no consensus [30, 48], we feel that symptomatic pulmonary embolism should be considered an absolute indication for anticoagulation, while asymptomatic pulmonary embolism, presence of bland IVC thrombus, complete or near complete IVC occlusion, and atrial tumor thrombus (level 4) should be considered relative indications. Anticoagulation can be administered preoperatively, held the day before the procedure, and resumed postoperatively when the bleeding risk is felt to be sufficiently low relative to the thromboembolic risk, usually by postoperative days 2–3. Conventional venous thromboembolism (VTE) prophylaxis should be considered while the patient is not on therapeutic-dose anticoagulation.

Although intraoperative placement of an IVC filter may have a role in some patients presenting with a large or locally advanced renal mass, preoperative percutaneous placement of an IVC filter should be avoided in patients with VTT. One reason to avoid preoperative filter placement in patients with VTT is that insertion of the device can dislodge clot or tumor thrombus leading to pulmonary embolus. Additionally, the presence of a filter can make dissection of the IVC more complicated due to reactive fibrosis. Finally, tumor incorporation into the filter has been described, which complicates the ensuing operation [49].

Neoadjuvant and Adjuvant Systemic Therapy

Neoadjuvant tyrosine kinase inhibitor (TKI) use may facilitate the resection of a locally advanced renal tumor or may facilitate nephron-sparing surgery for large tumors in a solitary kidney that would have otherwise required radical nephrectomy [50–52]. There are also reports where neoadjuvant TKI use reduced the level of a VTT to the extent that it altered the operative approach [53–55]. However, for the majority of patients, the impact of preoperative TKI use is limited. In a study of patients with clinical stage II or higher renal masses who received preoperative sorafenib, the median decrease in tumor size was only 9.6% [50]. Meanwhile, in another study of patients with VTT, a change in thrombus level was observed in 3 of 25 patients (12%) [56]. Therefore, the data are insufficient to support the routine use of neoadjuvant TKIs. Trials evaluating neoadjuvant immunotherapy are ongoing at this time.

TKI use in the adjuvant setting is controversial. The ASSURE randomized trial found no survival benefit with adjuvant sunitinib or sorafenib compared to placebo in 1943 patients with high-grade T1b or greater, completely resected, nonmetastatic renal cell carcinoma (RCC) [57]. Similar results were observed when looking at a high-risk subset of this trial [58]. In contrast, the S-TRAC trial found that adjuvant sunitinib resulted in improved disease-free survival compared to placebo (median 6.8 vs. 5.6 years, HR = 0.76, $p = 0.03$) in patients with higher-risk clear cell RCC, defined as tumor stage 3 or higher, regional nodal metastasis, or both [59]. At this time, S-TRAC is not sufficiently mature to assess differences in overall survival. Finally, the PROTECT trial comparing pazopanib to placebo in the adjuvant setting found no disease-free survival benefit [60]. Based on the S-TRAC trial, the United States Food and Drug Administration granted approval for sunitinib in the adjuvant setting, although in the absence of an overall survival benefit, its use in this setting remains controversial for now.

Perioperative Medical Management

Appropriate physician consultations should be made for medical optimization prior to major surgery. In all patients, diuretics and angiotensin-converting enzyme inhibitors should be held the day of surgery. In diabetic patients, perioperative glucose management should be directed by the severity of diabetes.

Following anesthetic induction, placement of an arterial line for continuous blood pressure monitoring and a central venous line for central venous pressure monitoring are helpful. The urethral catheter drainage bag should be accessible to the anesthesiologist to allow for monitoring of urine output. Efforts should be made to ensure ample hydration, particularly in anticipation of IVC clamping. In patients with a patent IVC despite tumor thrombus, IVC clamping may meaningfully reduce venous return and cardiac output. Active communication between the surgeons and anesthesiologists is crucial.

Operative Management

Surgical Approach

Large renal tumors including those with IVC tumor thrombi have traditionally been managed using an open approach. However, there is increasing experience at certain centers with minimally invasive approaches. The surgeon should use whichever approach allows for a safe and oncologically sound operation.

Although technically challenging, laparoscopic radical nephrectomy can be performed for large and locally advanced renal masses [61, 62]. Hand-assisted laparoscopy may also be an option, given that these tumors will require a large incision for

extraction [63]. Robotic-assisted laparoscopic radical nephrectomy is also increasingly being utilized, although it is unclear whether this offers a meaningful advantage over conventional laparoscopy [64]. One study of the Nationwide Inpatient Sample found that 32% of radical nephrectomies were done robotically between 2009 and 2011 [65]. In this study there were no differences in perioperative complications or mortality between robotic-assisted and conventional laparoscopic approaches, yet the robotic cases were associated with a $4565 more in-hospital costs and $11,267 more in-hospital charges.

Recently, cases of pure laparoscopic [66] and robotic IVC tumor thrombectomy [67] have been reported. These procedures are currently only being performed in highly selected patients at experienced centers. A full description of the nuances of these procedures is beyond the scope of this chapter.

Positioning, Incision, and Retroperitoneal Exposure

Regardless of approach, these procedures require excellent exposure and visualization. Therefore, the choice of incision for an open procedure is crucial (Fig. 9.4). The decision can be influenced by the location and size of the tumor, the presence and level of VTT, body habitus, costal flare, any anatomic abnormalities, and surgeon preference.

We have found that a midline incision can be used to approach virtually any renal tumor, and this is currently our preferred incision for open renal surgery. Adequate access to the entire abdomen including the lateral aspects of the tumor can be

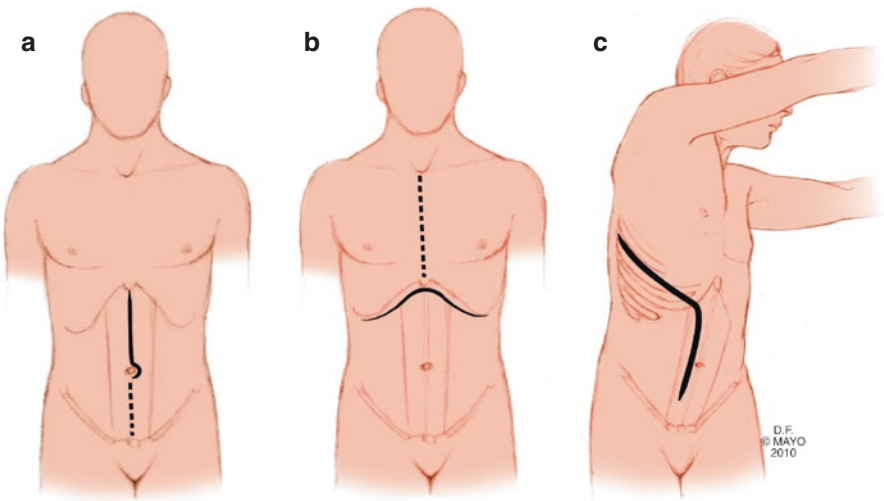

Fig. 9.4 Common surgical incisions used during radical nephrectomy. (**a**) Midline, (**b**) bilateral subcostal (chevron), and (**c**) thoracoabdominal. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

obtained with appropriate use of a self-retaining retractor. The incision can be continued cranially into a sternotomy when cardiopulmonary bypass (CPB) is needed.

An anterior bilateral subcostal (chevron) incision can be performed two fingerbreadths below the costal margin. It offers improved access to the lateral aspect of the tumor and allows for easier liver mobilization. This incision can also be joined with a sternotomy when required. In a randomized trial of midline versus transverse abdominal incisions, there were no differences in analgesic requirement, length of stay, pulmonary complications, median time to tolerance of solid food, or incision hernia risk at 1 year, although there were more wound infections in the transverse incision group [68]. Interestingly, one study found that Chevron incisions are associated with seven times more rectus abdominis atrophy than midline incisions [69].

A flank incision may also be used, which is typically made above the 11th or 12th rib. While this approach avoids anterior adiposity, hilar access can sometimes be difficult. For larger upper pole tumors, a thoracoabdominal approach using a higher rib level with the patient in a modified flank position may be useful; however, a postoperative chest drain will be necessary. The thoracoabdominal incision can also transition anteriorly to a midline incision, resulting in a hockey stick incision.

Following obtaining intraperitoneal access, a thorough exploration of the abdomen and retroperitoneum should be performed. Subsequently, the retroperitoneum should be accessed upon incision along the peritoneal reflection lateral to the ascending or descending colon for right and left renal masses, respectively. Following the avascular plane, the ipsilateral colon and its mesentery should be mobilized off from Gerota's fascia to expose the retroperitoneum. If IVC exposure for tumor thrombectomy is needed, the root of the small bowel mesentery can also be mobilized. For a right renal mass with tumor thrombus, the small and large bowel can all be displaced to the left to allow all relevant structures to be visualized in a single operative field. In contrast, for a left renal mass with IVC tumor thrombus, the IVC tumor thrombectomy is performed in the right hemi-abdomen, while the radical nephrectomy is performed in the left hemi-abdomen. Finally, for level III–IV tumor thrombi, the liver may need to be mobilized medially to gain exposure to the retrohepatic and suprahepatic IVC (Fig. 9.5). This is achieved by dividing the triangular and coronary ligaments, as well as ligating the short hepatic veins draining the caudate lobe of the liver.

Principles Radical Nephrectomy

Adjacent organ injury can be avoided by careful identification of structures and mobilization using the appropriate surgical planes. For a right-sided renal tumor, the duodenum should be reflected medially (Kocher maneuver), which will expose the IVC and renal hilum. On the left, the lateral peritoneal attachments of the spleen may require division to facilitate exposure of the upper pole. The tail of the pancreas, along with the splenic hilum, can be mobilized off from Gerota's fascia following an avascular plane. With this maneuver, the left renal vein should be apparent. If there is any difficulty in identifying the renal vein, the gonadal vein can be identified and traced upward.

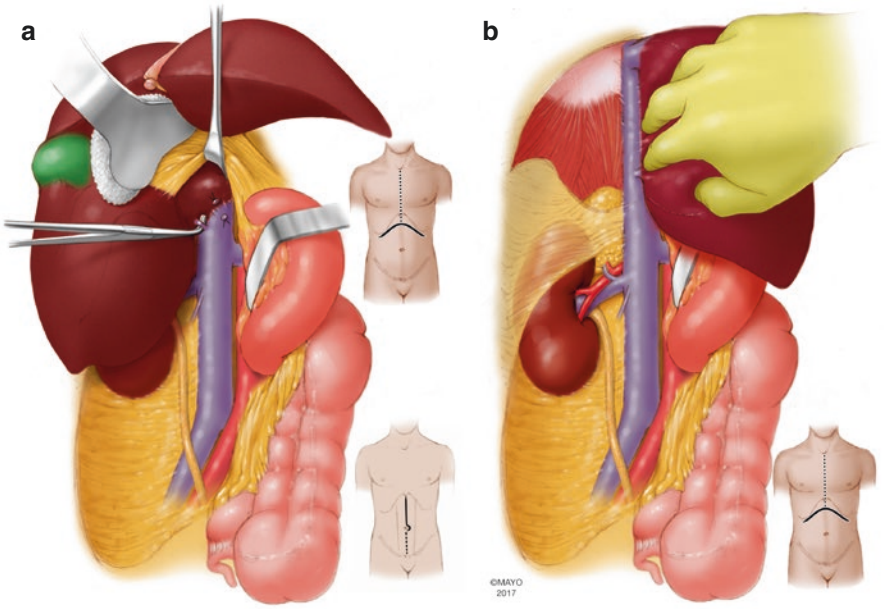

Fig. 9.5 Liver mobilization to gain access to retrohepatic and suprahepatic inferior vena cava. (**a**) The liver is retracted cranially, and the short hepatic veins draining the caudate lobe are divided in order to gain greater access to the infrahepatic IVC. (**b**) The right triangular and coronary ligaments of the liver have been divided, allowing for the liver to be rotated toward the patient's left in order to access the retrohepatic IVC. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

The ureter can be divided where convenient, as long as there is no concern for urothelial carcinoma. For both right- and left-sided renal tumors, we typically ligate the gonadal veins during the dissection.

Although surgeon preference and anatomic considerations vary significantly, our preferred approach is to dissect the hilar structures first and mobilize the kidney after ligation and division of the artery and vein. Early arterial control may be especially beneficial for large tumors, for those with parasitic vessels, and in the setting of an IVC thrombus. For bulky hilar tumors, consideration can be given to identifying the renal artery at its origin. For right-sided tumors, this can include identification of the renal artery in the interaortocaval space [34, 70]. Supernumerary veins can be divided prior to addressing arterial control in order to facilitate exposure, but all arteries should be controlled prior to dividing the main renal vein.

Adrenalectomy

The ipsilateral adrenal need not be routinely removed with the kidney if it is not involved by tumor. The preoperative CT scan is highly accurate in detecting ipsilateral adrenal gland involvement by kidney cancer, with a sensitivity of 100%, a

specificity of 95.2%, and a negative predictive value of 100% [71]. Thus, adrenal involvement can be accurately ruled out preoperatively, and upon intraoperative confirmation, adrenal sparing is usually feasible.

The risk of synchronous ipsilateral adrenal involvement is 2.2%, while the risk of developing a subsequent adrenal metastasis is 3.7% [72]. Moreover, this risk is similar in the ipsilateral and contralateral adrenal glands. As such, there is potential for harm with routine removal of the ipsilateral adrenal gland upon nephrectomy for a renal tumor if contralateral adrenal metastasis occurs. Meanwhile, no survival advantage has been demonstrated with adrenalectomy at the time of nephrectomy [72, 73], and in fact one study suggested worse survival with ipsilateral adrenalectomy [74].

Inferior Vena Cava Tumor Thrombectomy

The surgical management of a VTT is among the most technically challenging operative procedures in urologic surgery. The experience of the surgeon and the team is paramount. Involvement of vascular, hepatobiliary, and cardiac surgeons, as indicated, can be beneficial [15].

Vascular Bypass

The use of vascular bypass should be considered and anticipated ahead of time so that the appropriate personnel and equipment are available. For patients with a supradiaphragmatic (level IV) VTT, CPB with or without hypothermic circulatory arrest (HCA) is commonly utilized and affords a brief period with a bloodless field for complex tumor thrombus extraction and potential reconstruction. Vascular bypass may also be required for certain patients with a subdiaphragmatic IVC tumor thrombus if they are dependent on venous return from the IVC (i.e., collateral venous return is limited) and if a prolonged clamp time is anticipated due to the complexity of the thrombectomy and/or venous reconstruction. For such patients, either CPB and HCA or veno-venous bypass (VVB; e.g., from the infrarenal IVC to the right brachial vein) can be used [70]. However, VVB may not be possible in some instances when there are no acceptable areas to place the IVC cannula, for example, due to bland infrarenal IVC thrombus.

General Principles

Following retroperitoneal exposure, the key steps of the operation include (1) control of the renal artery or arteries, (2) venous tumor thrombectomy, and (3) radical nephrectomy. These steps should be performed in order. Early renal artery ligation reduces blood loss from venous collaterals. In some cases, whereby the risk of disturbing the tumor thrombus is felt to be low and bleeding from collateral vessels is limited, the kidney can be mobilized early.

The approach to VTT is dependent on many factors, but general principles are similar based on the level of the thrombus and the presence or absence of clot in addition to tumor thrombus.

Level 0–I VTT

The approach to the management of a VTT depends on its level (Fig. 9.6). For a level 0 VTT and minimal level I thrombus that can be gently milked into the renal vein, control can be achieved by renal vein ligation or by placing a vascular clamp at the level of the renal vein ostium. If using renal vein ligation, then the procedure does not meaningfully deviate from a radical nephrectomy without tumor thrombus. If using a vascular clamp, a venotomy can be made on the specimen side of the vascular clamp (Fig. 9.6a). Upon confirming a satisfactory margin, the venotomy can then be continued circumferentially to complete the venous resection.

Level I–II VTT

For many level I tumor thrombi and essentially all level II tumor thrombi, no attempt should be made to milk the thrombus into the renal vein. In these instances, it is necessary to obtain exposure and circumferential control of the infrahepatic IVC. The cranial extent of the tumor thrombus should be assessed by gentle palpation and/or ultrasound to guide the extent of IVC dissection. Lumbar veins may require ligation, and in some cases, short hepatic veins from the caudate lobe of the liver inserting into the anterior IVC need to be sacrificed to allow exposure of the IVC superior to the thrombus.

In the absence of bland thrombus inferior to the thrombus, a trial of IVC clamping inferior to the thrombus to confirm hemodynamic tolerability is often worthwhile [34, 70]. If clamping cannot be tolerated despite satisfactory hydration, or if a complex vascular reconstruction is anticipated, then vascular bypass may be necessary prior to clamping [70]. Conversely, if a trial of vascular clamping is tolerated, then vascular clamps should be sequentially placed on the infrarenal IVC, contralateral renal vein, and infrahepatic IVC (Fig. 9.6b). This is followed by cavotomy starting from the renal venal vein ostium and proceeding along the anterolateral aspect of the IVC. Upon extraction of the tumor thrombus and excision of the ipsilateral renal vein, the caval lumen should be inspected to ensure removal of all tumors and clot prior to venous reconstruction.

Level III VTT

For a level III thrombus (at or above the level of the major hepatic veins), transesophageal ultrasound is helpful to assess the proximal extent of the thrombus both prior to incision and following renal artery control. Additionally transesophageal ultrasound can be used to assess for residual tumor following tumor thrombectomy

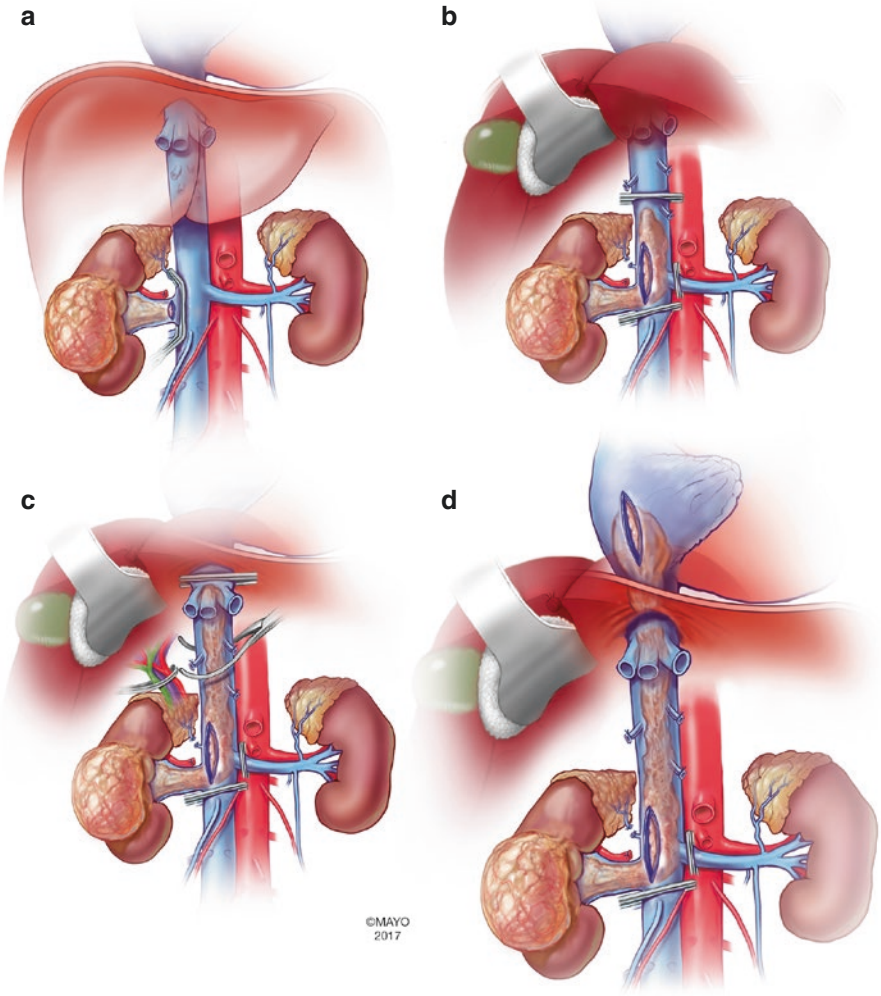

Fig. 9.6 Approach to the intraoperative management of a venous tumor thrombus according to its level. Shown are (**a**) level 0–I, (**b**) level II, (**c**) level III, and (**d**) level IV venous tumor thrombi with appropriate vascular clamps applied and cavotomies performed. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

and for flow around the tumor thrombus, which will aid in the decision of whether to perform IVC reconstruction or ligation following tumor thrombectomy.

In addition to the steps in managing a level II thrombus, we would additionally recommend liver mobilization to allow for exposure and mobilization of the retrohepatic and suprahepatic IVC (Fig. 9.5). For a level III tumor thrombus, vascular clamps should be sequentially placed on the infrarenal IVC, the contralateral renal vein, the hepatoduodenal ligament containing the portal vein and hepatic artery

(Pringle maneuver), and the suprahepatic IVC (Fig. 9.6c). Occasionally, clamping of the hepatic veins is also necessary. This is followed by cavotomy and extraction of the tumor thrombus, as described above. If the cavotomy does not extend to the hepatic veins, then an infrahepatic IVC clamp can be placed following tumor thrombectomy, so that the suprahepatic and Pringle clamps can be released, allowing for liver perfusion during vascular reconstruction of the IVC.

Level IV VTT

For a level IV thrombus, the standard approach includes sternotomy, CPB and HCA. Deep HCA is essential, as its use is associated with reduced in-hospital mortality and improved survival [75]. A total intra-abdominal approach has been described, whereby the right atrium was approached upon dissection through the central tendon of the diaphragm [76]. The use of VVB instead of CPB and HCA has also been reported; however, these cases were performed at highly experienced centers in well-selected patients [70].

The cardiothoracic and intra-abdominal components of the operation can proceed concurrently. The intra-abdominal approach is similar to that of a subdiaphragmatic tumor thrombus. Transesophageal ultrasound is recommended. An appropriate length of vena cava should be exposed and controlled. Liver mobilization may be required depending on hepatic vein involvement of the thrombus. Infrarenal and contralateral renal vein clamps should be placed. The thrombectomy should then be approached from above and below (Fig. 9.6d), ensuring completing removal of all tumor.

Venous Reconstruction Versus Inferior Vena Cava Ligation

The key factors in guiding the management of the IVC after tumor thrombectomy are whether the IVC has been completely occluded and whether collateral venous drainage has developed.

If the patient is dependent on the IVC for venous return, then the IVC must be reconstructed following caval thrombectomy. This can be accomplished by primary closure if there was minimal caval wall resection and the luminal diameter is relatively preserved. If the luminal diameter has been narrowed significantly (most surgeons set the threshold at 50%), then biologic or synthetic patch graft (Fig. 9.7) or tube interposition graft placement should be performed [77]. If there is bland thrombus in the pelvic veins that has not yet propagated to the IVC, consideration can be given to deploying a filter in the infrarenal IVC prior to reconstruction, pending initiation of postoperative anticoagulation [49].

If the infrarenal IVC is occluded with bland thrombus, consideration should be given to IVC ligation using ties or a vascular stapler [49]. This should be performed immediately below the level of the contralateral renal vein, with care to avoid leaving a blind-ending stump where stasis may develop, leading to new bland thrombus

formation. Segmental IVC resection should be performed as necessary, for example, if there is infrarenal extension of the IVC thrombus. Importantly, if the IVC is ligated, every effort must be made to preserve collateral venous drainage, such as lumbar veins, gonadal veins, and aberrant collateral veins in the contralateral retroperitoneum, colonic mesentery, and pelvis.

Once the vascular reconstruction or caval ligation is complete, the radical nephrectomy should be completed, ideally yielding a single en bloc specimen with the tumor thrombus.

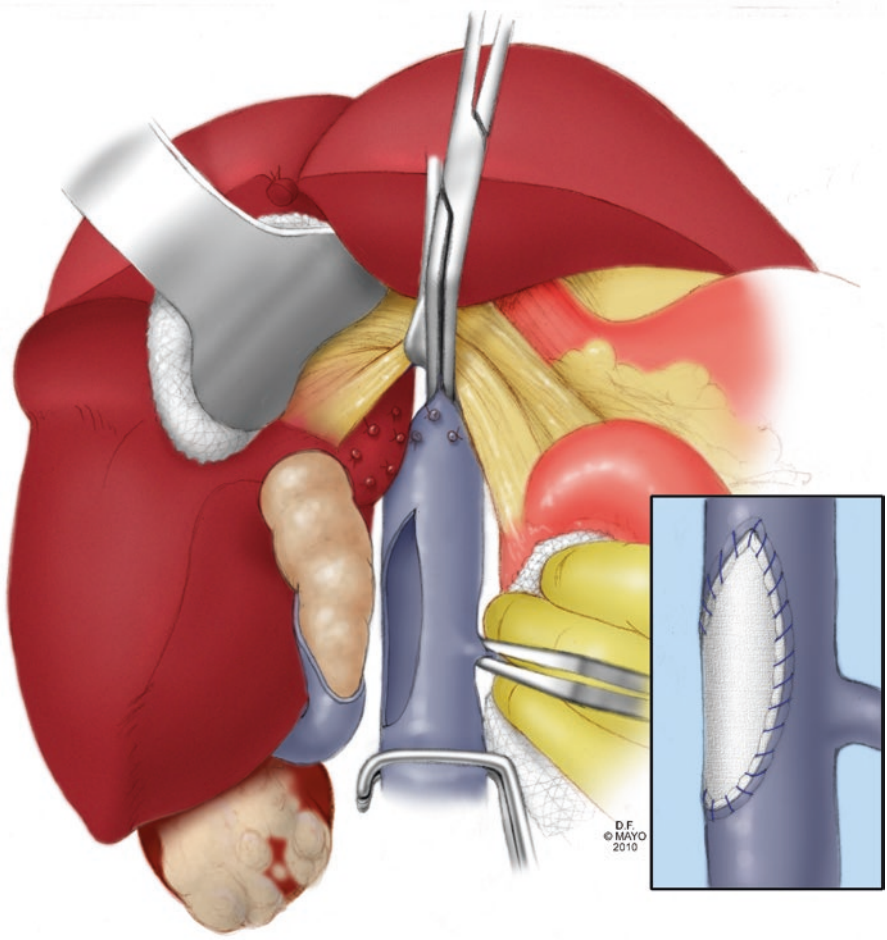

Fig. 9.7 Patch graft reconstruction of the inferior vena cava. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved)

Role of Lymphadenectomy

The relatively unpredictable nature of the lymphatic drainage of the kidney has made it difficult to define the appropriate template for lymphadenectomy for RCC. The primary lymphatic landing zone for RCC is the retroperitoneal lymph nodes between the first and fifth lumbar vertebrae. Lymph from the left kidney tends to drain into the paraaortic and preaortic nodes, while lymph from the right kidney tends to drain into the paracaval, precaval, retrocaval, and interaortocaval nodes. Lymph connections thereafter are unpredictable, with eventual drainage in the thoracic duct [78]. Moreover, direct drainage from the kidney into the thoracic duct is not uncommon [79].

Although lymphadenectomy can inform staging, there presently has no established role for lymph node resection in patients with nonmetastatic RCC [80]. This is primary driven by the findings of a randomized trial evaluating lymphadenectomy that failed to show a therapeutic benefit among patients with clinically localized RCC (EORTC 30881) [81]. Of note, most patients in this study were considered low risk, with approximately 70% of patients being clinical T1 as per modern staging [80]. With a pN0 rate of 96% among those who underwent lymphadenectomy, it is not surprising that no survival benefit was observed. There are, however, retrospective studies suggesting a benefit associated with lymphadenectomy for large and advanced tumors or those with high-risk pathologic features [82, 83]. Still other retrospective studies have found no difference [84, 85].

Isolated pN1M0 RCC carries a poor prognosis. In one study, median time to distant metastasis was 4.2 months, and estimated 5-year metastasis-free survival was only 16%, while cancer-specific and overall survival were 25% [86]. Although there is retrospective data to suggest that extent of lymphadenectomy, as evidenced by lymph node yield, is associated with better survival [82, 87], caution should be applied in using these fidnings to support extensive lymphadenectomy, as the robustness of these data has been questioned [88]. Moreover, it is possible that extent of lymphadenectomy and lymph node yield may merely be an indirect indicator of surgical quality and ability. Therefore, although resection of clinically positive nodes may be reasonable when technically feasible, these patients likely have micrometastatic disease elsewhere and extensive lymphadenectomy is unlikely to be curative. Finally, there is no evidence of survival benefit of added lymphadenectomy for patients undergoing cytoreductive nephrectomy for metastatic RCC [89].

Resection of Adjacent Organs with Tumor Invasion

Nonmetastatic locally advanced RCC with adjacent organ invasion is not a contraindication to surgery. Aggressive en bloc resection can be safely performed, including in the setting large bowel, small bowel, mesentery, adrenal, liver, pancreas, spleen, diaphragm, and/or retroperitoneal muscle invasion [90, 91]. Such cases should be performed at an experienced center in conjunction with the appropriate consulting services.

Outcomes of Nonmetastatic Advanced Renal Cell Carcinoma

Complications and Morbidity

Potential early complications of radical nephrectomy for large and locally advanced RCC can be classified as cardiac (myocardial infarction, postoperative cardiac arrest), respiratory (atelectasis, pneumonia, need for reintubation or prolonged ventilator support), neurologic (stroke, prolonged coma), thromboembolic (deep vein thrombosis, pulmonary embolism), renal/urinary (urinary tract infection, acute renal failure, need for renal replacement therapy), wound related (superficial or deep surgical site infection, wound dehiscence), hemorrhagic, and septic [92]. In addition, there is a risk of intraoperative injury to adjacent organs that may result in bowel leak, pancreatic leak, bile leak, or pneumothorax. Long-term effects can include chronic kidney disease, incisional hernia, and lower extremity edema in some cases if patent venous return is not restored and insufficient venous collaterals existed prior to surgery.

Based on data from the American College of Surgeons National Surgery Quality Improvement Program (ACS-NSQIP), the overall rate of complications following nephrectomy is 13% in-hospital and 17% overall [92]. The median length of hospital stay is 4 days, and the 30-day mortality rate is 0.7%. These complication and mortality rates, as well as this length of stay estimate, may be higher for patients undergoing surgical management of large and advanced renal tumors. Most major complications (88.1%) tend to occur in hospital, while the majority of minor complications (70.7%) tend to occur after hospital discharge.

Nephrectomy with IVC tumor thrombectomy is associated with significant perioperative risk. The risk of major complications is approximately 34%, in-hospital mortality rate is approximately 7%, and 90-day mortality rate is 10% [93, 94]. These risks depend heavily on surgeon experience. In one study, 75% of the deaths occurred in the first two cases of the surgeon's experience [94].

There is significant potential for VTE postoperatively following cavotomy and IVC reconstruction. The incidence of VTE in this setting is estimated to be 22%, diagnosed at a median of 6 days postoperatively [95]. Common presenting symptoms include lower extremity edema, hemodynamic compromise, and acute desaturation. There is an increased risk with tube interposition graft reconstruction versus primary repair and patch graft reconstruction [95]. Although uncommon, there is also potential for tube graft thrombosis [77, 95]. Nonetheless, while routine anticoagulation is not warranted beyond conventional postoperative prophylaxis, a high clinical suspicion and diagnostic vigilance is necessary.

The literature is mixed on whether CPB is associated with an increased risk of complications and inhospital mortality [93, 94]. However, if CPB is deemed necessary, it is essential to concurrently use deep HCA, as it is associated with reduced perioperative mortality (8.3% versus 37.5%) and longer median overall survival (15.8 months versus 7.7 months) [75].

Concurrent hepatic resection for locally advanced or metastatic disease is associated with acceptable morbidity. The estimated risk of Clavien grade 3–4 complications is 12%, and the estimated risk of perioperative mortality is 3% [90]. These risks are similar for patients undergoing non-hepatic resections for locally advanced RCC, although hepatic resections carry a slightly higher risk of VTE by comparison.

Oncologic Outcomes and Prognostic Factors

Various prognostic models have been developed for the preoperative and postoperative prediction of recurrence and survival [96, 97]. A comprehensive review of outcomes is beyond the scope of this chapter, but key points as they pertain to large and advanced RCC will be highlighted.

The oncologic outcomes for large and advanced RCC demonstrate a dramatic contrast to pT1a tumors, where the 10-year cancer-specific survival is 90–96% [7, 8]. In contrast, the 10-year cancer-specific survival for large organ-confined tumors decreases gradually with increasing tumor size and ranges from 85% for 4–5 cm tumors to 49% for >15 cm tumors [9]. Meanwhile, the 10-year cancer-specific survival among those treated for pT3a, pT3b, and pT3c RCC is 36%, 26%, and 25%, respectively. Oncologic outcomes for pT4 RCC are poor, with an estimated survival of 12% at 5 years [7].

Surgical treatment is particularly impactful in patients with a VTT. The median survival in those with RCC and VTT without treatment is 5–7 months [98, 99]. In contrast, if treated surgically, the 5-year survival is 40–65% [99–103]. Unfortunately, not all patients are good surgical candidates. Patients with poor performance status, acute or fulminant Budd-Chiari syndrome, or critical metastatic disease will likely have poor outcomes with upfront surgery and may be best managed with systemic therapy.

In addition to stage and tumor size, histologic subtype, grade, coagulative necrosis, and sarcomatoid differentiation are all important prognostic factors in RCC [9, 104–106]. Recent data also suggest that rhabdoid differentiation warrants classification as grade 4 but should not be grouped together with sarcomatoid differentiation, which is independently associated with worse cancer survival even among patients with grade 4 RCC [107].

Conclusion

The safe and efficacious surgical management of large and advanced renal tumors, particularly those with VTT, requires careful preoperative evaluation and preparation, a thoughtful surgical approach, and meticulous perioperative care. Appropriately managing all of these aspects of the patient's care is essential to maximize the chances of achieving satisfactory perioperative and oncologic outcomes.

References

1. Smaldone MC, Egleston B, Hollingsworth JM, Hollenbeck BK, Miller DC, Morgan TM, et al. Understanding treatment disconnect and mortality trends in renal cell carcinoma using tumor registry data. Med Care. 2017;55(4):398–404.
2. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International variations and trends in renal cell carcinoma incidence and mortality. Eur Urol. 2015;67(3):519–30.
3. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. Rising incidence of renal cell cancer in the United States. JAMA. 1999;281(17):1628–31.
4. Chow WH, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. Nat Rev Urol. 2010;7(5):245–57.
5. Sun M, Abdollah F, Bianchi M, Trinh QD, Jeldres C, Tian Z, et al. A stage-for-stage and grade-for-grade analysis of cancer-specific mortality rates in renal cell carcinoma according to age: a competing-risks regression analysis. Eur Urol. 2011;60(6):1152–9.
6. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. Cancer. 2008;113(1):78–83.
7. Kim SP, Alt AL, Weight CJ, Costello BA, Cheville JC, Lohse C, et al. Independent validation of the 2010 American Joint Committee on Cancer TNM classification for renal cell carcinoma: results from a large, single institution cohort. J Urol. 2011;185(6):2035–9.
8. Novara G, Ficarra V, Antonelli A, Artibani W, Bertini R, Carini M, et al. Validation of the 2009 TNM version in a large multi-institutional cohort of patients treated for renal cell carcinoma: are further improvements needed? Eur Urol. 2010;58(4):588–95.
9. Bhindi B, Lohse CM, Mason RJ, Westerman ME, Cheville JC, Tollefson MK, et al. Are we using the best tumor size cut-points for renal cell carcinoma staging? Urology. 2017;109:121–6.
10. Cases C, Garcia-Zoghby L, Manzorro P, Valderrama-Canales FJ, Munoz M, Vidal M, et al. Anatomical variations of the renal arteries: cadaveric and radiologic study, review of the literature, and proposal of a new classification of clinical interest. Ann Anat. 2017;211:61–8.
11. Baniel J, Foster RS, Donohue JP. Surgical anatomy of the lumbar vessels: implications for retroperitoneal surgery. J Urol. 1995;153(5):1422–5.
12. Mathews R, Smith PA, Fishman EK, Marshall FF. Anomalies of the inferior vena cava and renal veins: embryologic and surgical considerations. Urology. 1999;53(5):873–80.
13. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med. 2005;353(23):2477–90.
14. Psutka SP, Boorjian SA, Thompson RH, Schmit GD, Schmitz JJ, Bower TC, et al. Clinical and radiographic predictors of the need for inferior vena cava resection during nephrectomy for patients with renal cell carcinoma and caval tumour thrombus. BJU Int. 2015;116(3):388–96.
15. Psutka SP, Leibovich BC. Management of inferior vena cava tumor thrombus in locally advanced renal cell carcinoma. Ther Adv Urol. 2015;7(4):216–29.
16. Ciancio G, Soloway M. Renal cell carcinoma invading the hepatic veins. Cancer. 2001;92(7):1836–42.
17. Linehan WM, Pinto PA, Bratslavsky G, Pfaffenroth E, Merino M, Vocke CD, et al. Hereditary kidney cancer: unique opportunity for disease-based therapy. Cancer. 2009;115(10 Suppl):2252–61.
18. Reaume MN, Graham GE, Tomiak E, Kamel-Reid S, Jewett MA, Bjarnason GA, et al. Canadian guideline on genetic screening for hereditary renal cell cancers. Can Urol Assoc J. 2013;7(9–10):319–23.
19. Verine J, Pluvinage A, Bousquet G, Lehmann-Che J, de Bazelaire C, Soufir N, et al. Hereditary renal cancer syndromes: an update of a systematic review. Eur Urol. 2010;58(5):701–10.
20. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer (Version 2.2017). Available from: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.
21. Sheth S, Scatarige JC, Horton KM, Corl FM, Fishman EK. Current concepts in the diagnosis and management of renal cell carcinoma: role of multidetector CT and three-dimensional CT. Radiographics. 2001;21 Spec No:S237–54.

22. Larcher A, Dell'Oglio P, Fossati N, Nini A, Muttin F, Suardi N, et al. When to perform preoperative chest computed tomography for renal cancer staging. BJU Int. 2017;120(4):490–6.
23. Kutikov A, Smaldone MC, Uzzo RG, Haifler M, Bratslavsky G, Leibovich BC. Renal mass biopsy: always, sometimes, or never? Eur Urol. 2016;70(3):403–6.
24. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. J Urol. 2003;170(6 Pt 1):2217–20.
25. Rini BI, McKiernan JM, Chang SS, Choueiri TK, Kenney PA, Landman J, et al. Kidney. In: Amin MB, editor. AJCC Cancer Staging Manual. 8th ed. Chicago: Springer; 2017. p. 739–48.
26. Neves RJ, Zincke H. Surgical treatment of renal cancer with vena cava extension. Br J Urol. 1987;59(5):390–5.
27. Novick AC, Streem SB, Pontes E. Stewart's operative urology. 2nd ed. Philadelphia: Williams & Wilkins; 1989.
28. Hinman F. Atlas of urologic surgery. 2nd ed. Philadelphia: WB Saunders Co; 1998.
29. Robson CJ. Staging of renal cell carcinoma. Prog Clin Biol Res. 1982;100:439–45.
30. Pouliot F, Shuch B, Larochelle JC, Pantuck A, Belldegrun AS. Contemporary management of renal tumors with venous tumor thrombus. J Urol. 2010;184(3):833–41. quiz 1235
31. Gettman MT, Boelter CW, Cheville JC, Zincke H, Bryant SC, Blute ML. Charlson comorbidity index as a predictor of outcome after surgery for renal cell carcinoma with renal vein, vena cava or right atrium extension. J Urol. 2003;169(4):1282–6.
32. Kallman DA, King BF, Hattery RR, Charboneau JW, Ehman RL, Guthman DA, et al. Renal vein and inferior vena cava tumor thrombus in renal cell carcinoma: CT, US, MRI and venacavography. J Comput Assist Tomogr. 1992;16(2):240–7.
33. Oto A, Herts BR, Remer EM, Novick AC. Inferior vena cava tumor thrombus in renal cell carcinoma: staging by MR imaging and impact on surgical treatment. AJR Am J Roentgenol. 1998;171(6):1619–24.
34. Blute ML, Leibovich BC, Lohse CM, Cheville JC, Zincke H. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. BJU Int. 2004;94(1):33–41.
35. Goldfarb DA, Novick AC, Lorig R, Bretan PN, Montie JE, Pontes JE, et al. Magnetic resonance imaging for assessment of vena caval tumor thrombi: a comparative study with venacavography and computerized tomography scanning. J Urol. 1990;144(5):1100–3. discussion 3–4
36. Lawrentschuk N, Gani J, Riordan R, Esler S, Bolton DM. Multidetector computed tomography vs magnetic resonance imaging for defining the upper limit of tumour thrombus in renal cell carcinoma: a study and review. BJU Int. 2005;96(3):291–5.
37. Guzzo TJ, Pierorazio PM, Schaeffer EM, Fishman EK, Allaf ME. The accuracy of multidetector computerized tomography for evaluating tumor thrombus in patients with renal cell carcinoma. J Urol. 2009;181(2):486–90. discussion 91
38. Gershman B, Takahashi N, Moreira DM, Thompson RH, Boorjian SA, Lohse CM, et al. Radiographic size of retroperitoneal lymph nodes predicts pathological nodal involvement for patients with renal cell carcinoma: development of a risk prediction model. BJU Int. 2016;118(5):742–9.
39. Blute ML, Leibovich BC, Cheville JC, Lohse CM, Zincke H. A protocol for performing extended lymph node dissection using primary tumor pathological features for patients treated with radical nephrectomy for clear cell renal cell carcinoma. J Urol. 2004;172(2):465–9.
40. Crispen PL, Breau RH, Allmer C, Lohse CM, Cheville JC, Leibovich BC, et al. Lymph node dissection at the time of radical nephrectomy for high-risk clear cell renal cell carcinoma: indications and recommendations for surgical templates. Eur Urol. 2011;59(1):18–23.
41. Hutterer GC, Patard JJ, Perrotte P, Ionescu C, de La Taille A, Salomon L, et al. Patients with renal cell carcinoma nodal metastases can be accurately identified: external validation of a new nomogram. Int J Cancer. 2007;121(11):2556–61.
42. Capitanio U, Abdollah F, Matloob R, Suardi N, Castiglione F, Di Trapani E, et al. When to perform lymph node dissection in patients with renal cell carcinoma: a novel approach to the preoperative assessment of risk of lymph node invasion at surgery and of lymph node progression during follow-up. BJU Int. 2013;112(2):E59–66.

43. Schwartz MJ, Smith EB, Trost DW, Vaughan ED Jr. Renal artery embolization: clinical indications and experience from over 100 cases. BJU Int. 2007;99(4):881–6.
44. Bakal CW, Cynamon J, Lakritz PS, Sprayregen S. Value of preoperative renal artery embolization in reducing blood transfusion requirements during nephrectomy for renal cell carcinoma. J Vasc Interv Radiol. 1993;4(6):727–31.
45. May M, Brookman-Amissah S, Pflanz S, Roigas J, Hoschke B, Kendel F. Pre-operative renal arterial embolisation does not provide survival benefit in patients with radical nephrectomy for renal cell carcinoma. Br J Radiol. 2009;82(981):724–31.
46. Bergreen PW, Woodside J, Paster SB. Therapeutic renal infarction. J Urol. 1977;118(3):372–4.
47. Subramanian VS, Stephenson AJ, Goldfarb DA, Fergany AF, Novick AC, Krishnamurthi V. Utility of preoperative renal artery embolization for management of renal tumors with inferior vena caval thrombi. Urology. 2009;74(1):154–9.
48. Woodruff DY, Van Veldhuizen P, Muehlebach G, Johnson P, Williamson T, Holzbeierlein JM. The perioperative management of an inferior vena caval tumor thrombus in patients with renal cell carcinoma. Urol Oncol. 2013;31(5):517–21.
49. Blute ML, Boorjian SA, Leibovich BC, Lohse CM, Frank I, Karnes RJ. Results of inferior vena caval interruption by greenfield filter, ligation or resection during radical nephrectomy and tumor thrombectomy. J Urol. 2007;178(2):440–5. discussion 4
50. Cowey CL, Amin C, Pruthi RS, Wallen EM, Nielsen ME, Grigson G, et al. Neoadjuvant clinical trial with sorafenib for patients with stage II or higher renal cell carcinoma. J Clin Oncol. 2010;28(9):1502–7.
51. Powers MK, Sartor O, Lee BR. Neoadjuvant tyrosine kinase downstaging of T2 renal cell carcinoma in solitary kidney before robotic partial nephrectomy. J Endourol Case Rep. 2015;1(1):47–9.
52. Silberstein JL, Millard F, Mehrazin R, Kopp R, Bazzi W, DiBlasio CJ, et al. Feasibility and efficacy of neoadjuvant sunitinib before nephron-sparing surgery. BJU Int. 2010;106(9):1270–6.
53. Shuch B, Riggs SB, LaRochelle JC, Kabbinavar FF, Avakian R, Pantuck AJ, et al. Neoadjuvant targeted therapy and advanced kidney cancer: observations and implications for a new treatment paradigm. BJU Int. 2008;102(6):692–6.
54. Karakiewicz PI, Suardi N, Jeldres C, Audet P, Ghosn P, Patard JJ, et al. Neoadjuvant sutent induction therapy may effectively down-stage renal cell carcinoma atrial thrombi. Eur Urol. 2008;53(4):845–8.
55. Di Silverio F, Sciarra A, Parente U, Andrea A, Von Heland M, Panebianco V, et al. Neoadjuvant therapy with sorafenib in advanced renal cell carcinoma with vena cava extension submitted to radical nephrectomy. Urol Int. 2008;80(4):451–3.
56. Cost NG, Delacroix SE Jr, Sleeper JP, Smith PJ, Youssef RF, Chapin BF, et al. The impact of targeted molecular therapies on the level of renal cell carcinoma vena caval tumor thrombus. Eur Urol. 2011;59(6):912–8.
57. Haas NB, Manola J, Uzzo RG, Flaherty KT, Wood CG, Kane C, et al. Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomised, phase 3 trial. Lancet. 2016;387(10032):2008–16.
58. Haas NB, Manola J, Dutcher JP, Flaherty KT, Uzzo RG, Atkins MB, et al. Adjuvant treatment for high-risk clear cell renal Cancer: updated results of a high-risk subset of the ASSURE randomized trial. JAMA Oncol. 2017;3(9):1249–52.
59. Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med. 2016;375(23):2246–54.
60. Motzer RJ, Haas NB, Donskov F, Gross-Goupil M, Varlamov S, Kopyltsov E, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. J Clin Oncol. 2017;35:3916.
61. Simmons MN, Kaouk J, Gill IS, Fergany A. Laparoscopic radical nephrectomy with hilar lymph node dissection in patients with advanced renal cell carcinoma. Urology. 2007;70(1):43–6.
62. Stewart GD, Ang WJ, Laird A, Tolley DA, Riddick AC, McNeill SA. The operative safety and oncological outcomes of laparoscopic nephrectomy for T3 renal cell cancer. BJU Int. 2012;110(6):884–90.

63. Stifelman MD, Handler T, Nieder AM, Del Pizzo J, Taneja S, Sosa RE, et al. Hand-assisted laparoscopy for large renal specimens: a multi-institutional study. Urology. 2003;61(1):78–82.
64. Jeong IG, Khandwala YS, Kim JH, Han DH, Li S, Wang Y, et al. Association of robotic-assisted vs laparoscopic radical nephrectomy with perioperative outcomes and health care costs, 2003 to 2015. JAMA. 2017;318(16):1561–8.
65. Yang DY, Monn MF, Bahler CD, Sundaram CP. Does robotic assistance confer an economic benefit during laparoscopic radical nephrectomy? J Urol. 2014;192(3):671–6.
66. Shao P, Li J, Qin C, Lv Q, Ju X, Li P, et al. Laparoscopic radical nephrectomy and inferior vena cava thrombectomy in the treatment of renal cell carcinoma. Eur Urol. 2015;68(1):115–22.
67. Chopra S, Simone G, Metcalfe C, de Castro Abreu AL, Nabhani J, Ferriero M, et al. Robot-assisted level II-III inferior vena cava tumor thrombectomy: step-by-step technique and 1-year outcomes. Eur Urol. 2017;72(2):267–74.
68. Seiler CM, Deckert A, Diener MK, Knaebel HP, Weigand MA, Victor N, et al. Midline versus transverse incision in major abdominal surgery: a randomized, double-blind equivalence trial (POVATI: ISRCTN60734227). Ann Surg. 2009;249(6):913–20.
69. Vigneswaran Y, Poli E, Talamonti MS, Haggerty SP, Linn JG, Ujiki MB. Rectus abdominis atrophy after ventral abdominal incisions: midline versus chevron. Hernia. 2017;21:619.
70. Boorjian SA, Sengupta S, Blute ML. Renal cell carcinoma: vena caval involvement. BJU Int. 2007;99(5 Pt B):1239–44.
71. Nason GJ, Aslam A, Giri SK. Predictive ability of preoperative CT scan in determining whether the adrenal gland is spared at radical nephrectomy. Curr Urol. 2016;9(3):143–7.
72. Weight CJ, Kim SP, Lohse CM, Cheville JC, Thompson RH, Boorjian SA, et al. Routine adrenalectomy in patients with locally advanced renal cell cancer does not offer oncologic benefit and places a significant portion of patients at risk for an asynchronous metastasis in a solitary adrenal gland. Eur Urol. 2011;60(3):458–64.
73. O'Malley RL, Godoy G, Kanofsky JA, Taneja SS. The necessity of adrenalectomy at the time of radical nephrectomy: a systematic review. J Urol. 2009;181(5):2009–17.
74. Yap SA, Alibhai SM, Abouassaly R, Timilshina N, Margel D, Finelli A. Ipsilateral adrenalectomy at the time of radical nephrectomy impacts overall survival. BJU Int. 2013;111(3 Pt B):E54–8.
75. Shuch B, Crispen PL, Leibovich BC, Larochelle JC, Pouliot F, Pantuck AJ, et al. Cardiopulmonary bypass and renal cell carcinoma with level IV tumour thrombus: can deep hypothermic circulatory arrest limit perioperative mortality? BJU Int. 2011;107(5):724–8.
76. Ciancio G, Soloway MS. Renal cell carcinoma with tumor thrombus extending above diaphragm: avoiding cardiopulmonary bypass. Urology. 2005;66(2):266–70.
77. Hyams ES, Pierorazio PM, Shah A, Lum YW, Black J, Allaf ME. Graft reconstruction of inferior vena cava for renal cell carcinoma stage pT3b or greater. Urology. 2011;78(4):838–43.
78. Karmali RJ, Suami H, Wood CG, Karam JA. Lymphatic drainage in renal cell carcinoma: back to the basics. BJU Int. 2014;114(6):806–17.
79. Assouad J, Riquet M, Foucault C, Hidden G, Delmas V. Renal lymphatic drainage and thoracic duct connections: implications for cancer spread. Lymphology. 2006;39(1):26–32.
80. Capitanio U, Leibovich BC. The rationale and the role of lymph node dissection in renal cell carcinoma. World J Urol. 2017;35(4):497–506.
81. Blom JH, van Poppel H, Marechal JM, Jacqmin D, Schroder FH, de Prijck L, et al. Radical nephrectomy with and without lymph-node dissection: final results of European Organization for Research and Treatment of Cancer (EORTC) randomized phase 3 trial 30881. Eur Urol. 2009;55(1):28–34.
82. Capitanio U, Suardi N, Matloob R, Roscigno M, Abdollah F, Di Trapani E, et al. Extent of lymph node dissection at nephrectomy affects cancer-specific survival and metastatic progression in specific sub-categories of patients with renal cell carcinoma (RCC). BJU Int. 2014;114(2):210–5.
83. Schafhauser W, Ebert A, Brod J, Petsch S, Schrott KM. Lymph node involvement in renal cell carcinoma and survival chance by systematic lymphadenectomy. Anticancer Res. 1999;19(2C):1573–8.

84. Gershman B, Thompson RH, Moreira DM, Boorjian SA, Tollefson MK, Lohse CM, et al. Radical nephrectomy with or without lymph node dissection for nonmetastatic renal cell carcinoma: a propensity score-based analysis. Eur Urol. 2017;71(4):560–7.
85. Feuerstein MA, Kent M, Bazzi WM, Bernstein M, Russo P. Analysis of lymph node dissection in patients with >/=7-cm renal tumors. World J Urol. 2014;32(6):1531–6.
86. Gershman B, Moreira DM, Thompson RH, Boorjian SA, Lohse CM, Costello BA, et al. Renal cell carcinoma with isolated lymph node involvement: long-term natural history and predictors of oncologic outcomes following surgical resection. Eur Urol. 2017;72:300.
87. Whitson JM, Harris CR, Reese AC, Meng MV. Lymphadenectomy improves survival of patients with renal cell carcinoma and nodal metastases. J Urol. 2011;185(5):1615–20.
88. Sun M, Trinh QD, Bianchi M, Hansen J, Abdollah F, Tian Z, et al. Extent of lymphadenectomy does not improve the survival of patients with renal cell carcinoma and nodal metastases: biases associated with the handling of missing data. BJU Int. 2014;113(1):36–42.
89. Gershman B, Thompson RH, Moreira DM, Boorjian SA, Lohse CM, Costello BA, et al. Lymph node dissection is not associated with improved survival among patients undergoing cytoreductive nephrectomy for metastatic renal cell carcinoma: a propensity score based analysis. J Urol. 2017;197(3 Pt 1):574–9.
90. Joyce DD, Psutka SP, Groeschl RT, Thompson RH, Boorjian SA, Cheville JC, et al. Complications and outcomes associated with surgical management of renal cell carcinoma involving the liver: a matched cohort study. Urology. 2017;99:155–61.
91. Borregales LD, Kim DY, Staller AL, Qiao W, Thomas AZ, Adibi M, et al. Prognosticators and outcomes of patients with renal cell carcinoma and adjacent organ invasion treated with radical nephrectomy. Urol Oncol. 2016;34(5):237.e19–26.
92. Sood A, Abdollah F, Sammon JD, Kapoor V, Rogers CG, Jeong W, et al. An evaluation of the timing of surgical complications following nephrectomy: data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). World J Urol. 2015;33(12):2031–8.
93. Abel EJ, Thompson RH, Margulis V, Heckman JE, Merril MM, Darwish OM, et al. Perioperative outcomes following surgical resection of renal cell carcinoma with inferior vena cava thrombus extending above the hepatic veins: a contemporary multicenter experience. Eur Urol. 2014;66(3):584–92.
94. Toren P, Abouassaly R, Timilshina N, Kulkarni G, Alibhai S, Finelli A. Results of a national population-based study of outcomes of surgery for renal tumors associated with inferior vena cava thrombus. Urology. 2013;82(3):572–7.
95. Hicks CW, Glebova NO, Piazza KM, Orion K, Pierorazio PM, Lum YW, et al. Risk of venous thromboembolic events following inferior vena cava resection and reconstruction. J Vasc Surg. 2016;63(4):1004–10.
96. Meskawi M, Sun M, Trinh QD, Bianchi M, Hansen J, Tian Z, et al. A review of integrated staging systems for renal cell carcinoma. Eur Urol. 2012;62(2):303–14.
97. Lane BR, Kattan MW. Prognostic models and algorithms in renal cell carcinoma. Urol Clin North Am. 2008;35(4):613–25. vii
98. Reese AC, Whitson JM, Meng MV. Natural history of untreated renal cell carcinoma with venous tumor thrombus. Urol Oncol. 2013;31(7):1305–9.
99. Haferkamp A, Bastian PJ, Jakobi H, Pritsch M, Pfitzenmaier J, Albers P, et al. Renal cell carcinoma with tumor thrombus extension into the vena cava: prospective long-term followup. J Urol. 2007;177(5):1703–8.
100. Karnes RJ, Blute ML. Surgery insight: management of renal cell carcinoma with associated inferior vena cava thrombus. Nat Clin Pract Urol. 2008;5(6):329–39.
101. Lambert EH, Pierorazio PM, Shabsigh A, Olsson CA, Benson MC, McKiernan JM. Prognostic risk stratification and clinical outcomes in patients undergoing surgical treatment for renal cell carcinoma with vascular tumor thrombus. Urology. 2007;69(6):1054–8.
102. Klatte T, Pantuck AJ, Riggs SB, Kleid MD, Shuch B, Zomorodian N, et al. Prognostic factors for renal cell carcinoma with tumor thrombus extension. J Urol. 2007;178(4 Pt 1):1189–95. discussion 95

103. Sweeney P, Wood CG, Pisters LL, Slaton JW, Vaporciyan A, Munsell M, et al. Surgical management of renal cell carcinoma associated with complex inferior vena caval thrombi. Urol Oncol. 2003;21(5):327–33.
104. Parker WP, Cheville JC, Frank I, Zaid HB, Lohse CM, Boorjian SA, et al. Application of the Stage, Size, Grade, and Necrosis (SSIGN) Score for clear cell renal cell carcinoma in contemporary patients. Eur Urol. 2017;71(4):665–73.
105. Leibovich BC, Lohse CM, Crispen PL, Boorjian SA, Thompson RH, Blute ML, et al. Histological subtype is an independent predictor of outcome for patients with renal cell carcinoma. J Urol. 2010;183(4):1309–15.
106. Zhang BY, Thompson RH, Lohse CM, Leibovich BC, Boorjian SA, Cheville JC, et al. A novel prognostic model for patients with sarcomatoid renal cell carcinoma. BJU Int. 2015;115(3):405–11.
107. Zhang BY, Cheville JC, Thompson RH, Lohse CM, Boorjian SA, Leibovich BC, et al. Impact of rhabdoid differentiation on prognosis for patients with grade 4 renal cell carcinoma. Eur Urol. 2015;68(1):5–7.

Chapter 10
Pediatric Renal Tumors

Matthew Kasprenski and Heather Di Carlo

Wilms Tumor

Wilms tumor is the most common primary renal malignancy in the pediatric population [1, 2]. Also known as nephroblastoma, Wilms tumor is comprised on the histological level of a classic pattern of three different cell types including blastemal, stromal, and epithelial elements [3]. Histopathology of Wilms tumor has important implications on outcomes and treatment as those tumors with unfavorable histologic features and anaplasia carry a poor prognosis even at low-stage disease and are more resistant to chemotherapy [4]. Outcomes for Wilms tumor have dramatically improved with survival rates approaching 90% in part due to multimodal therapy [5–7].

Epidemiology

Each year approximately 500 new cases of Wilms tumor are diagnosed in the United States, with roughly 7.1 cases per one million patients younger than 15 years old and an equal distribution between male and female patients in unilateral cases [2]. The median age of onset for unilateral Wilms is 38 months; however, patients with bilateral disease typically present earlier in life (median 17–27 months) [2].

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Syndromes and Conditions Associated with Wilms Tumor

Wilms tumor is typically sporadic; however, approximately 10% of children have an associated congenital anomaly [8]. Congenital syndromes associated with Wilms tumor can be separated into those with and without somatic overgrowth.

WAGR syndrome is characterized by Wilms tumor, aniridia, genitourinary anomalies, and mental retardation. This syndrome is associated with chromosomal deletions at 11p13 which contains the *WT1* gene [9]. Denys-Drash syndrome is another congenital disorder that is associated with mutations in the *WT1* gene and the development of Wilms tumor. Denys-Drash syndrome is otherwise characterized by male pseudohermaphroditism and renal failure [10]. The risk of developing Wilms tumor in Denys-Drash is approximately 90% [10].

Beckwith-Wiedemann is a somatic outgrowth syndrome that carries an increased risk of Wilms tumor in up to 10% of cases [11]. This syndrome is characterized by macroglossia, macrosomia, midline defects, skin creases near the ears, and neonatal hypoglycemia. Beckwith-Wiedemann syndrome is associated with abnormalities at chromosome 11p15 [11]. 9q22.3 microdeletion syndrome also carries an increased risk of developing Wilms tumor [12] and is characterized by metopic craniosynostosis, hydrocephalus, macrosomia, and developmental delay [13].

It is recommended that children at high risk of developing Wilms tumor be screened with an abdominal ultrasound every 3 months until 8 years of age [14, 15]. These syndromes that carry an increased risk of tumor development have helped gain important insight and greater understanding of the genetic cause of Wilms tumor.

A complete list of syndromes and conditions with associated cancer risk can be found in Table 10.1.

Genetics

The *WT1* gene is located on the short arm of chromosome 11p13, and it is essential for normal genitourinary development [16, 17]. *WT1* mutations are identified in only 10–20% of cases of sporadic Wilms tumor [16, 18, 19]. Mutations in *WT1* have been found in WAGR syndrome, Denys-Drash syndrome, and Frasier syndrome [10, 20]. Somatic activation of the *CTNNB1* gene occurs in up to 15% of patients with Wilms tumor and is frequently found in association with *WT1* mutations [21, 22].

The *WTX* gene is located on the X chromosome at Xq11.1 and is altered in 15–20% of Wilms tumors [23, 24]. However, patients with germline mutations in *WTX* leading to osteopathia striata congenital with cranial sclerosis are not at increased risk of tumor development [25].

Loss of heterozygosity of 11p15.5, the *WT2* locus, is also frequently found in Wilms tumors, and approximately 80% of patients with Beckwith-Wiedemann syndrome have an abnormality of the 11p15 domain [26]. Children with sporadic Wilms tumor have been found to have 11p15 defects in 3% of cases without features of overgrowth with an increased risk of bilateral tumors [27].

Table 10.1 Conditions and syndromes associated with Wilms tumor

Syndrome or condition	Risk of Wilms tumor (%)	Clinical features
Associated with overgrowth		
Beckwith-Wiedemann	10%	Macroglossia, omphalocele, ear skin creases
Isolated hemihypertrophy	6%	Overgrowth of one or more body part
Perlman	40%	Fetal gigantism, renal dysplasia, nephroblastomatosis
Simpson-Golabi-Behmel	10%	Macrosomia, macroglossia, diaphragmatic hernia
Sotos	2–3%	Macrocephaly, central nervous system anomalies, developmental delay
9q22.3	Unknown	Craniofacial abnormalities, hydrocephalus, developmental delay
Non-overgrowth associated		
Denys-Drash	90%	Disorder of sexual differentiation, glomerulopathy
WAGR	>30%	Aniridia, genitourinary anomaly, mental retardation
Sporadic aniridia	5%	Partial or complete absence of the iris
Bohring-Opitz	7%	Distinctive facial features, microcephaly, hypertrichosis, severe myopia, nevus flammeus, unusual posture, intellectual disabilities
Familial Wilms	2%	Genitourinary malformations
Bloom syndrome	Unknown	Short stature, sun-sensitive skin
Trisomy 18	Unknown	Congenital heart disease
Fanconi anemia with biallelic mutations in BRCA2 or PALB2	Unknown	Growth retardation, congenital anomalies, bone marrow failure, cancer predisposition
Li-Fraumeni	Unknown	Early-onset sarcomas

Gain of chromosome 1q is found in approximately 30% of Wilms tumors and is associated with worse outcomes. In an analysis from the Children's Oncology Group of 1114 patients enrolled in NWTS-5, gain of 1q was associated with event-free survival across all stages of the disease [28]. With inferior survival, gain of 1q could potentially be incorporated into risk stratification and direct treatment intensity in the future. Additionally, loss of heterozygosity at chromosome 16q and 1p significantly increased the risk of relapse and death [29].

Diagnosis

Wilms tumor typically presents as an asymptomatic abdominal mass found by the parents or primary care physician during routine exam [30]. However, abdominal pain may be present in approximately 40% of children [3]. Additionally, gross hematuria occurs in 18% of children, and microscopic hematuria is seen in 24%

[30]. Hypertension may also be a presenting symptom resulting from activation of the renin-angiotensin-aldosterone system which is seen in up to 25% of patients with Wilms [31].

Work-up following a diagnosis of Wilms tumor should include complete physical exam with a focus on identifying aniridia, hemihypertrophy, or other clues to an underlying syndrome. A panel of labs should be drawn including complete blood count, liver function test, renal panel, and urinalysis. Coagulation studies should be considered as 1–8% of patients with Wilms tumor will have acquired von Willebrand disease [32]. Surgical findings in conjunction with pathologic review are used to stage the tumor and are key components of risk stratification and placement into Children's Oncology Group (COG) protocols. The staging system for Wilms tumor is found in Table 10.2. An ultrasound is often the initial imaging modality obtained in these patients and should prompt further axial imaging. Computed tomography scan (CT) or magnetic resonance imaging (MRI) should be obtained of the chest, abdomen and pelvis. Identifying the extent of the tumor in regard to size, location, and presence of tumor thrombus and evaluation of the contralateral kidney are crucial in staging and management of Wilms tumor. Identification of a contralateral tumor on imaging studies increases the clinical stage and changes the initial management from immediate surgery to potential chemotherapy and nephron-sparing surgery. CT scan can accurately identify presence or absence of tumor thrombus which eliminates the need for Doppler ultrasound (Fig. 10.1) [33]. Biopsy prior to surgery is controversial in stage I and II Wilms as it will upstage a patient to stage III and may cause local tumor spread [34].

Pathology

Wilms tumor consists of elements of the developing kidney including blastemal, epithelial, and stromal cell types [3]. Histologically Wilms tumor can be separated into two groups that have important prognostic implications: favorable histology and anaplastic histology. Anaplastic histology is found in approximately 10% of patients with Wilms tumor and is the most important histologic predictor of response and survival in patients with Wilms tumor [4, 35]. Tumors that harbor anaplasia are typically more resistant to chemotherapy. Patients aged 10–16 years with Wilms have a higher incidence of anaplastic histology [36]. Additionally, mutations in the *TP53* gene have been identified in anaplastic Wilms tumors [37]. This can serve as a molecular marker for anaplastic Wilms and have subsequent implications in treatment.

Nephrogenic rests are retained embryonic kidney cells that are arranged in clusters and are precursors to Wilms tumor [38]. Microscopic nephrogenic rests are found in about 1% of pediatric autopsies, and it is estimated that fewer than 1% of infants with microscopic rests will develop a Wilms tumor [39, 40]. There are two categories of rests currently recognized [38]. Perilobar nephrogenic rests are confined to the periphery of the kidney and frequently found in fetal overgrowth and overgrowth syndromes, whereas intralobar nephrogenic rests occur anywhere

Table 10.2 Wilms tumor staging

Stage	Criteria
I	Tumor limited to the kidney and completely excised
	Intact renal capsule
	No intraoperative rupture or prior biopsy
	No vascular extension
	Negative lymph nodes
	~40% of patients
II	Tumor extends beyond the kidney but was completely excised
	Vascular extension may be present but was completely removed en bloc
	No evidence at or beyond margin of resection
	Negative lymph nodes
	~20% of patients
III	Residual tumor present and limited to the abdomen
	Lymph node involvement in the abdomen or pelvis
	Tumor implants present on or through the peritoneal surface
	Incomplete tumor resection due to infiltration into adjacent structures
	Gross or microscopic tumor present at surgical margins
	Tumor rupture prior to or during surgery
	Renal biopsy prior to resection
	~20% of patients
IV	Metastasis to the lungs, liver, or bones
	Lymph node involvement outside the abdomen and pelvis
	~10% of patients
V	Bilateral tumors present at diagnosis
	~5% of patients

Adapted from www.childrensoncologygroup.org

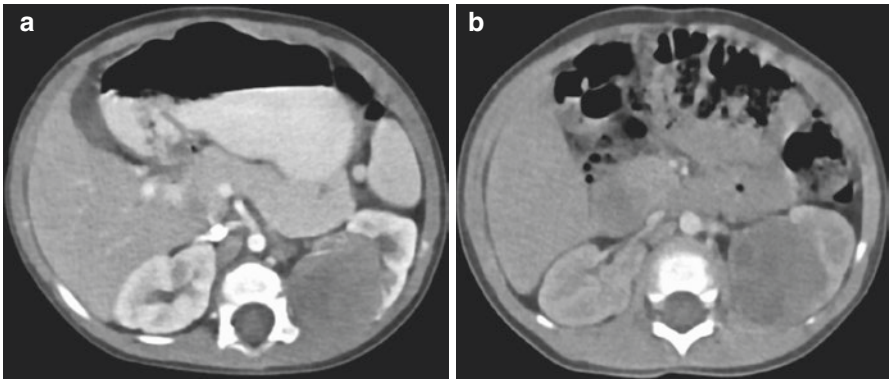

Fig. 10.1 Wilms tumor in a 2-year-old male with WAGR syndrome. (**a**) Axial CT scan prior to chemotherapy. (**b**) CT scan following chemotherapy with no significant change in tumor size

within the renal lobe and renal collecting system. Intralobar nephrogenic rests contain multiple cell types and have an indistinct border. Additionally, intralobar nephrogenic rests are frequently associated with deletions or mutations in *WT1* [41]. Diffuse hyperplastic perilobar nephroblastomatosis represents a unique category with multiple perilobar nephrogenic rests in the hyperplastic phase. It is considered a pre-neoplastic condition where the renal unit is enlarged due to the rind of thick nephroblastic tissue oftentimes making difficult to distinguish on a biopsy this entity from Wilms tumor [42].

Treatment

The initial treatment in the majority of unilateral Wilms tumors is radical nephrectomy with renal lymph node sampling using a transabdominal or thoracoabdominal incision [43]. Use of a flank incision is not typically recommended. Surgeons must be aware of the risk of intraoperative tumor rupture and through these approaches hopefully mitigate this risk and subsequent upstaging of the tumor.

The contralateral kidney does not need to be explored if preoperative imaging does not indicate a contralateral tumor. Preoperative or intraoperative biopsy should not be performed in the setting of unilateral resectable tumors as it would upstage the tumor [44]. There is a risk of ureteral involvement in Wilms tumors, and if present, the ureter should be taken en bloc to avoid tumor spill [45]. If preoperative gross hematuria is present, cystoscopy is recommended. Assessment of vascular extension into the inferior vena cava and renal vein should be conducted by palpation to check for tumor thrombus.

Treatment of patients with Wilms tumor should involve a multidisciplinary team that is well versed in pediatric malignancies. Additionally, patients with Wilms tumor should be considered for entry into a clinical trial. Risk stratification based on stage and pathologic findings dictates which treatment protocol patients are assigned. In the United States, the treatment of Wilms tumor is based on the results of clinical trials completed by the National Wilms Tumor Study (NWTS) group which has been incorporated into the Children's Oncology Group (COG) [4, 29, 46–48]. Results from NWTS and COG trials with rates of survival are provided in Table 10.3.

Bilateral Wilms tumors have had historically poor survival in comparison to unilateral favorable histology Wilms tumor [49]. A recent report from the COG investigated treatment of bilateral Wilms tumor in an effort to improve survival and preserve renal function [48]. Preoperative chemotherapy was intensified with the goal of performing bilateral partial nephrectomies and response was assessed on imaging after 6 weeks of treatment. Patients who did not respond received another two cycles of chemotherapy and open bilateral renal biopsies were performed in those who showed no evidence of response to asses for anaplasia. Postoperative chemotherapy and radiation were based on the kidney with the highest-stage local disease. Results of this trial are encouraging with bilateral favorable histology 4-year event-free survival and overall survival 84.2% and 97.3%, respectively.

Table 10.3 Treatment of Wilms tumor

Stage	Histology	Treatment	4-year survival
I	FH <24mo, tumor weight < 550 g	Surgery with lymph node biopsy	90% EFS, 100% OS[a]
	FH >24mo, tumor weight > 550 g	Nephrectomy + lymph node sampling followed by regimen EE-4A	94% RFS, 98% OS[b]
	FA	Nephrectomy + lymph node sampling followed by regimen EE-4A and XRT	Data not available
	DA	Nephrectomy + lymph node sampling followed by regimen EE-4A and XRT	Data not available
II	FH	Nephrectomy + lymph node sampling followed by regimen EE-4A	86% EFS, 98% OS[c]
	FA	Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A	80% EFS, 80% OS[d]
	DA	Nephrectomy + lymph node sampling followed by abdominal XRT and regimen I	83% EFS, 82% OS[d]
III	FH	Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A	87% RFS, 94% OS[c]
	FA	Nephrectomy + lymph node sampling followed by abdominal XRT and regimen DD-4A	88% RFS, 100% OS[d]
	FA (preoperative)	Preoperative treatment with DD-4A followed by nephrectomy +lymph node sampling and abdominal XRT	71% RFS, 71% OS[d]
	DA (preoperative)	Preoperative treatment with regimen I followed by nephrectomy +lymph node sampling and abdominal XRT	46% EFS, 53% OS[d]
	DA	Immediate nephrectomy +lymph node sampling followed by abdominal XRT and regimen I	65% EFS, 67% OS[d]
IV	FH	Nephrectomy + lymph node sampling, followed by abdominal XRT, radiation to sites of metastases, bilateral pulmonary XRT, and regimen DD-4A	76% RFS, 86% OS[c]
	FA	Nephrectomy + lymph node sampling, followed by abdominal XRT, radiation to sites of metastases, bilateral pulmonary XRT, and regimen DD-4A	61% EFS, 72% OS[d]
	DA	Immediate nephrectomy +lymph node sampling followed by abdominal XRT, radiation to sites of metastases, whole-lung XRT, and regimen I	33% EFS, 33% OS[d]
	DA (preoperative)	Preoperative treatment with regimen I followed by nephrectomy + lymph node sampling, followed by abdominal XRT, radiation to sites of metastases, and whole-lung XRT	31% EFS, 44% OS[d]
V	Preoperative chemotherapy	Vincristine, dactinomycin, and doxorubicin for 6 or 12 weeks based on radiographic response followed by surgery. Further chemotherapy dictated by histology. Radiation dictated by the postchemotherapy stage	82% EFS, 95% OS[e,f]

(continued)

Table 10.3 (continued)

Adapted from https://www.cancer.gov/types/kidney/hp/wilms-treatment-pdq
FH favorable histology, *FA* focal anaplasia, *DA* diffuse anaplasia, *RFS* recurrence-free survival, *EFS* event-free survival, *OS* overall survival
Regimen EE-4A = vincristine, dactinomycin for 18 weeks after nephrectomy
Regimen DD-4A = vincristine, dactinomycin, doxorubicin for 24 weeks
Regimen I = vincristine, doxorubicin, cyclophosphamide, etoposide for 24 weeks after nephrectomy
[a]Source: Fernandez et al. [47]
[b]Source: Shamberger et al. [46]
[c]Source: Grundy et al. [29]
[d]Source: Dome et al. [4]
[e]Source: Ehrlich et al. [48]
[f]In bilateral favorable histology

Late Effects of Therapy

Children treated for Wilms tumor are at risk of developing sequelae of their treatment. Secondary malignancies in the form of digestive and breast cancers have been reported with radiation therapy identified as a risk factor [50, 51]. There is also an increased risk of congestive heart failure resulting from doxorubicin as well as radiation [52, 53]. Although Wilms tumor survivors are thought to have a low risk of end-stage renal disease, a recent study reported impaired glomerular renal function in a majority of patients emphasizing the need for long-term follow-through to adulthood [54].

Renal Cell Carcinoma

Renal cell carcinoma (RCC) accounts for 2–5% of malignant renal masses found in children [55] and occurs most frequently in the second decade of life with an annual incidence of 0.01 per 100,000 [56]. Children and adolescents with RCC present with more advanced disease than those 20 to 30 years of age [57].

Diagnosis

RCC is found incidentally in the pediatric population in only 12% of patients [58]. Children typically present with fevers, abdominal mass, pain, hematuria, and weight loss. Unlike for RCC in adults, pediatric RCC has not experienced a downward stage in recent years [57, 59]. This may be explained in part by less abdominal imaging in children in efforts to reduce radiation exposure.

Imaging findings of RCC in pediatric patients may help to distinguish this entity from the more frequently found Wilms tumor (Fig. 10.2). Miniati and colleagues analyzed CT scans of 92 pediatric patients and reported an accuracy of 82% for

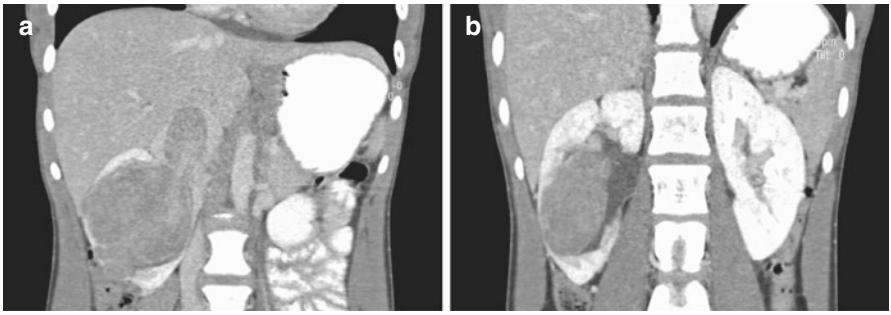

Fig. 10.2 Renal cell carcinoma in a 13-year-old female. (**a**) Sagittal CT image shows a mass with heterogeneous appearance and tumor thrombus in the inferior vena cava. (**b**) The tumor can be seen invading the renal sinus

predicting tumor histology [60]. Calcifications on imaging are more frequent in RCC compared to Wilms tumor [61]. Preoperative identification of RCC, however, is essential in the pediatric population as neoadjuvant chemotherapy is typically administered for advanced Wilms and delay to surgery as first-line treatment for RCC is associated with increased mortality [57].

Pathology

RCC in pediatric patients does not follow the typical distribution of tumor histologies observed in adults. More specifically, approximately 25% of pediatric RCCs demonstrate heterogeneous histologic features and cannot be classified as one of the common RCC subtypes [62]. Furthermore, papillary RCC is more common than the clear cell subtype and is frequently associated with aggressive disease [63, 64]. While histological features are used to classify pediatric RCC, another method currently being employed is molecular characterization. Specific genetic translocations can be identified in the majority of pediatric RCCs and can be used to classy tumors into distinct molecular subtypes [65].

Genetics

Translocation-associated RCC is the most common form of pediatric and adolescent RCC [66]. The most frequently found translocation involves the *TFE3* transcription factor found on chromosome Xp11.2. Upon translocation, the *TFE3* gene can fuse with a number of other genes. To date, a total of five fusion partners of *TFE3* have been identified [67]. These include *PRCC*, *ASPSCR1*, *SFPQ*, *NONO*, and *CLTC* [3, 68, 69]. Grossly, Xp11.2 translocation RCCs resemble clear cell RCC, and all of the Xp11.2 translocation RCCs demonstrate expression of *TFE3*

[58, 67]. Other immunohistochemical expression patterns include low expression of cytokeratin and vimentin [67]. Another less common translocation subtype is the t(6;11)(p21;q12) [70, 71]. Few cases have been reported, and the clinical course is typically less aggressive than Xp11.2 translocation tumors.

Treatment

The primary treatment for localized pediatric RCC is radical nephrectomy. There remains some debate over the utility of lymph node dissection during nephrectomy for pediatric RCC. Geller et al. reported on their experience with node-positive disease in combination with a review of the literature [72]. These authors found a 72.4% disease-free survival in node-positive patients and no improvement in disease-free or overall survival with adjuvant chemotherapy or radiation. They concluded that in the absence of clinical or radiographic evidence of disease, lymph node dissection does not confer any benefit. In contrast, Indolfi and colleagues reviewed their experience with 16 patients with RCC and node-positive disease and found that those who underwent a limited node dissection at the time of nephrectomy had significantly higher rate of relapse and mortality than those who underwent formal lymph node dissection [73]. Partial nephrectomy may be considered in select cases. In the setting of low-volume disease, well-selected patients have been found to have equivalent outcomes to those who had radical nephrectomies [74].

There is no standard treatment for unresectable metastatic RCC. Given the resistance of RCC to chemotherapy and radiation, metastatic disease remains difficult to treat. Despite this, there have been reports of advance disease treated with recombinant interleukin-2 [75, 76]. Additionally, the role of tyrosine kinase inhibitors continues to be defined in the pediatric population [77, 78].

Clear Cell Sarcoma of the Kidney

Clear cell sarcoma of the kidney (CCSK) is a rare renal tumor which accounts for approximately 3% of malignant pediatric renal tumors [79]. The mean age of presentation is 3 years. CCSK has a high propensity to metastasize to bone as noted in several series [80, 81]. On imaging, CCSK appears as a heterogeneous mass with decreased enhancement compared to the contralateral kidney with internal hemorrhage and necrosis (Fig. 10.3). Additionally, the outcome of relapses of CCSK is poor with a frequent site of recurrence being the brain. It is postulated that the brain may be a sanctuary site for cells protecting them from chemotherapy [82]. Late relapses have decreased with longer duration of chemotherapy including

vincristine, doxorubicin, and dactinomycin; however, long-term survival is unchanged [83]. Important predictors of survival are low stage, older age at diagnosis, treatment with doxorubicin, and the absence of tumor necrosis [79].

Genetics

Recent studies have identified several genetic changes associated with CCSK. The most frequently found are internal tandem duplications of the *BCOR* gene [84, 85]. In a recent series from Wong and colleagues, 10 of 11 tumors had *BCOR* exon 15 internal tandem duplications, and one had a fusion of the *BCOR* and *CCNB3* genes [86]. O'Meara et al. described the *YWHAE*-NUTM2 fusion in 12% of cases [87]. This gene fusion was found to be mutually exclusive of the *BCOR* internal tandem duplicates [88].

Treatment

Patients with CCSK should be considered for entry into a clinical trial given the rarity of this tumor. Nephrectomy followed by chemotherapy and radiation therapy is the typical treatment course in this group of patients. A variety of

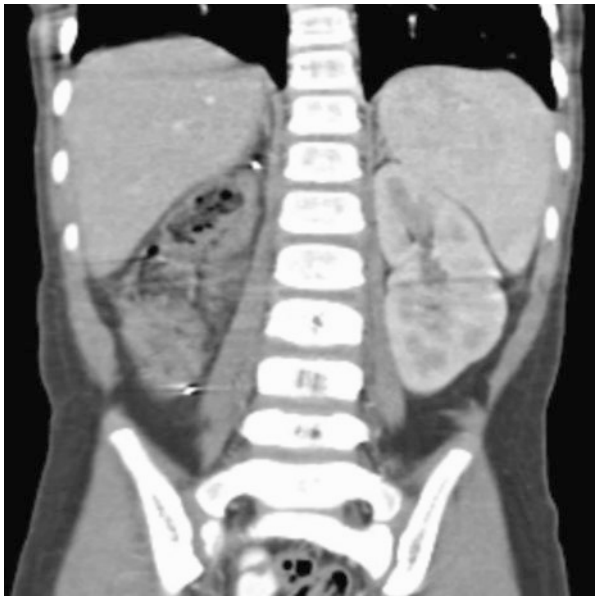

Fig. 10.3 Clear cell sarcoma with a heterogeneous appearance on CT with areas of hemorrhage and necrosis

chemotherapeutic regimens in combination with radiation have been described for the treatment of CCSK [79, 83, 89].

Rhabdoid Tumor of the Kidney

Rhabdoid tumors most commonly occur in the kidney and the central nervous system. Malignant rhabdoid tumor of the kidney (MRTK) is a rare highly aggressive malignancy. It accounts for about 2% of pediatric renal tumors [90]. The mean age at diagnosis is 11 months. In addition to young age of presentation, fever, hematuria, and advanced tumor stage suggest a diagnosis of MRTK [90]. MRTK has a propensity to metastasize to the lungs and the brain, with 10–15% of patients having lesions of the central nervous system [91]. This emphasizes the need for intracranial imaging and neurological monitoring for these patients. MRTK has a poor prognosis. Younger age at diagnosis and advanced stage significantly impact overall survival [91].

Genetics

The majority of MRTK are characterized by loss of function of the *SMARCB1/INI1/SNF5/BAF47* gene located in chromosome 22q11.2 [92]. SMARCB1 is a member of the SWI/INF chromosome remodeling complex and has an important role in controlling gene transcription [92]. Inactivation of both alleles of *SMARCB1* leads to tumorigenesis, and it has been proposed as a novel tumor suppressor gene [93]. While the majority of cases are sporadic, a recent study found 35% of cases to have germline mutations of *SMARCB1* [92]. Therefore, genetic counseling should be involved in the treatment of these patients.

Treatment

A multidisciplinary team well versed in treating renal tumors should dictate the treatment plan for patients with this rare tumor. Entry into a clinical trial should be strongly considered. Although preoperative chemotherapy especially with doxorubicin has been shown to decrease tumor volume, this may not translate to improved survival [94]. A recent report from the International Society of Pediatric Oncology renal tumor study group examined their experience with 107 patients with various stages of MRTK and varying pre- and postoperative chemotherapy regimens. They noted that although preoperative chemotherapy did decrease tumor volume significantly indicating chemosensitivity, overall survival was not improved [95]. Event-free survival was found to be 22% and overall survival was noted to be 26%.

Congenital Mesoblastic Nephroma

Congenital mesoblastic nephroma accounts for approximately 5% of pediatric renal tumors and is generally considered to be a benign tumor occurring most commonly in the first year of life [96]. It is the most common tumor found in the newborn with a median age at diagnosis of 1–2 months. Mesoblastic nephroma occurs twice as often in males than females. The 5-year event-free survival rate is 94%, and overall survival is 96% when diagnosed in the first 7 months of age [5]. In a recent review of 276 patients with available outcome data, there were only 12 (4%) deaths found, 7 of which were related to treatment [97].

Mesoblastic nephroma can be divided into three histologic subtypes: classic, cellular, and mixed [98, 99]. In the cellular subtype, two genetic variants have been identified including translocation t(12;15) (p13;q25) resulting in fusion of *ETV6* and *NTRK3* as well as trisomy 11 [100].

Treatment

Although congenital mesoblastic nephroma enjoys a high survival rate, the young age of these patients and potential adverse outcomes of treatment options cause some pause when deciding on timing and type of intervention. Nephrectomy is typically curative; however, the inherent risks of operating on an infant need to be taken into consideration. Patients with the cellular variant and stage III disease have a higher risk of recurrence and adjuvant chemotherapy is recommended for those greater than 3 months of age [98].

Multilocular Cystic Nephroma

Multilocular cystic nephroma (MLCN) has a bimodal age distribution occurring in children less than 2 years old and adults 40–69 years old [101]. MLCN is a benign neoplasm of the kidney containing both mesenchymal and epithelial elements. Imaging typically demonstrates a unilateral mass with irregular cysts and septa of variable thickness. It must be noted, however, that it is not possible to distinguish MLCN from other cystic renal tumors. In a recent study by Doros and colleagues, loss of function of *DICER1* was identified as the key genetic event in cystic nephroma [102].

Treatment of MLCN is typically total nephrectomy. Partial nephrectomy can be accomplished in select cases with masses of appropriate size and location. Intraoperative biopsies should be considered in these instances to rule out malignancy that would prompt total nephrectomy.

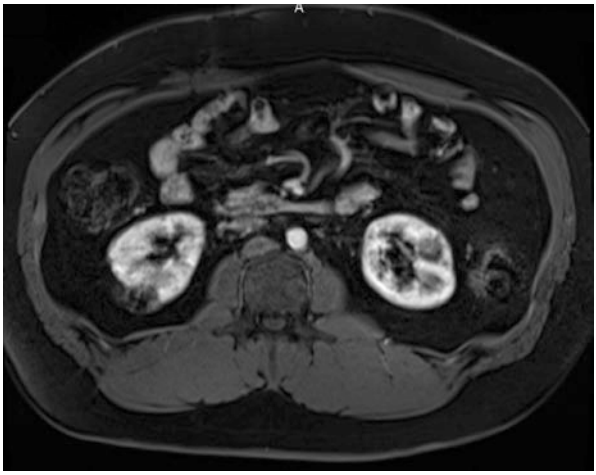

Fig. 10.4 Angiomyolipoma of the right kidney in a patient with tuberous sclerosis complex

Angiomyolipoma

Angiomyolipomas (AMLs) are hamartomatous lesions of the kidney that are associated with the tuberous sclerosis complex (TSC). AMLs are benign tumors composed of blood vessels, smooth muscle, and adipose tissue developing in up to 80% of TSC patients [103]. Mutations in the *TSC1* or *TSC2* gene are present in the majority of patients with TSC [104]. AMLs grow over time and lesions greater than 4 cm are at increased risk of hemorrhage (Fig. 10.4). In children with TSC, nephron-sparing approaches are necessary to preserve renal function due to the risk of development of new lesions. A recent study from Warncke and colleagues highlighted the often rapid and unpredictable growth of AMLs in children and emphasized the need for yearly ultrasounds for monitoring in hopes of identifying those at risk for future intervention [105].

Conclusions

Pediatric renal tumors can demonstrate a broad range of pathologic behaviors from benign to locally invasive to metastatic. As we have explored, modifications to surgical approach and tailoring of chemoradiation protocols have led to improved outcomes for pediatric patients with renal tumors. With these improved outcomes, the focus of many in the field has now shifted toward preservation of renal function in these young patients, as well as enhanced quality of life and survivorship efforts.

References

1. Ali AN, et al. A Surveillance, Epidemiology and End Results (SEER) program comparison of adult and pediatric Wilms tumor. Cancer. 2012;118(9):2541–51.
2. Breslow N, et al. Epidemiology of Wilms tumor. Med Pediatr Oncol. 1993;21(3):172–81.
3. Board, P.D.Q.P.T.E. Wilms Tumor and Other Childhood Kidney Tumors Treatment (PDQ(R)): Health Professional Version, in PDQ Cancer Information Summaries. Bethesda: National Cancer Institute (US); 2002.
4. Dome JS, et al. Treatment of anaplastic histology Wilms tumor: results from the fifth National Wilms Tumor Study. J Clin Oncol. 2006;24(15):2352–8.
5. van den Heuvel-Eibrink MM, et al. Characteristics and survival of 750 children diagnosed with a renal tumor in the first seven months of life: a collaborative study by the SIOP/GPOH/SFOP, NWTSG, and UKCCSG Wilms tumor study groups. Pediatr Blood Cancer. 2008;50(6):1130–4.
6. Dome JS, et al. Advances in Wilms tumor treatment and biology: progress through international collaboration. J Clin Oncol. 2015;33(27):2999–3007.
7. van den Heuvel-Eibrink MM, et al. Outcome of localised blastemal-type Wilms tumour patients treated according to intensified treatment in the SIOP WT 2001 protocol, a report of the SIOP Renal Tumour Study Group (SIOP-RTSG). Eur J Cancer. 2015;51(4):498–506.
8. Scott RH, et al. Syndromes and constitutional chromosomal abnormalities associated with Wilms tumour. J Med Genet. 2006;43(9):705–15.
9. Breslow NE, et al. Characteristics and outcomes of children with the Wilms tumor-Aniridia syndrome: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2003;21(24):4579–85.
10. Pelletier J, et al. Germline mutations in the Wilms tumor suppressor gene are associated with abnormal urogenital development in Denys-Drash syndrome. Cell. 1991;67(2):437–47.
11. Rump P, Zeegers MP, van Essen AJ. Tumor risk in Beckwith-Wiedemann syndrome: a review and meta-analysis. Am J Med Genet A. 2005;136(1):95–104.
12. Isidor B, et al. Wilms tumor in patients with 9q22.3 microdeletion syndrome suggests a role for PTCH1 in nephroblastomas. Eur J Hum Genet. 2013;21(7):784–7.
13. Muller EA, et al. Microdeletion 9q22.3 syndrome includes metopic craniosynostosis, hydrocephalus, macrosomia, and developmental delay. Am J Med Genet A. 2012;158a(2):391–9.
14. Choyke PL, et al. Screening for Wilms tumor in children with Beckwith-Wiedemann syndrome or idiopathic hemihypertrophy. Med Pediatr Oncol. 1999;32(3):196–200.
15. McNeil DE, et al. Screening for Wilms tumor and hepatoblastoma in children with Beckwith-Wiedemann syndromes: a cost-effective model. Med Pediatr Oncol. 2001;37(4):349–56.
16. Huff V. Wilms tumor genetics. Am J Med Genet. 1998;79(4):260–7.
17. Ozdemir DD, Hohenstein P. Wt1 in the kidney – a tale in mouse models. Pediatr Nephrol. 2014;29(4):687–93.
18. Knudson AG Jr, Strong LC. Mutation and cancer: a model for Wilms tumor of the kidney. J Natl Cancer Inst. 1972;48(2):313–24.
19. Charlton J, Pritchard-Jones K. WT1 mutation in childhood cancer. Methods Mol Biol. 2016;1467:1–14.
20. Barbosa AS, et al. The same mutation affecting the splicing of WT1 gene is present on Frasier syndrome patients with or without Wilms tumor. Hum Mutat. 1999;13(2):146–53.
21. Koesters R, et al. Mutational activation of the beta-catenin proto-oncogene is a common event in the development of Wilms tumors. Cancer Res. 1999;59(16):3880–2.
22. Maiti S, et al. Frequent association of beta-catenin and WT1 mutations in Wilms tumors. Cancer Res. 2000;60(22):6288–92.

23. Ruteshouser EC, Robinson SM, Huff V. Wilms tumor genetics: mutations in WT1, WTX, and CTNNB1 account for only about one-third of tumors. Genes Chromosomes Cancer. 2008;47(6):461–70.
24. Rivera MN, et al. An X chromosome gene, WTX, is commonly inactivated in Wilms tumor. Science. 2007;315(5812):642–5.
25. Jenkins ZA, et al. Germline mutations in WTX cause a sclerosing skeletal dysplasia but do not predispose to tumorigenesis. Nat Genet. 2009;41(1):95–100.
26. Satoh Y, et al. Genetic and epigenetic alterations on the short arm of chromosome 11 are involved in a majority of sporadic Wilms tumours. Br J Cancer. 2006;95(4):541–7.
27. Scott RH, et al. Constitutional 11p15 abnormalities, including heritable imprinting center mutations, cause nonsyndromic Wilms tumor. Nat Genet. 2008;40(11):1329–34.
28. Gratias EJ, et al. Association of chromosome 1q gain with inferior survival in favorable-histology Wilms tumor: a report from the Children's Oncology Group. J Clin Oncol. 2016;34(26):3189–94.
29. Grundy PE, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2005;23(29):7312–21.
30. Green DM. The diagnosis and management of Wilms tumor. Pediatr Clin N Am. 1985;32(3):735–54.
31. Voute PA Jr, van der Meer J, Staugaard-Kloosterziel W. Plasma renin activity in Wilms tumour. Acta Endocrinol. 1971;67(1):197–202.
32. Callaghan MU, Wong TE, Federici AB. Treatment of acquired von Willebrand syndrome in childhood. Blood. 2013;122(12):2019–22.
33. Khanna G, et al. Evaluation of diagnostic performance of CT for detection of tumor thrombus in children with Wilms tumor: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2012;58(4):551–5.
34. Shamberger RC, et al. Surgery-related factors and local recurrence of Wilms tumor in National Wilms Tumor Study 4. Ann Surg. 1999;229(2):292–7.
35. Breslow N, et al. Prognosis for Wilms tumor patients with nonmetastatic disease at diagnosis – results of the second National Wilms Tumor Study. J Clin Oncol. 1985;3(4):521–31.
36. Popov SD, et al. Renal tumors in children aged 10-16 years: a report from the United Kingdom Children's Cancer and Leukaemia Group. Pediatr Dev Pathol. 2011;14(3):189–93.
37. Bardeesy N, et al. Anaplastic Wilms tumour, a subtype displaying poor prognosis, harbours p53 gene mutations. Nat Genet. 1994;7(1):91–7.
38. Beckwith JB. Precursor lesions of Wilms tumor: clinical and biological implications. Med Pediatr Oncol. 1993;21(3):158–68.
39. Caiulo VA, et al. Nephrogenic rests: their frequency and their fate. J Pediatr Hematol Oncol. 2007;29(6):361–3.
40. Beckwith JB. Management of incidentally encountered nephrogenic rests. J Pediatr Hematol Oncol. 2007;29(6):353–4.
41. Beckwith JB. Nephrogenic rests and the pathogenesis of Wilms tumor: developmental and clinical considerations. Am J Med Genet. 1998;79(4):268–73.
42. Perlman EJ, et al. Hyperplastic perilobar nephroblastomatosis: long-term survival of 52 patients. Pediatr Blood Cancer. 2006;46(2):203–21.
43. Kieran K, et al. Lymph node involvement in Wilms tumor: results from National Wilms Tumor Studies 4 and 5. J Pediatr Surg. 2012;47(4):700–6.
44. Ritchey ML, et al. Fate of bilateral renal lesions missed on preoperative imaging: a report from the National Wilms Tumor Study Group. J Urol. 2005;174(4 Pt 2):1519–21. discussion 1521
45. Ritchey M, et al. Ureteral extension in Wilms tumor: a report from the National Wilms Tumor Study Group (NWTSG). J Pediatr Surg. 2008;43(9):1625–9.
46. Shamberger RC, et al. Long-term outcomes for infants with very low risk Wilms tumor treated with surgery alone in National Wilms Tumor Study-5. Ann Surg. 2010;251(3):555–8.

47. Fernandez CV, et al. Clinical outcome and biological predictors of relapse after nephrectomy only for very low-risk Wilms tumor: a report from Children's Oncology Group AREN0532. Ann Surg. 2017;265(4):835–40.
48. Ehrlich P, et al. Results of the first prospective multi-institutional treatment study in children with bilateral Wilms tumor (AREN0534): a report from the Children's Oncology Group. Ann Surg. 2017;266(3):470–8.
49. Hamilton TE, et al. The management of synchronous bilateral Wilms tumor: a report from the National Wilms Tumor Study Group. Ann Surg. 2011;253(5):1004–10.
50. Lange JM, et al. Breast cancer in female survivors of Wilms tumor: a report from the national Wilms tumor late effects study. Cancer. 2014;120(23):3722–30.
51. Wong KF, et al. Risk of adverse health and social outcomes up to 50 years after Wilms tumor: the British Childhood Cancer Survivor Study. J Clin Oncol. 2016;34(15):1772–9.
52. Green DM, et al. Congestive heart failure after treatment for Wilms tumor: a report from the National Wilms Tumor Study group. J Clin Oncol. 2001;19(7):1926–34.
53. Termuhlen AM, et al. Twenty-five year follow-up of childhood Wilms tumor: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer. 2011;57(7):1210–6.
54. Neu MA, et al. Prospective analysis of long-term renal function in survivors of childhood Wilms tumor. Pediatr Nephrol. 2017;32:1915.
55. Lipworth L, Tarone RE, McLaughlin JK. The epidemiology of renal cell carcinoma. J Urol. 2006;176(6 Pt 1):2353–8.
56. Silberstein J, et al. Renal cell carcinoma in the pediatric population: results from the California Cancer Registry. Pediatr Blood Cancer. 2009;52(2):237–41.
57. Akhavan A, et al. Renal cell carcinoma in children, adolescents and young adults: a National Cancer Database study. J Urol. 2015;193(4):1336–41.
58. Sausville JE, et al. Pediatric renal cell carcinoma. J Pediatr Urol. 2009;5(4):308–14.
59. Kane CJ, et al. Renal cell cancer stage migration: analysis of the National Cancer Data Base. Cancer. 2008;113(1):78–83.
60. Miniati D, et al. Imaging accuracy and incidence of Wilms and non-Wilms renal tumors in children. J Pediatr Surg. 2008;43(7):1301–7.
61. Lowe LH, et al. Pediatric renal masses: Wilms tumor and beyond. Radiographics. 2000;20(6):1585–603.
62. Bruder E, et al. Morphologic and molecular characterization of renal cell carcinoma in children and young adults. Am J Surg Pathol. 2004;28(9):1117–32.
63. Renshaw AA, et al. Renal cell carcinomas in children and young adults: increased incidence of papillary architecture and unique subtypes. Am J Surg Pathol. 1999;23(7):795–802.
64. Estrada CR, et al. Renal cell carcinoma: Children's Hospital Boston experience. Urology. 2005;66(6):1296–300.
65. Argani P, Ladanyi M. The evolving story of renal translocation carcinomas. Am J Clin Pathol. 2006;126(3):332–4.
66. Geller JI, et al. Characterization of adolescent and pediatric renal cell carcinoma: a report from the Children's Oncology Group study AREN03B2. Cancer. 2015;121(14):2457–64.
67. Argani P, Ladanyi M. Translocation carcinomas of the kidney. Clin Lab Med. 2005;25(2):363–78.
68. Sidhar SK, et al. The t(X;1)(p11.2;q21.2) translocation in papillary renal cell carcinoma fuses a novel gene PRCC to the TFE3 transcription factor gene. Hum Mol Genet. 1996;5(9):1333–8.
69. Argani P, et al. Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. Am J Pathol. 2001;159(1):179–92.
70. Argani P, et al. Xp11 translocation renal cell carcinoma (RCC): extended immunohistochemical profile emphasizing novel RCC markers. Am J Surg Pathol. 2010;34(9):1295–303.
71. Argani P, et al. A distinctive pediatric renal neoplasm characterized by epithelioid morphology, basement membrane production, focal HMB45 immunoreactivity, and t(6;11)(p21.1;q12) chromosome translocation. Am J Pathol. 2001;158(6):2089–96.

72. Geller JI, Dome JS. Local lymph node involvement does not predict poor outcome in pediatric renal cell carcinoma. Cancer. 2004;101(7):1575–83.
73. Indolfi P, et al. Local lymph node involvement in pediatric renal cell carcinoma: a report from the Italian TREP project. Pediatr Blood Cancer. 2008;51(4):475–8.
74. Cook A, et al. Pediatric renal cell carcinoma: single institution 25-year case series and initial experience with partial nephrectomy. J Urol. 2006;175(4):1456–60. discussion 1460
75. MacArthur CA, et al. Pediatric renal cell carcinoma: a complete response to recombinant interleukin-2 in a child with metastatic disease at diagnosis. Med Pediatr Oncol. 1994;23(4):365–71.
76. Bauer M, et al. A phase II trial of human recombinant interleukin-2 administered as a 4-day continuous infusion for children with refractory neuroblastoma, non-Hodgkin's lymphoma, sarcoma, renal cell carcinoma, and malignant melanoma. A Children's Cancer Group study. Cancer. 1995;75(12):2959–65.
77. De Pasquale MD, et al. Continuing response to subsequent treatment lines with tyrosine kinase inhibitors in an adolescent with metastatic renal cell carcinoma. J Pediatr Hematol Oncol. 2011;33(5):e176–9.
78. Wedekind MF, Ranalli M, Shah N. Clinical efficacy of cabozantinib in two pediatric patients with recurrent renal cell carcinoma. Pediatr Blood Cancer. 2017;64(11):1–4.
79. Argani P, et al. Clear cell sarcoma of the kidney: a review of 351 cases from the National Wilms Tumor Study Group Pathology Center. Am J Surg Pathol. 2000;24(1):4–18.
80. Marsden HB, Lawler W. Bone metastasizing renal tumour of childhood. Histopathological and clinical review of 38 cases. Virchows Arch A Pathol Anat Histol. 1980;387(3):341–51.
81. Marsden HB, Lawler W, Kumar PM. Bone metastasizing renal tumor of childhood: morphological and clinical features, and differences from Wilms tumor. Cancer. 1978;42(4):1922–8.
82. Gooskens SL, et al. Treatment and outcome of patients with relapsed clear cell sarcoma of the kidney: a combined SIOP and AIEOP study. Br J Cancer. 2014;111(2):227–33.
83. Seibel NL, et al. Effect of duration of treatment on treatment outcome for patients with clear-cell sarcoma of the kidney: a report from the National Wilms Tumor Study Group. J Clin Oncol. 2004;22(3):468–73.
84. Astolfi A, et al. Whole transcriptome sequencing identifies BCOR internal tandem duplication as a common feature of clear cell sarcoma of the kidney. Oncotarget. 2015;6(38):40934–9.
85. Ueno-Yokohata H, et al. Consistent in-frame internal tandem duplications of BCOR characterize clear cell sarcoma of the kidney. Nat Genet. 2015;47(8):861–3.
86. Wong MK, et al. Clear cell sarcomas of kidney are characterized by BCOR gene abnormalities including exon 15 internal tandem duplications and BCOR-CCNB3 gene fusion. Histopathology. 2018;72(2):320–9.
87. O'Meara E, et al. Characterization of the chromosomal translocation t(10;17)(q22;p13) in clear cell sarcoma of kidney. J Pathol. 2012;227(1):72–80.
88. Karlsson J, Valind A, Gisselsson D. BCOR internal tandem duplication and YWHAE-NUTM2B/E fusion are mutually exclusive events in clear cell sarcoma of the kidney. Genes Chromosomes Cancer. 2016;55(2):120–3.
89. Furtwangler R, et al. Clear cell sarcomas of the kidney registered on International Society of Pediatric Oncology (SIOP) 93-01 and SIOP 2001 protocols: a report of the SIOP Renal Tumour Study Group. Eur J Cancer. 2013;49(16):3497–506.
90. Amar AM, et al. Clinical presentation of rhabdoid tumors of the kidney. J Pediatr Hematol Oncol. 2001;23(2):105–8.
91. Tomlinson GE, et al. Rhabdoid tumor of the kidney in the National Wilms Tumor Study: age at diagnosis as a prognostic factor. J Clin Oncol. 2005;23(30):7641–5.
92. Eaton KW, et al. Spectrum of SMARCB1/INI1 mutations in familial and sporadic rhabdoid tumors. Pediatr Blood Cancer. 2011;56(1):7–15.
93. Roberts CW, Biegel JA. The role of SMARCB1/INI1 in development of rhabdoid tumor. Cancer Biol Ther. 2009;8(5):412–6.
94. Furtwangler R, et al. Malignant rhabdoid tumor of the kidney: significantly improved response to pre-operative treatment intensified with doxorubicin. Cancer Genet. 2014;207(9):434–6.

95. van den Heuvel-Eibrink MM, et al. Malignant rhabdoid tumours of the kidney (MRTKs), registered on recent SIOP protocols from 1993 to 2005: a report of the SIOP renal tumour study group. Pediatr Blood Cancer. 2011;56(5):733–7.
96. England RJ, et al. Mesoblastic nephroma: a report of the United Kingdom Children's Cancer and Leukaemia Group (CCLG). Pediatr Blood Cancer. 2011;56(5):744–8.
97. Gooskens SL, et al. Congenital mesoblastic nephroma 50 years after its recognition: a narrative review. Pediatr Blood Cancer. 2017;64(7):1–9.
98. Furtwaengler R, et al. Mesoblastic nephroma – a report from the Gesellschaft fur Padiatrische Onkologie und Hamatologie (GPOH). Cancer. 2006;106(10):2275–83.
99. Joshi VV, Kasznica J, Walters TR. Atypical mesoblastic nephroma. Pathologic characterization of a potentially aggressive variant of conventional congenital mesoblastic nephroma. Arch Pathol Lab Med. 1986;110(2):100–6.
100. Knezevich SR, et al. ETV6-NTRK3 gene fusions and trisomy 11 establish a histogenetic link between mesoblastic nephroma and congenital fibrosarcoma. Cancer Res. 1998;58(22):5046–8.
101. Granja MF, et al. Multilocular cystic nephroma: a systematic literature review of the radiologic and clinical findings. AJR Am J Roentgenol. 2015;205(6):1188–93.
102. Doros LA, et al. DICER1 mutations in childhood cystic nephroma and its relationship to DICER1-renal sarcoma. Mod Pathol. 2014;27(9):1267–80.
103. Ewalt DH, et al. Renal lesion growth in children with tuberous sclerosis complex. J Urol. 1998;160(1):141–5.
104. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med. 2006;355(13):1345–56.
105. Warncke JC, et al. Pediatric renal angiomyolipomas in tuberous sclerosis complex. J Urol. 2017;197(2):500–6.

Chapter 11
Thermoablation of Renal Tumors

Roshan M. Patel, Kamaljot S. Kaler, Zhamshid Okhunov, and Jaime Landman

Introduction

There has been a significant rise in the incidental detection of renal cortical neoplasms (RCNs) measuring ≤4 cm secondary to the increased use of cross-sectional abdominal imaging [1]. Historically, these tumors, also known as small renal masses (SRMs), were managed with open radical nephrectomy. In the 1990s, however, the first laparoscopic radical nephrectomy was performed by Clayman and colleagues, and with this, the treatment paradigm shifted toward more minimally invasive approaches for the treatment of SRMs [2].

As techniques in laparoscopy were further refined, a nephron-sparing approach became a feasible alternative for treating SRMs. The aim of nephron-sparing surgery is to prevent loss of renal function which is known to correlate with poor cardiovascular outcomes and decreased overall survival [3–5]. In 1996, Winfield and colleagues described the first laparoscopic partial nephrectomy [6], and in 2004, Gettman and colleagues described their experience using a robotic-assisted approach [7]. With well-documented outcomes, partial nephrectomy became the treatment of choice for the management of SRMs by the American Urological Association and European Association of Urology [8, 9].

The drive to advance minimally invasive techniques and provide a less-invasive alternative to surgical intervention has allowed thermoablation to emerge as a viable treatment alternative to partial nephrectomy. Two of the best-studied thermoablation modalities are cryoablation (CA) and radiofrequency ablation (RFA), which can be performed percutaneously or laparoscopically. These treatment modalities aim to decrease treatment-related morbidity while respecting oncological principals. Thermoablation therapy is often offered to patients that are poor surgical candidates

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and have a solitary kidney or those with bilateral tumors. However, as long-term data regarding the efficacy of thermoablation emerges, its role in the management of patients with RCNs will undoubtedly continue to expand. In this chapter, we review patient selection, surgical techniques, and perioperative outcomes of renal thermoablation using CA and RFA.

The Small Renal Mass Conundrum

Current guidelines from the American Urological Association and European Association of Urology consider active surveillance, thermoablation, and partial nephrectomy, all viable treatment options for T1a tumors [8, 9]. While partial nephrectomy remains the gold standard, factors such as patient age, patient preference, tumor size, and renal health all influence treatment decisions. Additionally, while large masses (>4 cm) are often removed by either partial nephrectomy or radical nephrectomy, the decision on management options for a <4 cm mass is more complex.

Almost 20% of SRMs are benign at the time of final pathology, and more than 6000 benign lesions undergo surgical excision, by either partial or radical nephrectomy, each year in the United States [10]. Additionally, given that 50–60% of small renal masses display low-grade features, surgical intervention may be delayed or entirely avoided following appropriate diagnostic workup [11, 12].

In older patients with a SRM, active surveillance may be a feasible alternative given that the growth rate for a small renal mass is 0.34 cm/year and the metastatic rate is 1.9% [13]. Additionally, active surveillance may provide equivalent oncological efficacy as compared to both ablative and extirpative surgery in both the short- and intermediate-term management of a SRM [14]. Growth rates for larger T1b and T2 RCNs were found to be 0.58 cm/year, similar to a SRM, and would allow for active surveillance to be a viable treatment option for patients with significant comorbidities and a larger tumor burden [15, 16].

While partial nephrectomy remains the gold standard treatment of SRMs, emerging studies involving active surveillance and long-term follow-up data on CA and RFA may warrant reassessment of treatment indications. The treatment algorithm directing immediate nephron-sparing surgery may continue to be amended to support increase use of surveillance and ablative therapy. These treatment alternatives should also be considered in patients seeking to avoid surgical resection, as long-term data supporting the routine use is promising. The emerging role of renal biopsy is expanding, and given the heterogeneity in the biological aggressiveness of RCNs, it may be seen as an initial option when providers encounter a SRM. This may allow for patients with nonaggressive forms of renal cell carcinoma to consider active surveillance or ablative therapy in both the initial management and in the case of a small recurrence.

Historical Perspective

While percutaneous RFA and CA are relatively new, the basic techniques for both have been described for over a century. In 1850, the English physician James Arnott demonstrated that freezing temperatures could be applied to cause tissue destruction [17]. The cryogen was applied topically and was used early on to treat tumors of the cervix and breast. The utility of liquid nitrogen was popularized in the 1950s when cotton swabs were first dipped in liquid nitrogen to treat skin lesions, and this was followed by the development of handheld sprays to improve the depth of penetration. In 1963, the Cooper device was one of the first instruments that utilized a self-contained cryoprobe to treat inoperable brain tumors and Parkinson's disease [18]. The development of the cryoprobe and its fusion with real-time image guidance was instrumental in ushering in the modern area of CA and increased the number and variety of applications. In the 1980s, liver tumors were the first cancer to be approached by this method. With the discovery of the sonographically visible iceball as well as the characterization of the "ablation" and "indeterminate" zones, surgeons now had the ability to monitor in real time the effects of CA to ensure accurate targeting and minimize surrounding injuries [19]. The most recent major breakthrough that has facilitated performance of thermoablation of SMRs was the development of an argon gas-based system for CA [20]. Based on the Joule-Thomson principle, argon gas allows for decreased procedure time while utilizing smaller probes. In 1995, CA of a renal tumor was first described by Uchida and colleagues, and it is currently the most studied form of renal ablation [21].

Radiofrequency ablation was first described in 1891, when D'Arsonval demonstrated that radiofrequency waves passed through tissue increased its temperature [22]. This technique was later popularized for medical applications in 1928 by Cushing and Bovie, whose instrument either cut or cauterized tissue by varying the RFA current [23]. In 1976, Organ demonstrated that RFA works by causing ionic agitation of the tissues causing coagulation and cellular necrosis with local tissue charring inhibiting further ionic agitation [24]. Later in 1990, McGahan and Rossi described a modification to RFA that allowed for this energy source to be applied via the percutaneous route [25, 26]. In 1993, the first liver tumors were treated in humans using RFA [27, 28], and in 1997, RFA was first performed by Zlotta and colleagues to treat exophytic renal masses [29].

Principles of Ablation

Cryoablation

Modern systems for CA utilize highly pressurized liquid state argon gas that is allowed to expand into the gaseous state near the tip of the probe. This expansion and phase change results in iceball formation secondary to an extreme drop in

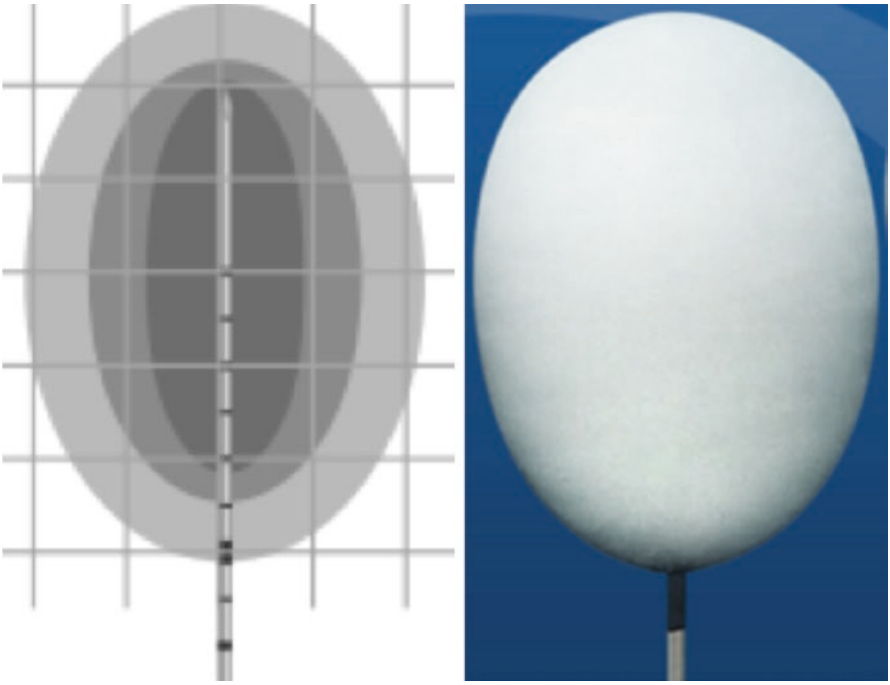

Fig. 11.1 Schematic representation of cryotherapy probe and thermoablation zones. The iceball extends radially along the shaft of the probe and less appreciably beyond the tip. Central zone corresponds to temperatures consistently below −40 °C, intermediate zone corresponds to temperatures between −40 and −20 °C, and the outer zone corresponds to temperatures between −20 and 0 °C

pressure. Local tissue properties and probe design affect iceball dimension and ablation zones. Importantly, the iceball expands radially and proximally along the shaft of the probe rather than beyond the tip (Fig. 11.1).

Uniform cellular death within the ablation zone occurs by direct, vascular, and delayed mechanisms [30]. Falling temperatures result in progressive structural and cellular metabolic failure. Freezing results first in extracellular ice crystal formation creating a hyperosmotic environment, which causes cell shrinkage and membrane damage. With further rapid cooling, intracellular ice crystals form, and drastic changes in intracellular pH result in protein denaturation. Vascular changes include microcirculatory failure that causes thrombosis, coagulation necrosis, and cellular apoptosis [31].

The optimal temperature needed to produce predictable and reliable tissue destruction has been demonstrated in animal models [32–34]. This is an important concept as cell damage depends on the cooling rate and number of freeze-thaw cycles [35]. The iceball that forms has a temperature gradient that comprises three distinct zones (Fig. 11.1). The central zone extends from the cryoprobe tip to surrounding areas that are consistently below −40 °C, which is characterized by uniform cellular necrosis. The intermediate zone comprises the area where

temperatures range between −40 and −20 °C, which has cellular elements that are both necrotic and viable. The outer zone extends from −20 °C to the warmer iceball edge, which is characterized by mostly viable tissue. The practice in CA of extending the iceball to 1 cm beyond the tumor edge is based on the fact that temperatures greater than −20 °C can be measured within 3.1 mm of the iceball edge [36]. The phenomenon known as freezing point depression results in a temperature below 0 °C at the edge of the iceball. When solutes are added to a solvent, in this case tissue, the ions in this saline environment interfere with ice formation requiring a temperature below freezing in the periphery. This critical property of the iceball is the main determinant in CA success or failure.

Radiofrequency Ablation

RFA relies on a transmission of a high-frequency electrical current through an electrode placed directly into a RCN. The alternating electrical current, with a wavelength of 460–500 kHz, causes ions in the surrounding tissues to vibrate causing frictional heat that results in tissue damage [37–40]. The two main types of RFA generators are either temperature or impedance based. On the molecular level, the electrical current causes tissue destruction in three phases [41]. The first phase, immediately post-ablation, is marked by protein denaturation and cellular destruction seconadary to molecular friction. The second phase, occuring days after ablation, results in tumor destruction secondary to coagulation necrosis as surrounding areas of cellular edema and inflammation are evident. The last phase is reabsorption of the necrotic foci resulting in the fibrotic scar as seen on contrast-enhanced imaging [42].

Cellular injury and death occur optimally at temperatures between 60 and 100 °C. Cellular injury does not occur until temperatures reach 50 °C for 4–6 min, and instantaneous coagulative necrosis occurs as temperatures rise over 60 °C [43]. While new generators can deliver upward of 200 W and temperatures consistently above 100 °C, this may lead to ineffective ablation, as temperatures over 105 °C induce tissue vaporization and boiling of tissue, which leads to gas bubbles, tissue carbonization, and eschar formation at the electrode. This cumulative effect increases impedance and reduces the extent of tissue ablation [44]. To ensure adequate treatment, similar to CA, the ablation zone is extended to 1 cm beyond the tumor periphery, and temperature or impedance probes are placed near the area of interest to determine the extent of the effect.

Indications and Contraindications of Thermoablation

Per the 2017 AUA guidelines on localized renal cancer, physicians should offer thermoablation as an alternate approach for the management of T1a renal masses <3 cm in size [8]. Further, a renal mass biopsy should also be performed prior to ablation to provide pathologic diagnosis and provide direction on subsequent

surveillance. The current rationale to treat a SRM with thermoablation is in patients who have a high surgical risk, renal transplant recipients, and those with renal insufficiency, solitary kidney, and multiple or bilateral renal masses with the potential to reduce morbidity of treatment. In these patient settings, the percutaneous approach is preferred, and it can be performed in the outpatient setting using image guidance. This less-invasive approach, which can be performed without general anesthesia, is an attractive option for patients with significant medical comorbidities and those averse to surgical extirpation.

Contraindications to thermoablation are tumor size and location. The chance for successful treatment decreases with increasing size of tumor greater than 3 cm [45]. Thermoablation relies on obtaining an adequate ablation zone, and the larger the lesion, the more difficult it is to completely cover the lesion. For CA, large lesions are at risk of tumor cracking and bleeding and thus should be avoided. Tumor location is another important factor, as posterior and lateral tumors are more amenable to a percutaneous approach. Anterior tumors can be treated laparoscopically or even in an open fashion, while hilar tumors, those close to the ureter or collecting system, should be avoided due to risk of major complication and increased risk of treatment failure [46].

Patient Preparation

The goal of proper preoperative patient preparation is to identify obstacles that may affect treatment. All patients should undergo a thorough history, physical examination, and investigations including bloodwork and imaging. Findings of advanced disease through these initial investigations may limit the role of local treatment. Thermoablation is contraindicated in patients actively on anticoagulants, including aspirin, and management should be coordinated with a medical team.

Recent contrast-enhanced abdominal imaging (CT or MRI) is critical to characterize the mass and is a key component to every preoperative workup. Imaging should be evaluated to understand the renal morphology of the affected and unaffected kidney. Special attention should be paid to the size of the tumor, its location in relation to the hilum and collecting system, and whether the mass is exophytic, mesophytic, or cystic in nature. The R.E.N.A.L. nephrometry score can aid in standardizing the preoperative approach as its use has been shown as a capable predictor of complication rates and outcomes of minimally invasive approaches for RCN including partial nephrectomy and both laparoscopic cryoablation (LCA) and percutaneous cryoablation (PCA) [47–50]. Okhunov and colleagues demonstrated that tumors with a R.E.N.A.L. nephrometry greater than 8 were associated with higher risks of complications and local tumor recurrences following LCA [49]. Blute and colleagues corroborated these findings in PCA patients and found that with each increase in R.E.N.A.L. score, the risk of complication and recurrence increases 1.5-fold [51]. Skin to tumor (STT) distance is an important factor for consideration as well (Fig. 11.2). Vernez and colleagues demonstrated that a STT distance greater than 10 cm had a fourfold increased risk of tumor treatment failure

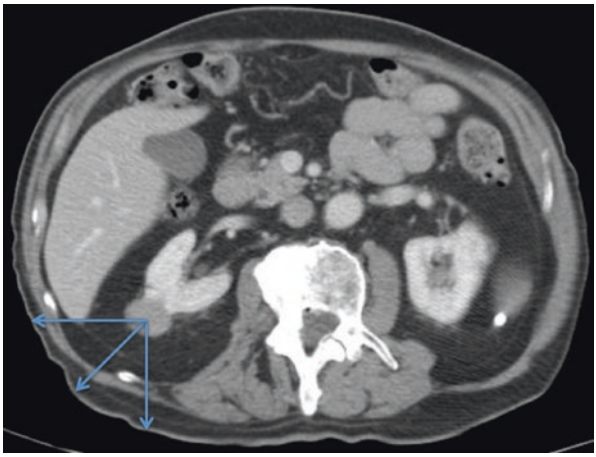

Fig. 11.2 Determination of skin to tumor distance when performing thermoablation. The average of the three measurements at 0° posteriorly, 45°, and 90° laterally from the skin to the center of the tumor is recorded as skin to tumor distance

following PCA [52]. While the R.E.N.A.L. nephrometry score has not been found predicative of complications in RFA [53, 54], a modified R.E.N.A.L. score may allow more accurate predication and stratification of outcomes [55].

Surgical Approach

Both CA and RFA can be performed percutaneously or laparoscopically, and the approach is largely dependent on the location of the tumor. When the RCN is located posteriorly and laterally, it is best approached either percutaneously or via a retroperitoneal laparoscopic technique. Tumors that are located on the anterior aspect of the kidney are best approached via a laparoscopic transperitoneal approach. CA has been extensively studied both percutaneously and laparoscopically, while the majority of RFA is performed via a percutaneous approach. If the tumor can be treated via a percutaneous approach, this is preferred given the decrease in morbidity. A good working relationship with interventional radiologists is key as their expertise in image-guided ablation can be vital for optimizing treatment outcomes.

Cryoablation Techniques

Successful CA involves appropriate patient selection, precise probe placement, accurate iceball management, and a willingness to make intraoperative adjustments to ensure complete tumor coverage (Fig. 11.3). The ideal patient has a RCN that is <3 cm, a STT distance <10 cm, and a R.E.N.A.L. nephrometry score < 8. It is important to obtain high-quality preoperative imaging to accurately characterize the RCN. Next, liberal use of imaging throughout the procedure is critical for tumor

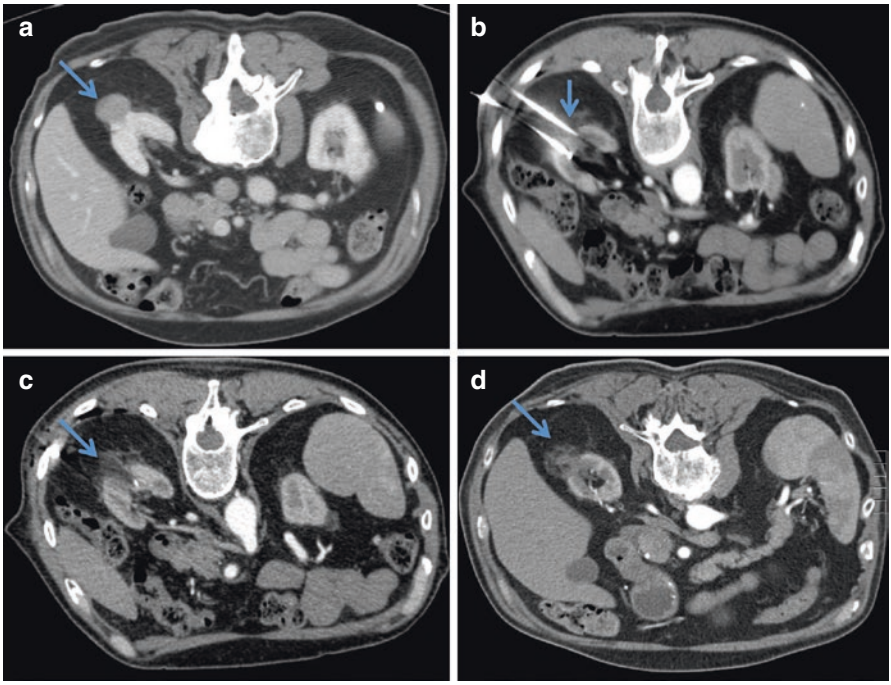

Fig. 11.3 Example of a small renal mass treated with percutaneous cryoablation. (**a**) Preoperative CT scan with enhancing right-sided small renal mass, (**b**) placement of cryoprobes, (**c**) hypodense ablation zone corresponding to iceball, and (**d**) follow-up CT scan showing no residual disease as there is no enhancement

evaluation and probe placement. During the laparoscopic approach, drop-in ultrasound (US) can be utilized, and during a percutaneous approach, US and computed tomography (CT) or a combination of both can be used. Lastly, careful iceball monitoring during freeze-thaw cycles to ensure that the iceball encompasses the entire tumor is critical, as the optimal outcome is achieved when the iceball extends beyond the mass. Initial probe placement is important as it cannot be repositioned once the iceball begins to form. The expanding iceball can create a large acoustic shadow that makes targeting of deep tissues difficult. Additionally, if the iceball fails to completely ablate the tumor, the probes should be allowed to thaw and then repositioned for a repeat cycle to ensure entire tumor coverage. The use of needle temperature probes during CA also allows for accurate and reproducible thermometry during ablation and has been shown to improve oncological outcomes [56].

Laparoscopic Cryoablation

When performing LCA, the patient is typically positioned in a 70- or 90-degree (full) flank position, and trocars are placed in a standard nephrectomy template after appropriate prepping and draping. The duodenum is Kocherized, and if on the right,

the colon is reflected medially. The psoas muscle is identified, and a laparoscopic retractor is placed through a 5 mm port positioned in the midaxillary line. This allows for the kidney to be elevated for the remainder of the dissection and stabilizes the renal mass position during ablation.

There is an increased risk of iceball cracking and bleeding in renal masses greater than 3.5 cm. If such a concern exists, the kidney is prepared as if a partial nephrectomy is to be performed with Gerota's fascia dissected away from the mass, and the renal hilum is completely exposed. If excessive bleeding were to occur, it would allow for prompt clamping of the renal artery, and performing a partial nephrectomy would be indicated.

The cryoprobes should be placed perpendicular to the mass, as tangentially placed probes are difficult to accurately position and may not allow for complete iceball coverage. Once the renal mass is exposed, a spinal needle is passed percutaneously in order to identify the appropriate trajectory. Next, a skin incision is made adjacent to the finder needle, and several biopsies of the mass are taken. Once biopsy is complete, the cryoprobes are placed to sit at right angles to the mass as predefined by the finder needle. The IceRod Plus or IceEDGE cryoprobes (Galil Medical, Minneapolis, MN) are preferred at our institution; however, there are a variety of commercially available cryoprobes.

Several principles of cryoprobe positioning must be maintained to optimize tumor ablation. First, to avoid a deep tumor recurrence, the cryoprobe distal tip should be placed 5 mm beyond the tumor when feasible. For lesions with cystic components, the cryoprobes are commonly placed just outside the margins of the tumor (freeze out to in) to avoid rupture and tumor spillage. For solid lesions, the probes are placed within the tumor's margin. It is critical for initial probe placement to be as precisely as possible, as once the freeze cycle begins cryoprobe repositioning is difficult.

A laparoscopic ultrasound probe should be used for tumor identification, during probe deployment, and to monitor the iceball to ensure the iceball extends 1 cm beyond the margins. A double freeze-thaw cycle is utilized for optimal results. Freeze cycles should be approximately 10 min with either an active or passive thaw cycle, although freeze time should largely be determined by the time it takes for the iceball to extend to the 1 cm margin beyond the tumor. The probes are then removed atraumatically and the tumor site is observed for bleeding. Hemostatic agents can be applied if necessary.

Percutaneous Cryoablation

A percutaneous approach is ideal for posterior and lateral tumors, as an anterior mass would require traversing a large portion of the kidney and is not recommended. A close partnership with interventional radiology is critical for optimizing successful outcomes of PCA.

When performing PCA, the patient is placed in prone or modified flank position depending on tumor location. In CT-guided cases, ultrasound is initially used to

localize the tumor and for initial probe placement. A non-contrast-axial image is then obtained and compared to the preoperative contrast image, and if the tumor margins are not clearly seen, then a repeat scan with a half bolus of intravenous contrast can be performed. Additional cryoprobes (up to three total) are placed one at a time ensuring that the tips extend at least 5 mm past the deep margin. Similar to the LCA, two freeze-thaw cycles are utilized with the goal of extending the iceball 1 cm beyond the tumor margins in all directions. Limited axial CT images are obtained at the end of the first freeze and again at the midpoint of the second freeze cycle to assess iceball geometry. At the conclusion of the freeze-thaw cycles, a repeat half-dose contrast-enhanced limited CT is obtained to confirm complete ablation. Residual tumor will demonstrate enhancement, and at this point, redeployment of additional cryoprobes with repeat ablation can be performed.

Radiofrequency Ablation Technique

The majority of RFA is performed via the percutaneous approach. Laparoscopic RFA is similar to LCA and also affords the same benefit of being able to observe the tumor following treatment and having the ability to apply hemostatic agents if needed. However, unlike LCA where intraoperative ultrasound can be used to visualize treatment progress, success during RFA relies on generator feedback and accurate placement of probes [57].

Percutaneous RFA is performed in the prone position, and the patient is prepped and draped in the standard sterile fashion. Several grounding pads are placed on the upper thigh. Vital structures such as nearby organs are displaced using carbon dioxide or water if needed. Next, under image guidance, the ablation probes are placed in the RCN. Once probes are placed, tumor biopsy can be performed. Ablation with a 5–10 mm margin with cycles of 5, 7, and 8 min is performed with a 30-second cooldown. Impedance is measured using single multilined probes or multiple single-shaft probes to ensure complete tumor coverage. The probe tract may be ablated on removal and CT is performed to assess for completion and to monitor for complications.

Complications

When comparing complications between CA and RFA, studies are limited by their retrospective nature and differences in reporting tumor complexity, surgeon experience, and differences between patient cohorts. In one of the largest available series, Atwell and colleagues retrospectively reviewed the records of 385 patients and found that major complication rates were 4.3% and 4.5% for PCA and RFA, respectively [58]. In a recent meta-analysis, Pierorazio and colleagues found that partial nephrectomy comparatively had higher rates of acute kidney injury and

cardiovascular, hematological, and respiratory harm but lower rates of infectious disease and wound complications [59].

Costs

A cost analysis performed by Bhan and colleagues found that active surveillance with later CA, if needed, was the most cost-effective approach for the management of patients presenting with a SRM [60]. Notably, PCA was more cost-effective than percutaneous RFA. Immediate CA had a cost of $3101 more with similar quality-adjusted life expectancies than active surveillance and delayed ablation. RFA, on the other hand, had costs of $3231–$6398 and reduced quality-adjusted life expectancy compared to active surveillance plus CA. Not surprisingly, active surveillance was the most cost-effective, and their data suggested a slight preference for CA.

Outcomes

Contrast-enhanced CT imaging can be used to evaluate for treatment success of thermoablated tumors. Following CA, treated RCNs demonstrate significant shrinkage and loss of contrast enhancement [61]. On the other hand, RFA-treated RCNs demonstrate minimal shrinkage on CT with loss of contrast enhancement [62]. MRI may also be used to gauge treatment success, and on gadolinium-enhanced imaging, successfully treated RCNs will display no enhancement. Occasionally on early post-procedural MRI following thermoablation, there may be rim enhancement but that resolves over time.

A recent meta-analysis from Pierorazio and colleagues aimed to identify the comparative effectiveness of active surveillance, thermoablation (both CA and RFA), and radical and partial nephrectomy of clinically localized RCNs [59]. Cancer-specific survival among all management strategies was 95% to 100%. There was no difference in metastasis-free survival between partial nephrectomy and thermoablation with a median follow-up of 39.3 and 42.3 months, respectively. Rates of local recurrence-free survival were worse for thermoablation compared to partial nephrectomy, but after salvage CA, this difference was no longer significant with efficacy ranging from 97 to 100%. Renal functional outcomes between thermoablation and PN were also similar.

Studies comparing CA and RFA are often retrospective and have small sample size, discrepancies in tumor size and location, poorly defined end-points, and limited follow-up. Among contemporary publications, Pirasteh and colleagues noted a similar recurrence rate on imaging of ~10% among patients treated with RFA and CA [63]. Similarly, Atwell and colleagues retrospectively reviewed 256 tumors treated with RFA and 189 tumors treated with CA that were less than 3 cm and

found no significant difference in terms of local recurrence-free survival among cases of biopsy-proven RCC between the two treatment modalities [58].

Cryoablation Outcomes

Long-term follow-up data assessing the efficacy of CA demonstrates that this technique provides excellent oncological outcomes [64]. For LCA, Caputo and colleagues demonstrated 10-year disease-free survival, cancer-specific survival, and overall survival of 86.5%, 92.6%, and 53.8%, respectively [46]. Similarly, Johnson and colleagues determined that after a median of 97.9 months following LCA, progression-free survival, cancer-specific survival, and overall survival were 91%, 98.5%, and 98.5%, respectively [65].

CA was historically performed laparoscopically, and now an increasing number of patients receive treatment via a percutaneous approach. Studies comparing LCA versus PCA have found no difference in overall mortality or recurrence rates. Kim and colleagues compared 145 LCA and 118 PCA cases with a mean follow-up of 71.4 months for LCA and 38.6 months for PCA. The reported 5-year overall survival and recurrence-free survival were 79.3% and 85.5% for LCA and 86.3% and 86.3% for PCA [66].

Radiofrequency Ablation Outcomes

RFA provides durable oncological outcomes comparable to partial nephrectomy. Olweny and colleagues compared patients treated with percutaneous RFA to partial nephrectomy with a median follow-up of 6.5 years [67]. No statistical difference was found in overall survival (97.2% versus 100%), cancer-specific survival (97.2% versus 100%), disease-free survival (89.2% versus 89.2%), local recurrence-free survival (91.7% versus 94.6%), and metastasis-free survival (97.2% and 91.8%). Similarly, Chang and colleagues compared a propensity-matched cohort of patients treated with RFA and laparoscopic partial nephrectomy and found no differences in oncological outcomes at a median follow-up of 67.6 months [53]. In a recent study by Thompson and colleagues, 1424 patients with SRMs were treated with partial nephrectomy, CA, or RFA. While RFS was similar among the three treatments, metastasis-free survival was superior for PN and CA when compared to RFA [68].

Salvage Cryoablation

The management of recurrent disease after thermoablation represents a technical challenge as local fibrosis and distortion of anatomical surgical planes make extirpation exceedingly difficult [69]. Given this, salvage CA has emerged as a common

treatment modality following failure of primary CA with approximately 66–73% of patients being managed with repeat focal therapy [70]. Hegg and colleagues reported a major complication rate of 5.7% in patients who underwent repeat PCA after local recurrence following partial nephrectomy [71]. In a multicenter study, Okhunov and colleagues evaluated 250 patients who underwent PCA for a SRM [72]. In this series, 8% developed a recurrence, and, of these, 86% were treated successfully following salvage CA at a median follow-up of 30 months without any documented complications. Salvage CA for a local recurrence is technically feasible, has a low complication rate, and demonstrates acceptable short-term oncological outcomes.

Conclusions

Thermoablation plays an important role in the treatment of patients with a SRM. In light of promising recent long-term follow-up data, thermoablation is likely to gain more popularity in the future. This treatment approach should be discussed with patients presenting with a SRM, in particular with those patients for whom there are concerns regarding the potential morbidity associated with surgical extirpation.

References

1. Birkhauser FDKN, Pantuck AJ. Etiology of renal cell carcinoma: incidence, demographics, and environmental factors. In: Campbell SC, Rini BI, editors. Renal cell carcinoma clinical management. Totowa: Humana Press; 2013. p. 1 online resource.
2. Clayman RV, Kavoussi LR, Soper NJ, Dierks SM, Merety KS, Darcy MD, et al. Laparoscopic nephrectomy. N Engl J Med. 1991;324(19):1370–1.
3. McKiernan J, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. Urology. 2002;59(6):816–20.
4. Moskowitz D, Chang J, Ziogas A, Anton-Culver H, Clayman RV. Treatment for T1a renal cancer substratified by size: “less is more”. J Urol. 2016;196(4):1000–7.
5. Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED, Cheville JC, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. J Urol. 2008;179(2):468–71. discussion 72–3
6. Winfield HN, Donovan JF, Lund GO, Kreder KJ, Stanley KE, Brown BP, et al. Laparoscopic partial nephrectomy: initial experience and comparison to the open surgical approach. J Urol. 1995;153(5):1409–14.
7. Gettman MT, Blute ML, Chow GK, Neururer R, Bartsch G, Peschel R. Robotic-assisted laparoscopic partial nephrectomy: technique and initial clinical experience with DaVinci robotic system. Urology. 2004;64(5):914–8.
8. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA guideline. J Urol. 2017;198:520.
9. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015;67(5):913–24.
10. Johnson DC, Vukina J, Smith AB, Meyer AM, Wheeler SB, Kuo TM, et al. Preoperatively misclassified, surgically removed benign renal masses: a systematic review of surgical series and United States population level burden estimate. J Urol. 2015;193(1):30–5.

11. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. J Urol. 2003;170(6 Pt 1):2217–20.
12. Richard PO, Jewett MA, Bhatt JR, Kachura JR, Evans AJ, Zlotta AR, et al. Renal tumor biopsy for small renal masses: a single-center 13-year experience. Eur Urol. 2015;68(6):1007–13.
13. Rosales JC, Haramis G, Moreno J, Badani K, Benson MC, McKiernan J, et al. Active surveillance for renal cortical neoplasms. J Urol. 2010;183(5):1698–702.
14. Patel N, Cranston D, Akhtar MZ, George C, Jones A, Leiblich A, et al. Active surveillance of small renal masses offers short-term oncological efficacy equivalent to radical and partial nephrectomy. BJU Int. 2012;110(9):1270–5.
15. Mehrazin R, Smaldone MC, Kutikov A, Li T, Tomaszewski JJ, Canter DJ, et al. Growth kinetics and short-term outcomes of cT1b and cT2 renal masses under active surveillance. J Urol. 2014;192(3):659–64.
16. Mues AC, Haramis G, Badani K, Gupta M, Benson MC, McKiernan JM, et al. Active surveillance for larger (cT1bN0M0 and cT2N0M0) renal cortical neoplasms. Urology. 2010;76(3):620–3.
17. Arnott J. Practical illustrations of the remedial efficacy of a very low or anaesthetic temperature-I: in cancer. Lancet. 1850;56(1409):257–9.
18. Copper IS. Cryogenic surgery: a new method of destruction or extirpation of benign or malignant tissues. N Engl J Med. 1963;268:743–9.
19. Onik G, Cooper C, Goldberg HI, Moss AA, Rubinsky B, Christianson M. Ultrasonic characteristics of frozen liver. Cryobiology. 1984;21(3):321–8.
20. Rewcastle JC, Sandison GA, Saliken JC, Donnelly BJ, McKinnon JG. Considerations during clinical operation of two commercially available cryomachines. J Surg Oncol. 1999;71(2):106–11.
21. Uchida M, Imaide Y, Sugimoto K, Uehara H, Watanabe H. Percutaneous cryosurgery for renal tumours. Br J Urol. 1995;75(2):132–6. discussion 6–7
22. D'Arsonval M. Action physiologique des courants alternatifs. C R Soc Biol. 1891;43:283–6.
23. Clark W. Oscillatory desiccation in the treatment of accessible malignant growths and minor surgical conditions. J Adv Ther. 1911;29:169–83.
24. Organ LW. Electrophysiologic principles of radiofrequency lesion making. Appl Neurophysiol. 1976;39(2):69–76.
25. McGahan JP, Browning PD, Brock JM, Tesluk H. Hepatic ablation using radiofrequency electrocautery. Investig Radiol. 1990;25(3):267–70.
26. Rossi S, Fornari F, Pathies C, Buscarini L. Thermal lesions induced by 480 KHz localized current field in guinea pig and pig liver. Tumori. 1990;76(1):54–7.
27. McGahan JP, Brock JM, Tesluk H, Gu W-Z, Schneider P, Browning PD. Hepatic ablation with use of radio-frequency electrocautery in the animal model. J Vasc Interv Radiol. 1992;3(2):291–7.
28. JP MG, Schneider P, Brock JM, Tesluk H. Treatment of liver tumors by percutaneous radiofrequency electrocautery. Semin Interv Radiol. 1993;10(2):143–9. Copyright© 1993 by Thieme Medical Publishers, Inc
29. Zlotta AR, Wildschutz T, Raviv G, Peny MO, van Gansbeke D, Noel JC, et al. Radiofrequency interstitial tumor ablation (RITA) is a possible new modality for treatment of renal cancer: ex vivo and in vivo experience. J Endourol. 1997;11(4):251–8.
30. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. Cryobiology. 1998;37(3):171–86.
31. Theodorescu D. Cancer cryotherapy: evolution and biology. Rev Urol. 2004;6(Suppl 4):S9–S19.
32. Chosy SG, Nakada SY, Lee FT Jr, Warner TF. Monitoring renal cryosurgery: predictors of tissue necrosis in swine. J Urol. 1998;159(4):1370–4.
33. Nakada SY, Lee FT Jr, Warner T, Chosy SG, Moon TD. Laparoscopic cryosurgery of the kidney in the porcine model: an acute histological study. Urology. 1998;51(5A Suppl):161–6.
34. Nakada SY, Lee FT Jr, Warner TF, Chosy SG, Moon TD. Laparoscopic renal cryotherapy in swine: comparison of puncture cryotherapy preceded by arterial embolization and contact cryotherapy. J Endourol. 1998;12(6):567–73.

35. Woolley ML, Schulsinger DA, Durand DB, Zeltser IS, Waltzer WC. Effect of freezing parameters (freeze cycle and thaw process) on tissue destruction following renal cryoablation. J Endourol. 2002;16(7):519–22.
36. Campbell SC, Krishnamurthi V, Chow G, Hale J, Myles J, Novick AC. Renal cryosurgery: experimental evaluation of treatment parameters. Urology. 1998;52(1):29–33. discussion –4
37. De Filippo M, Bozzetti F, Martora R, Zagaria R, Ferretti S, Macarini L, et al. Radiofrequency thermal ablation of renal tumors. Radiol Med. 2014;119(7):499–511.
38. Kwan KG, Matsumoto ED. Radiofrequency ablation and cryoablation of renal tumours. Curr Oncol. 2007;14(1):34–8.
39. Ramanathan R, Leveillee RJ. Ablative therapies for renal tumors. Ther Adv Urol. 2010;2(2):51–68.
40. Hsu TH, Fidler ME, Gill IS. Radiofrequency ablation of the kidney: acute and chronic histology in porcine model. Urology. 2000;56(5):872–5.
41. Hong K, Georgiades C. Radiofrequency ablation: mechanism of action and devices. J Vasc Interv Radiol. 2010;21(8 Suppl):S179–86.
42. Crowley JD, Shelton J, Iverson AJ, Burton MP, Dalrymple NC, Bishoff JT. Laparoscopic and computed tomography-guided percutaneous radiofrequency ablation of renal tissue: acute and chronic effects in an animal model. Urology. 2001;57(5):976–80.
43. Zagoria RJ, Hawkins AD, Clark PE, Hall MC, Matlaga BR, Dyer RB, et al. Percutaneous CT-guided radiofrequency ablation of renal neoplasms: factors influencing success. AJR Am J Roentgenol. 2004;183(1):201–7.
44. Goldberg SN, Gazelle GS. Radiofrequency tissue ablation: physical principles and techniques for increasing coagulation necrosis. Hepato-Gastroenterology. 2001;48(38):359–67.
45. Kunkle DA, Egleston BL, Uzzo RG. Excise, ablate or observe: the small renal mass dilemma – a meta-analysis and review. J Urol. 2008;179(4):1227–33. discussion 33–4
46. Caputo PA, Ramirez D, Zargar H, Akca O, Andrade HS, O'Malley C, et al. Laparoscopic cryoablation for renal cell carcinoma: 100-month oncologic outcomes. J Urol. 2015;194(4):892–6.
47. Camacho JC, Kokabi N, Xing M, Master VA, Pattaras JG, Mittal PK, et al. R.E.N.A.L. (Radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, and location relative to polar lines) nephrometry score predicts early tumor recurrence and complications after percutaneous ablative therapies for renal cell carcinoma: a 5-year experience. J Vasc Interv Radiol. 2015;26(5):686–93.
48. Hayn MH, Schwaab T, Underwood W, Kim HL. RENAL nephrometry score predicts surgical outcomes of laparoscopic partial nephrectomy. BJU Int. 2011;108(6):876–81.
49. Okhunov Z, Shapiro EY, Moreira DM, Lipsky MJ, Hillelsohn J, Badani K, et al. R.E.N.A.L. nephrometry score accurately predicts complications following laparoscopic renal cryoablation. J Urol. 2012;188(5):1796–800.
50. Schmit GD, Thompson RH, Kurup AN, Weisbrod AJ, Boorjian SA, Carter RE, et al. Usefulness of R.E.N.A.L. nephrometry scoring system for predicting outcomes and complications of percutaneous ablation of 751 renal tumors. J Urol. 2013;189(1):30–5.
51. Blute ML Jr, Okhunov Z, Moreira DM, George AK, Sunday S, Lobko II, et al. Image-guided percutaneous renal cryoablation: preoperative risk factors for recurrence and complications. BJU Int. 2013;111(4 Pt B):E181–5.
52. Vernez SL, Okhunov Z, Kaler K, Youssef RF, Dutta R, Palvanov A, et al. Skin-to-tumor distance predicts treatment failure of T1a renal cell carcinoma following percutaneous cryoablation. Urology. 2017;108:195.
53. Chang X, Liu T, Zhang F, Qian C, Ji C, Zhao X, et al. The comparison of R.E.N.A.L., PADUA and centrality index score in predicting perioperative outcomes and complications after laparoscopic radio frequency ablation of renal tumors. J Urol. 2015;194(4):897–902.
54. Seideman CA, Gahan J, Weaver M, Olweny EO, Richter M, Chan D, et al. Renal tumour nephrometry score does not correlate with the risk of radiofrequency ablation complications. BJU Int. 2013;112(8):1121–4.

55. Gahan JC, Richter MD, Seideman CA, Trimmer C, Chan D, Weaver M, et al. The performance of a modified RENAL nephrometry score in predicting renal mass radiofrequency ablation success. Urology. 2015;85(1):125–9.
56. Martin JW, Patel RM, Okhunov Z, Vyas A, Vajgrt D, Clayman RV. Multipoint thermal sensors associated with improved oncologic outcomes following cryoablation. J Endourol. 2017;31(4):355–60.
57. Rendon RA, Gertner MR, Sherar MD, Asch MR, Kachura JR, Sweet J, et al. Development of a radiofrequency based thermal therapy technique in an in vivo porcine model for the treatment of small renal masses. J Urol. 2001;166(1):292–8.
58. Atwell TD, Schmit GD, Boorjian SA, Mandrekar J, Kurup AN, Weisbrod AJ, et al. Percutaneous ablation of renal masses measuring 3.0 cm and smaller: comparative local control and complications after radiofrequency ablation and cryoablation. AJR Am J Roentgenol. 2013;200(2):461–6.
59. Pierorazio PM, Johnson MH, Patel HD, Sozio SM, Sharma R, Iyoha E, et al. Management of renal masses and localized renal cancer: systematic review and meta-analysis. J Urol. 2016;196(4):989–99.
60. Bhan SN, Pautler SE, Shayegan B, Voss MD, Goeree RA, You JJ. Active surveillance, radiofrequency ablation, or cryoablation for the nonsurgical management of a small renal mass: a cost-utility analysis. Ann Surg Oncol. 2013;20(11):3675–84.
61. Tsivian M, Kim CY, Caso JR, Rosenberg MD, Nelson RC, Polascik TJ. Contrast enhancement on computed tomography after renal cryoablation: an evidence of treatment failure? J Endourol. 2012;26(4):330–5.
62. Matsumoto ED, Watumull L, Johnson DB, Ogan K, Taylor GD, Josephs S, et al. The radiographic evolution of radio frequency ablated renal tumors. J Urol. 2004;172(1):45–8.
63. Pirasteh A, Snyder L, Boncher N, Passalacqua M, Rosenblum D, Prologo JD. Cryoablation vs. radiofrequency ablation for small renal masses. Acad Radiol. 2011;18(1):97–100.
64. Rodriguez Faba O, Akdogan B, Marszalek M, Langenhuijsen JF, Brookman-May S, Stewart GD, et al. Current status of focal cryoablation for small renal masses. Urology. 2016;90:9–15.
65. Johnson S, Pham KN, See W, Begun FP, Langenstroer P. Laparoscopic cryoablation for clinical stage T1 renal masses: long-term oncologic outcomes at the Medical College of Wisconsin. Urology. 2014;84(3):613–8.
66. Kim EH, Tanagho YS, Saad NE, Bhayani SB, Figenshau RS. Comparison of laparoscopic and percutaneous cryoablation for treatment of renal masses. Urology. 2014;83(5):1081–7.
67. Olweny EO, Park SK, Tan YK, Best SL, Trimmer C, Cadeddu JA. Radiofrequency ablation versus partial nephrectomy in patients with solitary clinical T1a renal cell carcinoma: comparable oncologic outcomes at a minimum of 5 years of follow-up. Eur Urol. 2012;61(6):1156–61.
68. Thompson RH, Atwell T, Schmit G, Lohse CM, Kurup AN, Weisbrod A, et al. Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. Eur Urol. 2015;67(2):252–9.
69. Breda A, Anterasian C, Belldegrun A. Management and outcomes of tumor recurrence after focal ablation renal therapy. J Endourol. 2010;24(5):749–52.
70. Patel SR, Abel EJ, Hedican SP, Nakada SY. Ablation of small renal masses: practice patterns at academic institutions in the United States. J Endourol. 2013;27(2):158–61.
71. Hegg RM, Schmit GD, Boorjian SA, McDonald RJ, Kurup AN, Weisbrod AJ, et al. Percutaneous renal cryoablation after partial nephrectomy: technical feasibility, complications and outcomes. J Urol. 2013;189(4):1243–8.
72. Okhunov Z, Chamberlin J, Moreira DM, George A, Babaian K, Shah P, et al. Salvage percutaneous cryoablation for locally recurrent renal-cell carcinoma after primary cryoablation. J Endourol. 2016;30(6):632–7.

Chapter 12
Novel Ablative Therapies for Renal Tumors

Maria del Pilar Laguna Pes and Jean J.M.C.H. de la Rosette

Introduction

Ablative therapies are used in the treatment of 7–10% of all kidney tumors [1, 2]. Renal tumor ablation is most commonly performed with either cryoablation (CA) or radiofrequency ablation (RFA). Recent versions of major guidelines consider ablation as alternative to surgery in the elderly and patients at high surgical risk due to pre-existing medical comorbidities [3–5]. These guidelines, however, remain cautious regarding the use of ablation in young and healthy individuals despite recent encouraging data.

Compared to partial nephrectomy, thermal ablation with CA and RFA is associated with a slightly higher risk of local recurrence but a lower rate of complications [6]. The outcomes of thermal ablation in the treatment of renal tumors are well described, although frequently retrospectively [6–8]. Limitations of CA and RFA include possible damage to vital structures in the vicinity of the ablation zone, unpredictable results because of difficult procedural monitoring of the target zone, and the "thermal sink" effect which reduces treatment efficacy. New ablative technologies that aim to overcome these limitations are in various stages of development. This chapter summarizes the current evidence for investigational ablation methods for the treatment of primary renal tumors, including irreversible electroporation (IRE), microwave (MWA), stereotactic ablative radiation therapy (SABR), high-intensity focused ultrasound (HIFU), and photodynamic therapy (PDT).

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Irreversible Electroporation (IRE)

Technology Electroporation is an ablative technology in which high-voltage ultrashort (microseconds) electrical current pulses travel between electrodes and across the tissue to create nanoscale defects ("nanopores") in the phospholipid bilayer of the cell membrane [9–11]. The process can be reversible or permanent. Above a certain electrical threshold, the nanopores become permanent, and cell death occurs due to the inability to maintain cellular homeostasis [12–14].

Although the presence of nanopores following delivery of electrical pulses has been visualized by electron microscopy [9, 10], it remains unclear if these pores are the true mechanism of IRE-induced cell death [15, 16]. IRE appears to offer two main advantages over existing technologies for renal mass ablation. First, IRE is not dependent on thermal energy and therefore is not influenced by thermal sink. Second, IRE damages only the membranes of cells within its field of treatment thereby minimizing damage to adjacent blood vessels, nerves, and the renal collecting system [17].

Device and Procedure At the present time, only one IRE platform has specific clearance for the ablation of soft tissue, the NanoKnife IRE console (AngioDynamics Inc., Queensbury, New York), also registered as the HVP-01 Electroporation System. This platform consists of a low-energy direct current generator capable of connecting up to six 16-gauge monopolar needle electrodes [11–14, 18, 19].

Procedural parameters used for IRE ablation of kidney tumors have been extrapolated from experience in other organs [19]. The parameters that can be adjusted during IRE procedures include voltage, pulse number, pulse length, electrode number, and electrode spacing. Common settings used for IRE of renal tumors are depicted in Fig. 12.1. Due to the fast repetition and microsecond pulse length of IRE treatment (pulse cycle), this procedure takes only 5–10 min to complete.

IRE should be performed under general anesthesia with muscle relaxation in order to prevent severe muscle contractions as a result of the electrical pulses [20]. Because IRE pulses have the potential of causing cardiac arrhythmia, synchronization of the IRE pulses with the cardiac rhythm is advised (Fig. 12.2). IRE electrodes are placed in a similar fashion to probes used for CA or RFA. Parallel insertion of

Voltage	1.500 V/cm
Pulse number	70–90
Pulse length	70–90 µs
Electrode number	3–6 (size lesion)
Electrode spacing	1.5–2 cm
Active tip length	1.5–2 cm

Fig. 12.1 Standard settings for irreversible electroporation kidney tumor ablation

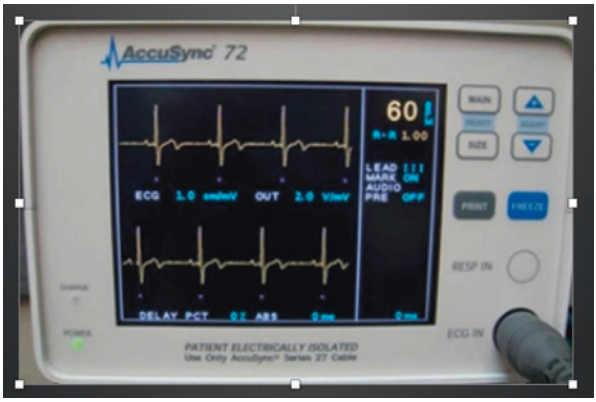

Fig. 12.2 Interface for the synchronization of the irreversible electroporation pulses with the refractory period of the cardiac rhythm

the probes is important to guarantee an equal distribution of the electrical field. The needles are visible under ultrasound or CT guidance. Target ablation zone sizes can be tailored by changing the length of the applicator between 1 and 2 cm. When treating tumors with a diameter of >2 cm, a double pass with retraction of the probe is performed. The distance between the tips of the probes should not exceed 2 cm.

Animal Studies The first animal study of IRE was performed on rat livers and showed ablation of the parenchyma with a sharp definition between treated and untreated tissue [21]. Preservation of blood vessels and ductal structures was also observed. IRE has additionally been performed on porcine kidneys and has demonstrated acceptable acute, short-term, and mid-term safety [13, 22–24]. Of note, compared to monopolar IRE, bipolar IRE has been found to result in smaller ablation volumes, more frequent urothelial erosion, and a greater degree tissue necrosis [22]. Thus, monopolar IRE is preferred by most investigators.

A comparison of ablation boundaries in porcine kidneys treated with CA, RFA, IRE, and MWA demonstrated that the treatment effect from each of these technologies conforms to a similar radial distribution with three distinct histologic zones [25]. At the center of the ablation volume necrosis and hemorrhage are observed. Surrounding this zone there is a second circumferential zone of coagulative, necrotic nonviable tissue, and more peripherally a third transition zone is encountered composed by a mixture of healthy and necrotic tissue. Notably, the widths and uniformity of the ablation zones vary among the techniques, with lobular and less uniform margins observed with IRE and RFA. Using transferase dUTP nick end labeling vitality staining (TUNEL), IRE was found to have the widest transition zone. This suggests that wider procedural safety margins may be necessary for this procedure.

Acute and subacute monopolar IRE of porcine kidneys shows complete cortical necrosis without intervening live cells [23, 24]. Although damage of the urothelium exists, the pelvic collagen extracellular matrix and the basement membrane and fibroblasts remain intact [23, 26, 27]. After 14–27 days, histological evaluation shows cortical fibrosis and onset of cellular repair and repopulation [13, 22, 23, 27]. These results support the theory that IRE could spare vital structures within the ablation zone.

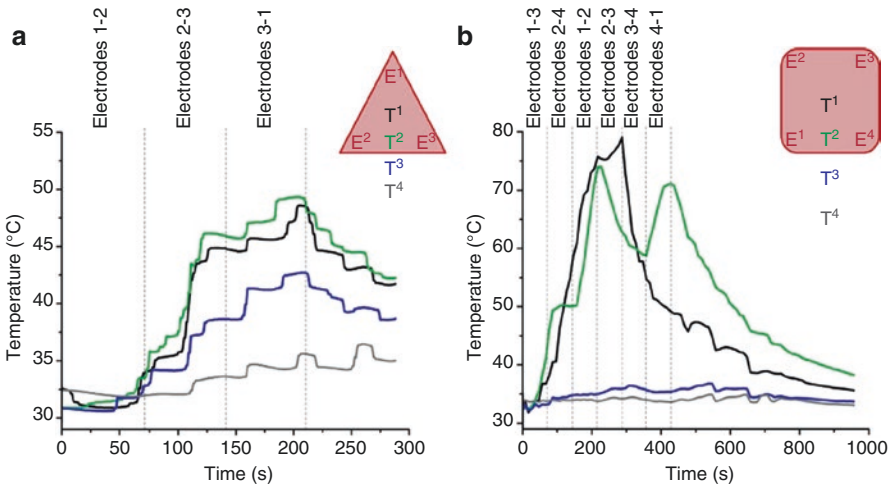

Fig. 12.3 Peak temperatures registered in an animal study during kidney irreversible electroporation with (**a**) a three-needle template and (**b**) a four-needle template. T1 central ablation core in black line, T3 in blue line, [1 cm outside the ablation zone]. (From Wagstaff et al. [28], with permission of Elsevier)

The repetitive high-intensity electric pulses used in IRE have the potential of causing resistive heating. Changes consistent with thermal injury within 0.5 mm of the needle tract (applicator edges) have been found [23]. Temperature variation and distribution during monopolar IRE has been studied using porcine kidneys [20]. Using standard settings and a three-needle template for kidney ablation, a peak temperature of 57 °C was observed in the core of the ablation zone [28]. Additionally, at 1 cm outside of the ablation zone, a peak temperature of 40 °C was observed. With a four-needle configuration, peak temperatures of 70 and 42 °C were found within the core and 1 cm outside the ablation zone, respectively (Fig. 12.3). These temperatures lead to thermal damage warranting the consideration of safety measures, such as temperature monitoring.

Imaging with CT scan 24 h after ablation will generally reveal a sharp transition to contrast-enhancing tissue outside the ablation zone irrespective of the ablation technique used. However, subtle differences in the CT appearance of ablation zones can be seen depending on the ablation technique. More specifically, attenuation on CT within the ablation zone is lowest after IRE and CA, whereas lobulated boundaries are characteristic of RFA [25]. In general, CT features are not adequate to estimate ablation boundaries at 24 h, as mid-term CT imaging shows cortical retraction and urothelial regeneration [23]. Dynamic contrast-enhanced MRI shows inhomogeneous necrosis with small perifocal edema at short-term follow-up and sharp identifiable scars at mid-term follow-up [24].

Human Studies The safety and feasibility of IRE for treating renal tumors were first explored in a study of six patients undergoing open resection of RCC [14]. In this study, IRE was performed under general anesthesia immediately prior to tumor resection.

So as to avoid induction of cardiac arrhythmias, the investigators synchronized IRE pulses with the refractory period of the cardiac rhythm. Analysis of ST waveforms and axis deviation on 12-lead electrocardiogram showed the absence of relevant changes. Only one patient developed transient supraventricular systole during the procedure, without any further cardiac abnormalities in the postoperative period. There were no changes in central hemodynamics during or 5 min after IRE or in hematological and serum biochemical variables. Notably, no changes were observed in serum creatine kinase MB, troponin T, lactate, or lactate dehydrogenase levels indicating the absence of ischemia or cell death. On histopathological examination of the resection specimens, the tumor cells displayed a mismatch between plasma and nuclear volume consistent with cell swelling but not actual cell death. It is likely that a longer time interval between treatment and tissue resection is required in order to see a more substantial treatment effect, as IRE is thought to predominantly cause cell death by induction of apoptosis secondary to disruption of cellular membranes.

Safety and clinical outcomes of IRE were next reported in a prospective single-center study of volunteers with advanced malignancy of the liver, kidney, and lung [29]. In total, seven patients underwent treatment of a renal tumor. CT follow-up at 3 months confirmed successful tumor ablation in five of the seven treated patients, with two patients requiring a second IRE procedure. In terms of complications, one patient developed obstruction of the ureter, and two patients developed transient hematuria following IRE treatment extending into the central portion of the kidney.

Trimmer et al. next evaluated percutaneous IRE in the treatment of 20 small masses [30]. Follow-up imaging was performed at 6 weeks showing residual tumor in two cases. Both were treated with salvage RFA. Six- and 12-month follow-up was available for 15 and 6 cases, respectively. Only one radiological recurrence was diagnosed at 1 year and this was successfully treated with partial nephrectomy. No major complications were observed. More recently, a larger series from the same group has been published that included 42 tumors (median size 2 cm) treated by percutaneous IRE [31]. Same-day discharge occurred in 71% of patients without major perioperative complications. The initial treatment success rate in this series was 93%. At a mean follow-up of 22 months, the 2-year actuarial local recurrence-free survival was 83% in patients with RCC confirmed in the biopsy. Regarding preservation of renal function, a small report on IRE in solitary kidney tumors (five patients) showed no significant decrease in glomerular filtration rate over 3 months following this procedure [32].

An ongoing phase 2a trial (IRENE) aims to explore the efficacy of IRE for the treatment of clinical T1a renal tumors [33]. In this study, partial nephrectomy will be performed 28 days after percutaneous IRE, with MRI imaging preformed prior to resection. Detailed histopathological data on three resection specimens is already available [34]. Histological evaluation with hematoxylin and eosin staining as well as immunohistochemistry with the proliferation marker Mib1 was performed to determine cell viability. IRE leads to a high degree of damage in the three small tumors (size range 1.5–1.7 cm) with a zonal structuring of the ablation zone and negative margins. The foci of tumor in the center of the lesion showed coagulation

necrosis in all cases. Radially a zone of necrosis of variable width with chronic inflammation and giant cells followed, where ghost-like structures could still be discerned. Within the necrotic zone, small foci of preserved tumor accounting for 2.8–62.4% of the total tissue were found without signs of proliferative activity. Necrosis and urothelial sloughing were observed in those sections. Adjacent to the outer borders of the lesion, there was a gradual transition to a zone of granulation tissue with a width of 1–5 mm followed externally by unaffected renal parenchyma.

Another clinical trial evaluating percutaneous IRE in the treatment of small renal tumors is ongoing in the Netherlands [19]. Additionally a third study on IRE in unresectable kidney tumors is ongoing in China (ClinicalTrials.gov identifier NCT02335827).

An example of a patient treated with IRE is displayed *in* Fig. 12.4.

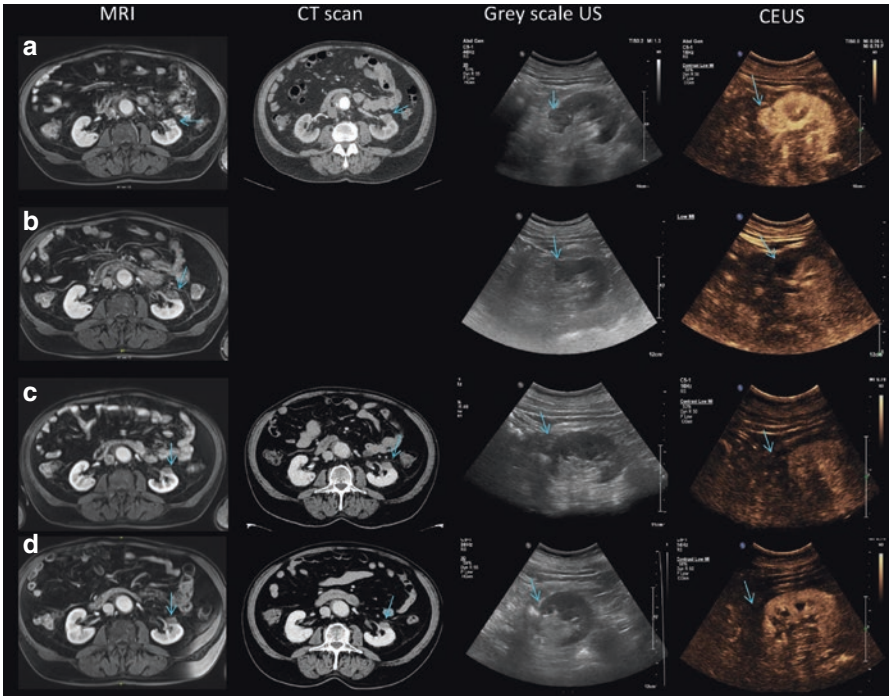

Fig. 12.4 Initial and follow-up imaging after irreversible electroporation of a kidney tumor. (**a**) Small renal mass in the anterior kidney. MRI T2-weighted imaging and CT scan show enhancement of the mass clearly depicted in the gray-scale ultrasound and with vascularity present on contrast-enhanced ultrasound (CEUS). (**b**) One week after irreversible electroporation, there is no enhancement in T2 contrast-weighted MRI, and there is a slight increase in the size of the ablated lesion and absence of vascularity on CEUS. (**c**) Three months after IRE, MRI and CT show contraction of the ablated lesion without enhancement. Additionally, there is absence of contrast diffusion on CEUS. (**d**) At 6 months there is absence of contrast enhancement on MRI and CT, hyperechogenicity on gray-scale ultrasound which is a possible indirect sign of fibrosis, and an absence of vascularity on CEUS

Microwave Ablation (MWA)

Technology and Devices MWA is a heat-based needle ablation technology that is currently used in treatment of lesions of the breast, liver and lung. MWA uses alternating electrical current to generate electromagnetic microwaves in the frequency range of 900–2.450 MHz. Oscillating microwaves agitate water molecules causing friction and increased tissue temperatures [35]. Similar to RFA, the high temperature caused by MWA induces cellular death by coagulative necrosis. However, MWA does not require grounding pads and is not limited by tissue impedance. MWA also offers more consistent and larger ablation volumes than RFA in a shorter time [36–38]. Additionally, the minimal thermal dispersion reduces "heat sinking" and MWA seems to be less sensitive to tissue type [36, 39–43].

The electromagnetic field induced depends on antenna design and this drives the size and shape of the ablated zone. To date, three generations of MWA systems have been developed. The first-generation MWA system lacked active antenna cooling and was unpowered to reach high temperatures [44]. The second-generation system included antenna cooling but still offered only limited generator power. The third generation integrates shaft antenna cooling (water, saline, or CO_2) and a high generator power delivering increased energy to the target and minimizing injury to surrounding tissue [35, 43]. Overall fluid-based cooling systems require larger antenna diameters, while gas-cooled antennas maintain a 17-guage diameter.

New antenna designs aim to produce a round and forward-weighted heating zone that at least theoretically should conform to the shape of renal masses. The higher temperature is reached within 1 cm of the antenna tip and the effect of multiple antennas is synergistic [45]. CO_2 cooled systems permit creation of an early small ice ball that stabilizes the position of the antenna. Frequencies of 915 MHz and 2.45 GHz create large ablation zones, with the longer wavelength of 915 MHZ resulting in the largest treatment volumes [46–48]. System performance varies depending on a combination of antenna diameter, number of antennas, power generated, frequency, and power lost between the generator and the tip of the antenna. Understanding the characteristics of the system used is critical to properly select patients and evaluate outcomes [39, 49].

Animal Studies A considerable number of studies evaluating MWA of the liver, lung, and kidney have been conducted. These studies utilize a range of different ablation protocols in terms of generator power, number of antennas, and ablation time but show consistent ablation zones between 2 and 4.2 cm using a single antenna [50–56].

The first generation of MWA systems showed inconsistent and asymmetric ablation zones, denuded urothelium, antenna charring, and damage to the collecting system of porcine kidneys in vivo [50]. Advanced systems assessed the effect of different MWA powers (60–180 W) and times of application (2–6 min) for a 1.8 mm antenna with a 2.45 GHz system in bovine liver and porcine muscle and kidney [51]. Increased power setting (up to 140 W) and time significantly increased

ablation volume in the three tissues. Optimal efficiency of this novel probe/system was found at settings ≤ 140 W for 6 min. Furthermore, lesions created at 50 W over 10 min seem to be predictable in the porcine kidney [51, 52].

Ex vivo studies show that after MWA, the degree of contraction of the ablated lesion is higher in the liver and lung than in the kidney, and it is proportional to tissue vascularization and desiccation [53, 54]. In an ex vivo porcine kidney study, significant variations in post-interventional volumes (− 3.8% to −7.2%) were found depending on application time although dehydration rates were similar [55]. The coagulation zone was underestimated by visualization, and the greater the deployed energy, the larger the coagulation volume.

At equal number of antennas, larger ablation zones in the kidney are achieved with MWA as compared to RFA [43]. Novel refrigerated antennas (Amica, StenlØse, DK) showed mean diameter ablations of 1.2–4.2 cm depending on power time and exposure [56]. Fifty watts of power resulted in optimal lesion size and spherical index. Pathological evaluation with NADH staining did not show skip lesion in any of the ablated tissues.

Animal kidney studies have failed to show the protective effect on the collecting system using antegrade pyeloperfusion (cooled 5% glucose) MWA [57]. Consequently, MWA of central lesions abutting the collecting systems should be carefully considered. Lastly, comparison of temperature- or power-controlled MW systems in a porcine kidney model showed no differences in ablation zone geometry [55]. System failures occurred less frequently with a temperature control system (0% vs 13%).

Attempts to establish treatment guidelines in terms of power and time have been performed in vivo with a porcine model [58]. Diameter of ablated tissue varies significantly by time and power applied and their interaction. In fact, those studies show that the optimal MWA protocol is highly dependent on the system characteristics and the technical procedure should be adapted to the desired targeted ablation zone.

Human Studies Three phase I studies have evaluated the safety and feasibility of kidney tumor MWA prior to surgical resection [59–61]. Despite the implementation of different protocols and probes used, all showed presence of coagulative necrosis, uniform and reproducible ablation lesions, and absence of vital tumor cells inside the induced lesion. The use of three probes resulted in larger mean ablative lesions. Importantly, the surrounding healthy tissue was preserved. Complications were negligible in these studies.

A meta-analysis comparing CA to MWA for the treatment of small renal masses was published in 2013 [62]. This analysis included data from 7 studies with 164 patients treated by MWA [44, 60, 63–66]. At a mean follow-up of 18 months, the primary effectiveness was 91.3%, and the cancer-specific survival was 96.8%. Local tumor progression was described in 2.54% of patients without any metastatic progression. The results of several other series on MWA have been reported since the publication of the meta-analysis [67–73]. These series support the previously reported outcomes with emphasis in dependence on tumor size and complexity.

Of note, all systems delivered high power through cooled antennas and mostly included small renal masses of low/intermediate complexity. One study, however, did include sinusal tumors [71]. Treatment was performed percutaneously, mostly under general anesthesia, and when necessary hydrodisplacement of neighbor organs was used.

Special mention is deserved for the randomized control trial by Guan et al. comparing partial nephrectomy to MWA (open/ laparoscopically assisted) in the treatment of small renal masses [64]. With a minimum follow-up of 2 years (median 32 and 36 months for MW and partial nephrectomy, respectively), operative and hospitalization times were similar in both arms. The estimated blood loss and complication rate were significantly lower in the MWA group. Of note, one patient treated with MWA developed a urinary leak. Decline in postoperative renal function was significantly lower in the MWA group although at last follow-up, renal functional decreases were similar. Recurrence-free survival in cases of RCC were 90.4% and 96.6% for MWA and partial nephrectomy ($p = 0.46$), respectively [64].

High-Intensity Focused Ultrasound (HIFU)

HIFU is an ablative method that utilizes ultrasound to cause tissue damage through heat and cavitation [74]. Heat is produced as the ultrasound beam propagates through the tissue reaching 80 °C in the target [75, 76]. Acoustic cavitation also results in cell necrosis by combination of mechanical stress and thermal injury. Cavitation depends on pulse length, frequency, and intensity [77].

HIFU can be delivered extracorporeally without tumor puncture, preventing risk of hemorrhage and avoiding tumor spillage [78]. Additionally, HIFU can be delivered laparoscopically. Animal studies of extracorporeal HIFU have shown problems with skin damage and unpredictable tissue ablation [74, 79]. At present, research focuses on the development of laparoscopic probes able to optimize the ablation zone dimensions [80] and on noninvasive approaches such as respiratory-gated magnetic resonance imaging-guided HIFU [81].

Initial phase 1b and 2a trials on the safety and feasibility of extracorporeal HIFU have resulted in variable rates of ablation success depending on the assessment modality [78–82]. More specifically, only 25% of ablations were judged to be successful on the basis of histopathological evaluation [82], whereas two thirds of ablations were found to be successful on the basis of posttreatment imaging [83]. Some authors suggest that ablation is impeded by subcutaneous and perinephric fat as well as intervening ribs [84]. High acoustic outputs are therefore needed to compensate for the loss of intensity, leading to an increased risk of peritumor tissue damage [74].

Similar results have been seen in other studies. For example, histological evaluation of resected kidney tumors treated with HIFU revealed limited signs of tissue ablation in 80% of 19 treated patients [85]. Additionally, in another study of 14 small renal masses removed after HIFU, ablated tissue was found in only 15–35%

of the targeted volume [86]. In another study of 17 renal tumors (mean size 2.5 cm), radiological evidence of treatment effect was seen in 47% of patients 12 days after procedure [87]. Repeat imaging was available for 14 patients of which 6 (43%) showed a mean decrease in the tumor area of 12%.

Problems with respiratory movement and anatomical interphases can be avoided when an intracorporeal probe is brought directly to the target [80]. A phase I trial of laparoscopic-assisted HIFU and immediate surgical resection investigated the histology of the treated tumors [88]. Among the seven treated patients with small renal masses (mean tumor size 2.2 cm), four (51.7%) showed complete tumor ablation, two (28.6%) tumors had a 1–3 mm peripheral rim of cancer viable tissue, and one (14.3%) tumor showed a central area with vital tumor [86]. Similar results were described in a proof-of-concept trial in which the ablated zones were within the targeted area in all patients and amounted for 90% to 100% of target zones [89]. No intra-lesion skipping was seen although small areas of subcapsular skipping at the tumor surface were observed in two patients. At present, there are no data regarding the oncological efficacy of laparoscopic HIFU with the tumor left in situ after ablation.

Stereotactic Ablative Radiation Therapy (SABR)

RCC has long been considered a radioresistant tumor [90]. This is premised on historical data evaluating conventionally fractionated radiation, i.e., radiation delivered in small doses over multiple treatment sessions. More recent data, however, now suggests a role for radiotherapy in the treatment of RCC when delivered in relatively few high-dose fractions [91]. SABR, also known as stereotactic body radiotherapy, uses an external coordinate system to deliver a safe and single dose of radiation up to 25 Gy [92]. These techniques may potentially be curative for primary renal tumors. SABR does not require anesthesia and can be performed as an outpatient. A wide range of devices, doses, and dose fractionation schedules have been recently reviewed [93].

A specific challenge for the treatment of the kidney is respiratory-synchronous organ movement. The CyberKnife system (Accuray, Sunnyvale, CA, USA) uses a true robotic manipulator, which corrects for the kidney and tumor movement throughout the respiratory cycle. In vivo studies have shown that the effect of CyberKnife is focal and that surrounding renal parenchyma remains unaffected [94]. Percutaneous insertion of gold fiducials in the renal parenchyma or the tumor is usually necessary to facilitate tumor tracking.

Several noncontrolled prospective case series of CyberKnife for primary renal tumors have been published [91, 95–97]. A phase I dose-escalation trial of SABR in 19 poor surgical candidates with nonmetastatic cT1-3 renal tumors (median volume 58 cm^3) explored several dose levels delivered in 4 fractions [91]. With 3–6 patients treated per dose cohort, none of the 15 evaluable patients developed local progression (12 stable and 3 partial response). Acute treatment-related toxicity was observed

in two patients (10.5%, one grade 2 fatigue and one grade 4 duodenal ulcer). Chronic treatment-related toxicity occurred in four patients – two grade 3 renal toxicities, one grade 2 urinary incontinence, and one grade 4 ulcus duodenal in the same patient that presented it acutely. This low toxicity was supported by small series on inoperable patients or patients with severe comorbidity [95, 96]. Doses of 39Gy in three fractions or 40Gy in three fractions are able to achieve tumor local control (stable or partial response) at 1 year with mild and self-limited toxicity [95, 96].

The largest series in the literature includes the outcomes of 40 patients (30 RCCs and 15 urothelial tumors) treated with SABR [97]. At a dose of 25 Gy in a single fraction, the local control rate at 9 months was 98%. However, from the 42% of tumors that achieved complete response, most were urothelial tumors, while the complete response in RCC reached only 20%. Renal function was preserved and only minor toxicity was present in six patients. Currently a phase II trial is recruiting patients with results expected in 2019 (ClinicalTrials.gov NCT01890590).

Photodynamic Therapy (PDT)

PDT has been investigated as an ablation method for primary renal tumors. PDT requires administration of a photosensitizer that accumulates in the target tissue. The tissue is then illuminated percutaneously or interstitially leading to tissue ablation. Using mTHPC as a sensitizer, complete loss of cell viability has been reported in a mouse renal tumor model [98]. More recently, vascular-targeted PDT with the water-soluble photosensitizer WST-11 has shown promising clinical results in a porcine model [99]. Following ablation with this agent, normal renal tissue, blood vessels, and the collecting system were completely spared, supporting its clinical evaluation for tumors close to sensitive structures such as the renal hilum or renal pelvis. A phase I/II trial of PDT for the treatment of renal tumors is currently underway (ClinicalTrials.gov NCT01573156).

Conclusion

IRE ablation of kidney tumors is safe when performed under general anesthesia and provided that IRE pulses are synchronized with the refractory period of the cardiac rhythm. Because the temperature delivered during the procedure is low and the extracellular matrix is preserved, IRE has the unique feature of allowing for preservation of vital tissue. Short-term outcomes with IRE are favorable, but information on longer-term oncological outcomes are scarce. For MWA there is evidence on procedural safety when using the high-powered cooled devices. Retrospective studies have shown the effectiveness of MWA and the potential for minimal complications. While clinical data exists for both IRE and MWA, large prospective studies as well as comparative studies to both tumor resection and ablation with CA and RFA

are lacking. HIFU, SABR, and PDT are other novel ablation techniques that have been evaluated for the primary treatment of renal tumors. Data with these techniques, however, are less mature than IRE and MWA, and additional human data is needed at this time.

References

1. Choueri TK, Schutz FA, Hevelone ND, Nguyen PL, Lipsitz SR, Williams SB, Silverman SG, Hu JC. Thermal ablation vs surgery for localized kidney cancer: a Surveillance, Epidemiology, and End Results (SEER) database analysis. Urology. 2011;78:93–8.
2. Laguna MP, Algaba F, Cadeddu J, Clayman R, Gill I, Gueglio G, Hohenfellner M, Joyce A, Landman J, Lee B, van Poppel H. Current patterns of presentation and treatment of renal masses: a clinical research office of the endourological society prospective study. J Endourol. 2014;28:861–70.
3. Finelli A, Ismaila N, Bro B, Durack J, Eggener S, Evans A, Gill I, Graham D, Huang W, Jewett MAS, Latcha S, Lowrance W, Rosner M, Shayegan B, Thompson HR, Uzzo R, Russo P. Management of Small Renal Masses: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017;35:1–13.
4. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015;67:913–24.
5. Campbell S, Uzzo RG, Allaf ME, et al. Renal mass and localized renal cancer: AUA guideline. J Urol. 2017;198:520–9.
6. Laguna MP, Walz J, Atwell T, Autorino R, Cestari A, Gahan J, Klatte T, van Lienden K, Teber D, Wagstaff PGK, Zondervan PJ. Chapter 8: Available ablation energies to treat small renal masses. In: Sanchez-Salas R, Desai M, editors. Image-guided therapies for prostate and kidney cancers. A joint SIU-ICUD International Consultation. Melbourne. 15–18 Oct 2015. p. 521–90. Available at: http://www.siu-urology.org/society/siu-icud. Accessed 14 July 2017.
7. Trudeau V, Becker A, Roghmann F, et al. Local tumor destruction in renal cell carcinoma – an inpatient population-based study. Urol Oncol. 2014;32:54.e1–7.
8. Patel HD, Pierorazio PM, Johnson MH, et al. Renal functional outcomes after surgery, ablation and active surveillance of localized renal tumors: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2017;12:1057–69.
9. Lee EW, Wong D, Prikhodko SV, Perez A, Tran C, Loh CT, et al. Electron microscopic demonstration and evaluation of irreversible electroporation-induced nanopores on hepatocyte membranes. J Vasc Interv Radiol. 2012;23(1):107–13.
10. Chang DC, Reese TS. Changes in membrane-structure induced by electroporation as revealed by rapid-freezing electron-microscopy. Biophys J. 1990;58(1):1–12.
11. Wagstaff PG, de Bruin DM, Zondervan PJ, Savci Heijink CD, Engelbrecht MR, van Delden OM, et al. The efficacy and safety of irreversible electroporation for the ablation of renal masses: a prospective, human, in-vivo study protocol. BMC Cancer. 2015;15:165.
12. Al-Sakere B, Andre F, Bernat C, Connault E, Opolon P, Davalos RV, et al. Tumor ablation with irreversible electroporation. PLoS One. 2007;2(11):e1135.
13. Olweny EO, Kapur P, Tan YK, Park SK, Adibi M, Cadeddu JA. Irreversible electroporation: evaluation of nonthermal and thermal ablative capabilities in the porcine kidney. Urology. 2013;81(3):679–84.
14. Pech M, Janitzky A, Wendler JJ, Strang C, Blaschke S, Dudeck O, et al. Irreversible electroporation of renal cell carcinoma: a first-in-man phase I clinical study. Cardiovasc Intervent Radiol. 2011;34(1):132–8.
15. van Gemert MJ, Wagstaff PG, de Bruin DM, van Leeuwen TG, van der Wal AC, Heger M, et al. Irreversible electroporation: just another form of thermal therapy? Prostate. 2015;75:332–5.

16. Davalos RV, Bhonsle S, Neal RE. Implications and considerations of thermal effects when applying irreversible electroporation tissue ablation therapy. Prostate. 2015;75(10):1114–8.
17. Golberg A, Yarmush ML. Nonthermal irreversible electroporation: fundamentals, applications, and challenges. IEEE Trans Biomed Eng. 2013;60(3):707–14.
18. Bertacchini C, Margotti PM, Bergamini E, Lodi A, Ronchetti M, Cadossi R. Design of an irreversible electroporation system for clinical use. Technol Cancer Res Treat. 2007;6(4):313–20.
19. Buijs M, van Lienden KP, Wagstaff PGK, Scheltema MJV, de bruin DM, Zondervan PJ, van Delden OM, van leeuwen TG, de la Rosette JJMCH, Laguna MP. Irreversible electroporation for the ablation of renal cell carcinoma: a prospective, human, in vivo study protocol (IDEAL phase 2b). JMIR Res Protoc. 2017;6(2):e21. 1–12
20. Nielsen K, Scheffer HJ, Vieveen JM, van Tilborg AA, Meijer S, van KC, et al. Anaesthetic management during open and percutaneous irreversible electroporation. Br J Anaesth. 2014;113(6):985–92.
21. Edd JF, Horowitz L, Davalos RV, Mir LM, Rubinsky B. In vivo results of a new focal tissue ablation technique: irreversible electroporation. IEEE Trans Biomed Eng. 2006;53:1409–15.
22. Tracy CR, Kabbani W, Cadeddu JA. Irreversible electroporation (IRE): a novel method for renal tissue ablation. BJU Int. 2011;107(12):1982–7.
23. Deodhar A, Monette S, Single GW Jr, Hamilton WC Jr, Thornton R, Maybody M, et al. Renal tissue ablation with irreversible electroporation: preliminary results in a porcine model. Urology. 2011;77(3):754–60.
24. Wendler JJ, Porsch M, Huhne S, Baumunk D, Buhtz P, Fischbach F, et al. Short- and mid-term effects of irreversible electroporation on normal renal tissue: an animal model. Cardiovasc Intervent Radiol. 2013;36(2):512–20.
25. Cornelis FH, Durak JC, Kimm SY, Wimmer T, coleman JA, Solomon SB, Srimathveeravalli G. A comparative study of ablation boundary sharpness after percutaneous radiofrequency, cryo-, microwave and irreversible electroporation ablation in normal swine liver and kidneys. Cardiovasc Intervent Radiol. 2017;40:1600. https://doi.org/10.1007/s00270-017-1692-3.
26. Morgan MS, Ozayar A, lucas E, Friedlander JI, Shakir NA, Cadeddu JA. Comparative effects of irreversible electroporation, radiofrequency ablation and partial nephrectomy on renal function preservation in a porcine solitary kidney model. Urology. 2016;94:281–7.
27. Sommer CM, Fritz S, Wachter MF, Vollherbst D, Stampfl U, Bellemann N, et al. Irreversible electroporation of the pig kidney with involvement of the renal pelvis: technical aspects, clinical outcome, and three-dimensional CT rendering for assessment of the treatment zone. J Vasc Interv Radiol. 2013;24(12):1888–97.
28. Wagstaff PG, de Bruin DM, van den Bos W, Ingels A, van Gemert MJ, Zondervan PJ, et al. Irreversible electroporation of the porcine kidney: temperature development and distribution. Urol Oncol. 2015;33:168.e1–7.
29. Thomson KR, Cheung W, Ellis SJ, Federman D, Kavnoudias H, Loader-Oliver D, et al. Investigation of the safety of irreversible electroporation in humans. J Vasc Interv Radiol. 2011;22(5):611–21.
30. Trimmer CK, Khosla A, Morgan M, Stephenson SL, Ozayar A, Cadeddu JA. Minimally invasive percutaneous treatment of small renal tumors with irreversible electroporation: a single-center experience. J Vasc Interv Radiol. 2015;26:1465–71.
31. Canvasser NE, Sorokin I, Lay AH, Morgan MSC, Ozayar A, Trimmer C, Cadeddu JA. Irreversible electroporation of small renal masses: suboptimal oncologic efficacy in an early series. World J Urol. 2017;35:1549. https://doi.org/10.1007/s00345-017-2025-5.
32. Diehl SJ, Rathmann N, Kostrzewa M, Ritter M, Smakic A, Schoenberg SO, Kriegmair MC. Irreversible electroporation for surgical renal masses in solitary kidneys: short-term interventional and functional outcomes. J Vasc Interv Radiol. 2016;27:1407–13.
33. Wendler JJ, Porsch M, Nitschke S, Kollermann J, Siedentopf S, Pech M, et al. A prospective Phase 2a pilot study investigating focal percutaneous irreversible electroporation (IRE) ablation by NanoKnife in patients with localised renal cell carcinoma (RCC) with delayed interval tumour resection (IRENE trial). Contemp Clin Trials. 2015;43:10–9.

34. Wendler JJ, Ricke J, Pech M, Fischbach F, Jurgens J, Siedentopf S, Roessner A, Porsch M, Baukumk D, Schostak m KJ, Liehr UB. First delayed resection findings after Irreversible Electroporation (IRE) of human localised renal cell carcinoma (RCC)in the IRENE pilot phase 2a trial. Cardiovasc Intervent Radiol. 2016;39:239–50.
35. Hinshaw JL, Lubner MG, Ziemlewicz TJ, Lee FT, Brace CL. Percutaneous tumor ablation tools: microwave, radiofrequency, or cryoablation- what should you use and why? Radiographics. 2014;34:1344–62.
36. Brace CL. Radiofrequency and microwave ablation of the liver, lung, kidney and bone: what are the differences ? Curr Probl Diagn Radiol. 2009;38:135–43.
37. Andreano A, Cl B. A comparison of direct heating during radiofrequency and microwave ablation in ex vivo liver. Cardiovasc Interv Radiol. 2013;36:505–11.
38. Duffey BG, Anderson JK. Current and future technology for minimally invasive ablation of renal cell carcinoma. Indian J Urol. 2010;26:410–7.
39. Brace CL. Microwave tissue ablation: biophysics, technology and applications. Crit Rev Biomed Eng. 2010;38:65–78.
40. Lubner MG, Brace CL, Hinshaw JL, Lee FT Jr. Microwave tumor ablation: mechanism of action, clinical results and devices. J Vasc Interv Radiol. 2010;21(suppl 8):S192–203.
41. Knavel EM, Hinshaw JL, Lubner MG, et al. High-powered gas-cooled microwave ablations; shaft cooling creates an effective stick function without altering the ablation zone. AJR Am J Roentgenol. 2012;198:W260–5.
42. Li X, Zhang L, Fan W, et al. Comparison of microwave ablation and multipolar radiofrequency ablation, both using a pair of internally cooled interstitial applicators: results in ex vivo porcine livers. Int J Hyperth. 2011;27:240–8.
43. Laeseke PF, Lee FT Jr, Sampson LA, Van der Weide DW, Brace CL. Microwave ablation versus radiofrequency ablation in the kidney: high-power triaxial antennas create larger ablation zones than similarly sized internally cooled electrodes. J Vac Interv Radio. 2009;20: 1224–9.
44. Castle SM, Salas N, Leveillee RJ. Initial experience using microwave ablation therapy for renal tumor treatment: 18-months follow-up. Urology. 2011;77:792–7.
45. Oshima F, YamakadoK NA, Takaki H, Makita M, Takeda K. Simultaneous microwave ablation using multiple antennas in explanted bovine livers: relationship between ablative zone and antenna. Radiat Med. 2008;26:408–14.
46. Durick NA, Laeseke PF, Broderick LS, et al. Microwave ablation with triaxial antennas tuned for lug: results in an in vivo porcine model. Radiology. 2008;247:80–7.
47. Sun Y, Wang Y, Ni X, et al. Comparison of ablation zone between 915- and 2.450-mhz cooled – shaft microwave antenna: results in in vivo porcine livers. AJR Am J Roentgenol. 2009;192:511–4.
48. Stickland AD, Clegg PJ, Cronin NJ, et al. Experimental study of large-volume microwave ablation in the liver. Br J Surg. 2002;89:1003–7.
49. Bertram JM, Yang D, Converse MC, Webster JG, Mahvi DM. A review of coaxial-based interstitial antennas for hepatic microablation. Crit Rev Biomed Eng. 2006;34:187–213.
50. Moore C, Salas N, Zaias J, Shields J, Bird V, Leveillee R. Effects of microwave ablation of the kidney. J Endourol. 2010;24:439–44.
51. Niemeyer DJ, Simo KA, MT MM, et al. Optimal ablation volumes are achieved at submaximal power settings in a 2.45-GHz microwave ablation system. Surg Innov. 2015;22:41–5.
52. He X, McGee S, Coad JE. Investigation of the thermal and tissue injury behaviour in microwave thermal therapy using a porcine kidney model. Int J Hyperth. 2004;20:567–93.
53. Brace CL, Duaz TA, Hinshaw JL, Lee FT Jr. Tissue contraction caused by radiofrequency and microwave ablation: a laboratory study in liver rand lung. J Vasc Interv Radiol. 2010;21: 1280–6.
54. Sommer CM, Sommer SA, Mokry T, et al. Quantification of tissue shrink and dehydration caused by microwave ablation: experimental study in kidneys for the estimation of effective coagulation volume. J Vasc Interv Radiol. 2013;24:1241–8.

55. Sommer CM, Arnegger F, Koch V, et al. Microwave ablation of porcine kidneys in vivo: effect of two different ablation modes ("temperature control" and "power control") on procedural outcome. Cardiovasc Intervent Radiol. 2012;35:653–60.
56. Bartoletti R, Cai T, Tosoratti N, et al. In vivo microwave-induced porcine kidney thermoablation: results and perspectives from a pilot study of a new probe. BJU Int. 2010;106:1817–21.
57. Isfort P, Penzkofer T, Tanaka T, et al. Efficacy on antegrade pyeloperfusion to protect renal pelvis in kidney microwave ablation using and in vivo swine model. Investig Radiol. 2013;48:863–8.
58. Hope WW, Schmelzer TM, Newcomb WL, et al. Guidelines for power and time variables for microwave ablation in an in vivo porcine kidney. J Surg Res. 2009;153:263–7.
59. Clark P, Woodruff R, Zagoria R. Microwave ablation of renal parenchymal tumors before nephrectomy: phase I study. AJR. 2007;188:121–14.
60. Muto G, Castelli E, Migliari R, et al. Laparoscopic microwave ablation and enucleation of small renal masses: preliminary experience. Eur Urol. 2011;60:173–6.
61. Bartoletti R, Meliani E, Simonato A, et al. Microwave induced thermoablation with Amica-probe is a safe and reproducible method to treat solid renal masses: results from a phase I study. Oncol Rep. 2012;28:1243–8.
62. Martin J, Athreya S. Meta-analysis of cryoablation versus microwave ablation for small renal masses: is there a difference in outcome? Diagn Interv Radiol. 2013;19:501–7.
63. Yu J, Liang P, Xu XL, et al. US-guided percutaneous microwave ablation of renal cell carcinoma: intermediate-term results. Radiology. 2012;263:900–8.
64. Guan W, Vai J, Liu J, et al. Microwave ablation versus partial nephrectomy for small renal tumors: intermediate-term results. J Surg Oncol. 2012;106:316–21.
65. Bai J, Hu Z, Guan W, et al. Initial experience with retroperitoneoscopic microwave ablation of clinical T(1a) renal tumors. J Endourol. 2010;24:2017–22.
66. Carafiello G, Mangini M, Fontana F, et al. Single-antenna microwave ablation under contrast-enhanced ultrasound guidance for treatment of small renal cell carcinoma: preliminary experience. Cardiovasc Intervent Radiol. 2009;33:367–74.
67. Moreland AJ, Ziemlewicz TJ, Best SL, et al. High powered microwave ablation of T1a renal cell carcinoma: safety and initial clinical evaluation. J Endourol. 2014;28:1046–52.
68. Horn JC, Patel RS, Kim E, Nowakowski FS, Lookstein RA, Fischman AM. Percutaneous microwave ablation of renal tumors using a gas-cooled 2.4-GHz probe: technique and initial results. J Vasc Interv Radiol. 2014;25:448–53.
69. Carrafiello G, Dionigi G, Ierardi AM, et al. Efficacy , safety and effectiveness of image-guided percutaneous microwave ablation in cystic renal lesions Bosniak III or IV after 24 months follow up. Int J Surg. 2013;11(S1):S30–5.
70. Lin Y, Liang P, Yu XL, et al. Percutaneous microwave ablation of renal cell carcinoma is safe in patients with a solitary kidney. Urology. 2014;83:357–63.
71. Gao Y, Liang P, Yu X, Yu J, Cheng Z, Han Z, Duan S, Huang H. Microwave treatment of renal cell carcinoma adjacent to renal sinus. Eur J Radiol. 2016;85:2083–9.
72. Klapperich ME, Abel EJ, Ziemlewicz TJ, Best S, Lubner MG, Nakada SY, Hinshaw JL, Brace CL, Lee FT, Wells SA. Effect of tumor complexity and technique on efficacy and complications after percutaneous microwave ablation of stage T1a renal cell carcinoma: a single-center, retrospective study. Radiology. 2017;284:272–80.
73. Ierardi AM, Puliti A, Angileri SA, Petrillo M, Duka E, Floridi C, Lecchi M, Carrafiello G. Microwave ablation of malignant renal tumors: intermediate-term results and usefulness of RENAL and mRENAL scores for predicting outcomes and complications. Med Oncol. 2017;34:97.
74. Cranston D. A review of high intensity focused ultrasound in relation to the treatment of renal tumors and other malignancies. Ultrason Sonochem. 2015;27:654–8.
75. ter Haar GR, Clarke RL, Vaughan MG, Hill CR. Trackless surgery using focused ultrasound: technique and case report. Min Invest Ther. 1991;1:13–5.

76. Cranston Hilll CR, ter haar GR. High-intensity ultrasound potential for cancer treatment. Br J Radiol. 1995;68:1296–303.
77. Hynynen K. The threshold for thermally significant cavitation in dog's thigh muscle in vivo. Ultrasound Med Biol. 1991;17:157–69.
78. Klatte T, Marberger M. High-intensity focused ultrasound for the treatment of renal masses: current status and future potential. Curr Opin Urol. 2009;19:188–91.
79. Daum DR, Smith NB, King R, Hynynen K. In vivo demonstration of non-invasive thermal surgery of the liver and kidney using and ultrasonic phased array. Ultrasound Med Biol. 1999;25:1087–98.
80. Sea JC, Bahler CD, Ring JD, Amstutz S, Sanghvi NT, Cheng L, Sundaram CP. Calibration of a novel, laparoscopic, 12-mm, ultrasound, image-guided, high-intensity focused ultrasound probe for ablation of renal neoplasms. Urology. 2015;85:953–8.
81. van Breugel JMM, de Greef M, Wijlemans JW, Schubert G, van den Bosch MAAJ, Moonen CTW, Ries MG. Thermal ablation of a confluent lesion in the porcine kidney with a clinically available MR-HIFU system. Phys Med Biol. 2017;62:5312–26.
82. Illing RO, Kennedy JE, Wu F, et al. The safety and feasibility of extracorporeal high-intensity focused ultrasound (HIFU) for the treatment of liver and kidney tumours in a Western population. Br J Cancer. 2005;93:890–5.
83. Ritchie RW, Leslie TA, Phillips R, et al. Extracorporeal high intensity focused ultrasound for renal tumors: a 3-year follow up. BJUI. 2010;106:1004–9.
84. Ritchie R, Collin R, Coussious JC, Leslie T. Attenuation and de-focusing during high intensity focused ultrasound therapy through perinephric fat. Ultrasound Med Biol. 2013;39:1785–93.
85. Häcker A, Michel MS, Marlinghaus E, et al. Extracorporeally induced ablation of renal tissue by high-intensity focused ultrasound. BJU Int. 2006;97:779–85.
86. Marberger M, Schatzl G, Cranston D, et al. Extracorporeal ablation of renal tumours with high-intensity focused ultrasound. BJU Int. 2005;95(Suppl 2):52–5.
87. Ritchie RW, Leslie T, Phillips R, et al. Extracorporeal high intensity focused ultrasound for renal tumours: a 3-year follow-up. BJU Int. 2010;106:1004–9.
88. Klingler HC, Susani M, Seip R, et al. A novel approach to energy ablative therapy of small renal tumours: laparoscopic high-intensity focused ultrasound. Eur Urol. 2008;53:810–8.
89. Ritchie RW, Leslie TA, Turner GD, et al. Laparoscopic high-intensity focused ultrasound for renal tumours: a proof of concept study. BJU Int. 2011;107:1290–6.
90. De Meerler G, Khoo V, Escudier B, et al. Radiotherapy for renal cell carcinoma. Lancet. 2014;15:e170–7.
91. Ponsky L, Lo SS, Zhang Y, et al. Phase I dose-escalation study of stereotactic body radiotherapy (SBRT) for poor surgical candidates with localized renal cell carcinoma. Radiother Oncol. 2015;117:183–7.
92. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? Int J Radiat Oncol Biol Phys. 2014;88:254–62.
93. Siva S, Pham D, Gill S, et al. A systematic review of stereotactic radiotherapy ablation for primary renal cell carcinoma. BJU Int. 2012;110:E737–43.
94. Ponsky LE, Crownover RL, Rosen MJ, et al. Initial evaluation of Cyberknife technology for extracorporeal renal tissue ablation. Urology. 2003;61:498–501.
95. Nair VJ, Szanto J, Vandervoort E, et al. CyberKnife for inoperable renal tumors: Canadian pioneering experience. Can J Urol. 2013;20:6944–9.
96. Lo CH, Huang WY, Chao HL, et al. Novel application of stereotactic ablative radiotherapy using CyberKnife for early-stage renal cell carcinoma in patients with pre-existing chronic kidney disease: initial clinical experiences. Oncol Lett. 2014;8:355–60.
97. Staehler M, Bader M, Schlenker B, et al. Single fraction radiosurgery for the treatment of renal tumors. J Urol. 2015;193:771–5.

98. Kroeze SG, Grimbergen MC, Rehmann H, et al. Photodynamic therapy as novel nephron sparing treatment option for small renal masses. J Urol. 2012;187:289–95.
99. Kimm SY, Tarin TV, Monette S, Srimathveeravalli G, Gerber D, Durack JC, Solomon SB, Scardino PT, Scherz A, Coleman J. Nonthermal ablation by using intravascular oxygen radical generation with WST11: dynamic tissue effects and implications for focal therapy. Radiology. 2016;281:109–18.

Chapter 13
The Impact of Renal Tumor Surgery on Kidney Function

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Introduction

The American Cancer Society estimated that more than 63,000 new cases of kidney cancer would be diagnosed in the United States in 2017, representing the ninth most common malignancy [1]. Surgical excision is the most frequently used treatment for

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localized disease [2–4]. Historically, radical nephrectomy (RN) was the treatment of choice in such patients, and partial nephrectomy (PN) was reserved for imperative indications such as solitary kidney or bilateral renal tumors. Once the potential association of chronic kidney disease (CKD) with increased cardiovascular events and reduced survival was understood [5], the role of PN was expanded for small renal masses even in patients with bilateral kidneys to preserve maximum renal function [4].

In addition to oncologic outcomes, renal function preservation has become an important objective in renal cancer survivors [6–9]. Accordingly, most treatment guidelines recommend PN as the standard of care for small renal masses, while RN is favored for large or anatomically complex masses not amenable to PN [3, 4]. However, these advances in the field of renal surgery have been controversial. The validity of the hypothesis that improved functional outcomes after PN translates into better survival has been questioned [10, 11]. Additionally, the notion that CKD primarily due to surgery has similar implications as CKD due to medical comorbidities has been challenged [12–14]. Moreover, there is ongoing debate about the important predictors of functional outcomes after PN [6, 7]. These issues are of great importance as they can affect surgical approach and intraoperative management and can have important implications for cancer survivorship. In this chapter, we review the evidence that addresses these issues and provide an update on recent advances in the field.

Chronic Kidney Disease

The Kidney Disease: Improving Global Outcomes (KDIGO) foundation defines CKD as glomerular filtration rate (GFR) <60 ml/min/1.73 m^2 or presence of markers of kidney damage, such as proteinuria, for greater than 3 months [15]. The overall prevalence of CKD in the general population in the United States is approximately 14% [16]. Although the association of end stage renal disease with higher mortality rates has long been appreciated, the importance of even mild to moderate CKD was not well understood until the landmark study published in 2006 by Go and colleagues [5]. In a large population-based study including more than a million subjects, Go reported that increasing degrees of CKD were associated with increased cardiovascular events, hospitalization, and mortality, even after adjusting for medical comorbidities. The hazard ratio (HR) of mortality increased in a dose-dependent fashion from 1.2 in subjects with GFR 45–59 ml/min/1.73 m^2 to 5.9 in subjects with GFR <15 ml/min/1.73 m^2.

After the significance of CKD was highlighted in terms of increased all-cause mortality, Huang and colleagues studied the prevalence of CKD in patients with renal masses presenting for surgical resection and the impact of surgical removal of nephrons on the development or progression of CKD [17, 18]. In their cohort, 25–30% of patients with a localized renal mass had CKD, and after surgery the 3-year probability of freedom from new-onset CKD (GFR < 60 ml/min/1.73 m^2)

was 80% after PN but only 35% after RN. Studies from other centers have confirmed these findings with similar prevalence of CKD noted in patients undergoing surgery for renal tumors (Reviewed in [9]).

With increased recognition of CKD prevalence and its potential long-term deleterious effects, renal function preservation has become an important objective in the management of patients with kidney cancer. For patients with small renal masses, RN represents gross overtreatment, and the trend has shifted toward nephron-sparing approaches. Recognizing that there are many ongoing controversies in this field, the American Urologic Association (AUA) recently updated their evidence-based guidelines for the management of patients with localized kidney cancer, with particular focus on the roles of PN and RN and functional preservation related to renal surgery [4].

PN Versus RN

Historically, nephron-sparing surgery using PN was reserved for imperative indications such as a renal tumor in a solitary kidney or bilateral renal tumors. Long-term studies from Cleveland Clinic and Memorial Sloan Kettering confirmed overall survival of greater than 90% after PN for early-stage kidney cancer [19, 20]. However, adoption of PN was slow in the urologic community due to higher risk of bleeding and urinary fistula formation and uncertainty about the management of such complications [8].

PN gained greater acceptance after several studies demonstrated strong local control and metastasis-free survival in appropriately selected patients with localized kidney cancer [9, 21, 22]. With further understanding of association of CKD with future cardiovascular events and increased mortality in the general population, application of PN beyond the conventional indications was explored. Eventually, it was recognized that RN represents therapeutic overkill for many patients with localized kidney cancer, particularly those with small renal masses [9]. Based on developments in the field as of 2009, the AUA guidelines recommended PN as the standard of care for the clinical T1a renal tumor [3]. Upon further understanding of the functional advantages of PN and increased comfort level with the surgical techniques and management of complications, PN has been widely adopted in academic centers and to some degree in community settings as well. Various groups have expanded the role of PN to larger renal masses and tumors with increased complexity [23, 24]. However, a fundamental question persists, particularly when a normal contralateral kidney is present, does PN provide a survival advantage over RN?

Data from several observational studies confirm a functional advantage for PN even in the most challenging of circumstances and many also suggest an overall survival advantage (Table 13.1a) [25–27]. However, these studies are potentially contaminated by both measured and unmeasured biases. A large meta-analysis by Kim and colleagues of 36 retrospective studies comprising more than 40,000

patients showed a 61% risk reduction in the development of CKD ($p < 0.001$) and a 19% risk reduction in all-cause mortality ($p < 0.001$) for PN when compared to RN [25]. However, a 29% risk reduction for cancer-specific mortality in favor of PN was also reported ($p = 0.002$). This finding can only be explained by the selection biases that may reside within the included studies – it is difficult to understand how PN can provide an oncologic advantage over RN based on the basic tenets of surgical oncology.

Subsequent studies have used advanced statistical methods such as propensity scores and instrumental variables to control for the selection bias in these studies and to facilitate a more sophisticated comparison of the PN and RN cohorts (Table 13.1a) [26, 27]. Using a propensity score-based model, Weight et al. reported that patients undergoing RN for T1b renal tumors with a normal contralateral kidney were at higher risk of postoperative CKD and reduced survival [27]. Similarly, Tan et al., studying a cohort of Medicare beneficiaries with early-stage kidney cancer with an instrumental variable approach, reported increased survival with PN when compared with RN [26]. However, propensity score methods only account for measured biases and imbalance from unrecognized confounders may still persist.

Table 13.1 Selective studies comparing the outcomes of partial and radical nephrectomy

Study	Design	Main outcomes	Findings	Limitations/perspective
(a) Retrospective studies comparing PN vs. RN outcomes				
Kim SP, et al., 2012 [25]	Meta-analysis: 36 studies	ACM CSM CKD	PN correlated with 19% risk reduction for ACM, 29% risk reduction in CSM, and 61% risk reduction for CKD	Potential selection and publication biases *Perspective*: Lower CSM in PN cohort likely due to selection bias, as PN is not a stronger oncologic intervention
Tan HJ, et al., 2012 [26]	Study of Medicare beneficiaries with cT1a renal tumors, instrumental variable approach	OS CSS	Improved OS with PN No significant difference in CSS between PN and RN	Only cT1a included, instrument variable assumptions cannot be verified, and cannot control for unrecognized confounders *Perspective*: Selection bias remains a concern
Weight CJ, et al., 2010 [27]	Retrospective series using propensity score method for cT1b renal masses	OS,CSS, and cardiac-specific survival	PN associated with increased 5-year OS (85% vs. 78%, $p = 0.01$) and equivalent CSS (94% vs. 89%). Postoperative renal insufficiency independent predictor of OS and cardiac-specific survival	Single center, retrospective with concern about potential selection bias, hidden bias not tested, and cannot control for unrecognized confounders *Perspective*: Selection bias remains a concern

Table 13.1 (continued)

Study	Design	Main outcomes	Findings	Limitations/perspective
Shuch B, et al., 2013 [28]	Matched cohort study using SEER Medicare dataset	OS	OS was similar between RN and controls (low-grade bladder cancer and noncancer controls) However, PN had improved survival compared to controls (HR; 1.25, $p < 0.001$)	Retrospective design, dataset has limitations *Perspective*: RN had similar survival to age and comorbidity matched controls with no cancer or nonlife-threatening cancer suggesting that reduced renal function did not impact survival. PN patients fared better suggesting selection bias
(b) Randomized trial comparing PN vs. RN				
Poppel HV, et al., 2011, Scosyrev E, et al., 2013 (EORTC 30904) [11, 29]	Randomized trial of PN vs. RN for renal mass < 5 cm and normal contralateral kidney	OS Incidence CKD	10-year OS for RN vs. PN (81% vs. 75%, HR 1.5, $p = 0.03$) At median follow-up of 6.7 years RN vs. PN, eGFR<60: 86% vs. 64% RN vs. PN, eGFR <30: 10% vs. 6.3% RN vs. PN, eGFR <15: 1.5% vs.1.6%	Suboptimal accrual, underpowered, crossover between treatment arms, normal function defined by serum creatinine level, not GFR *Perspective*: Despite flaws, results are provocative, suggesting that survival advantage related to PN may not be as large as previously thought
(c) Impact of CKD primarily due to surgical nephron loss (CKD-S)				
Lane BR, et al., 2013 [12]	Large cohort study of patients undergoing RCS	Progression of renal function decline	Annual renal function decline was 4.7% for CKD-M and 0.7% for CKD-S Annual renal function decline >4% associated with 43% increase in mortality ($p < 0.0001$).	Single tertiary center retrospective study *Perspective*: CKD-M had decreased survival and less stable renal function. Decline of function for CKD-S approximates normal aging process
Zabell J, et al., 2017 [30]	Analysis of >4000 patients undergoing RCS	Predictors of 5-year CKD and 10-year nonrenal cancer mortality	Preoperative GFR and GFR loss related to surgery correlate with 5-year risk of CKD. Preoperative GFR, new baseline GFR, and age correlated with 10-year nonrenal cancer mortality GFR loss with typical PN vs. RN only changed absolute mortality risk by 1–3%	Validation of the predictors needed *Perspective*: Age and preoperative GFR strongly associated with nonrenal cancer mortality. Although choice of PN versus RN influences risk of developing CKD, it has less impact on survival

(continued)

Table 13.1 (continued)

Study	Design	Main outcomes	Findings	Limitations/perspective
Gor R, et al., 2015 [14]	Analysis of >1400 patients from renal tumor registry to study impact of CKD subtypes	Impact of CKD-M and CKD-S on risk of mortality	CKD-M associated with higher risk of mortality compared to CKD-S. CKD-S had similar mortality as no CKD cohort	Tertiary center retrospective study *Perspective*: Validated the findings that CKD-S has mortality risk similar to no CKD patients
Capitanio U, et al., 2015 [31]	Multicenter analysis of 1189 patients: RN or PN for ≤cT1b renal mass and preoperative GFR≥60	CKD and other-cause mortality	On multivariable analysis, PN associated with lower risk of CKD, but there was no significant difference in other-cause mortality (HR 0.8, CI 0.67–1.40)	Retrospective study *Perspective*: PN associated with better preservation of renal function compared to RN, but this did not translate into a survival benefit
Lane BR; et al., 2015 [13]	Large cohort study of patients undergoing RCS with long follow-up	Impact of new baseline eGFR	CKD-M/S had higher rates of GFR decline, all-cause mortality, and nonrenal cancer mortality CKD-S survival and stability of renal function approximated the no CKD cohort	Tertiary center retrospective study *Perspective*: CKD-S has good prognosis as long as new baseline GFR is >45 ml/min/1.73 m^2
(d) Collaborative review of literature comparing PN and RN				
Kim SP, et al., 2016 [9]	Critical review of available literature comparing outcomes of PN and RN for anatomically complex tumors	Risks and benefits of PN over RN	For anatomically complex tumors, PN preserves renal parenchyma, although PN has increased perioperative risk Prospective randomized trial is needed to provide better data about the merits of PN versus RN	Comparison of retrospective studies with selection bias and one imperfect randomized clinical trial *Perspective*: Available literature unable to establish the superiority of PN over RN in complex renal tumors and a randomized trial is needed

ACM all-cause mortality, *CKD* chronic kidney disease, *CKD-M* chronic kidney disease due to medical diseases, *CKD-S* chronic kidney disease primarily due to surgical removal of nephrons, *CSM* cancer-specific mortality, *CSS* cancer-specific survival, *eGFR* estimated glomerular filtration rate, *GFR* glomerular filtration rate, *HR* hazard ratio, *OS* overall survival, *PN* partial nephrectomy, *RN* radical nephrectomy, *RCS* renal cancer surgery, *SEER* surveillance, epidemiology, and end results

Furthermore, Shuch et al. demonstrated potential selection bias in this literature using the Surveillance, Epidemiology, and End Results Medicare dataset [28]. In their matched cohort study, subjects with PN had better overall survival even when compared to noncancer controls, suggesting that the PN population had advantages with respect to unrecognized confounders. Patients selected for PN may just be

healthier on average than patients in other cohorts and manipulation of the identified covariates may not be able to control for this reality. Conclusions drawn from these retrospective studies showing an overall survival advantage associated with PN may therefore be unreliable [10, 28].

The best study design to avoid selection bias and thus allow for more reliable conclusions is, of course, a randomized controlled trial. There is, however, only one such trial in this domain, namely, EORTC 30904 (Table 13.1b) [11, 29]. Patients with a single, clinically localized tumor up to 5 cm with a normal contralateral kidney were randomized to either PN ($n = 268$) or RN ($n = 273$). As expected PN provided better functional outcomes, while surgical morbidity was less with RN. Surprisingly, PN was not associated with better overall survival. At a median follow-up of 9.3 years, the intention to treat analysis showed 10-year overall survival of 81% for RN compared to 76% for PN ($p = 0.03$). A follow-up analysis of functional outcomes confirmed the advantage of PN over RN in terms of preservation of renal function; however, this did not translate into a survival advantage in subjects with a normal contralateral kidney [29].

EORTC 30904 thus raised the possibility that CKD due to surgical loss of nephrons (CKD-S) may not have same adverse implications as CKD due to medical diseases (CKD-M). Lane and colleagues explored this hypothesis in over 4000 patients managed with PN or RN [12]. Their population included over 1000 patients with preexisting CKD-M who required surgery for a renal mass (thus designated CKD-M/S) compared to a similar number of patients with CKD primarily due to surgical removal of nephrons (CKD-S). The control group comprised almost 2000 patients with no CKD even after renal surgery. The prevalence of CKD-M/S and CKD-S in this series were 28% and 22% of all patients, respectively (Table 13.1c, Fig. 13.1). Several important observations were gleaned from this study. First, GFR decline per year was substantially increased in the CKD-M/S cohort compared to CKD-S (4.7% vs. 0.7%, $p < 0.05$). Furthermore, an annual decline of renal function of >4% was associated with a substantial increase (43%) in mortality ($p < 0.0001$). In a follow-up study, patients with CKD-M/S had the highest rate of GFR decline, nonrenal cancer-related mortality, and all-cause mortality on multivariable analysis [13]. In contrast, the CKD-S cohort had GFR stability and nonrenal cancer mortality rates that were similar to the no CKD group. Gor et al. validated these findings, reporting that CKD-S has similar mortality rates as patients with no CKD even after surgery for a renal mass [14]. Thus etiology of CKD appears to play an important role in the outcomes of patients undergoing surgery. Patients with CKD due to medical etiology by definition have comorbidities that are impactful, and most, such as diabetes, are longstanding. Thus their renal function will typically continue to decline and eventually this leads to increased mortality rates. Patients with CKD primarily due to surgical removal of nephrons typically do not require further surgery, and their renal function can thus stabilize, leaving them in a better position for long-term survival.

Although PN is associated with better preservation of renal function compared to RN, this functional advantage may not always translate into a substantial survival benefit, at least for patients with a normal contralateral kidney. This hypothesis was recently explored by developing predictive models from our population of

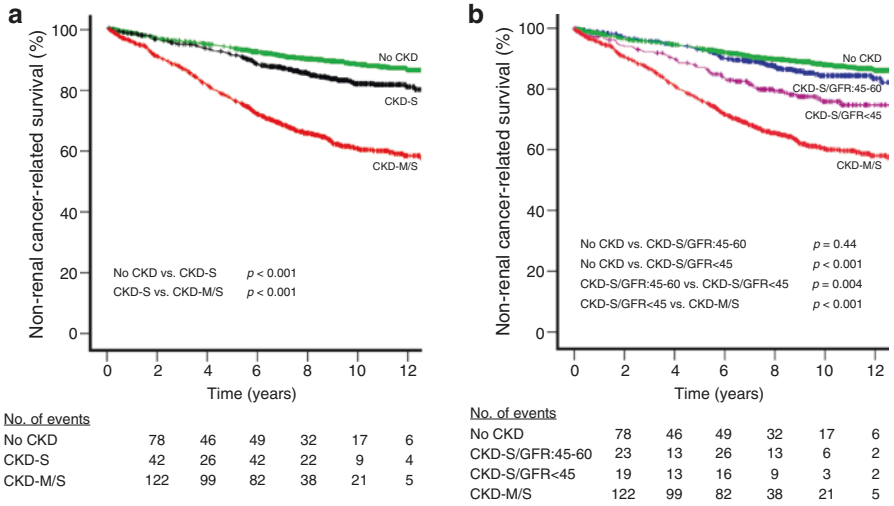

Fig. 13.1 Nonrenal cancer-related survival stratified by etiology of chronic kidney disease (CKD) in patients requiring renal cancer surgery. **a**) Patients with preexisting CKD due to medical comorbidities who then required surgery (CKD-M/S, $n = 1113$) experienced significantly reduced survival when compared to patients with CKD primarily due to surgical removal of nephrons (CKD-S, $n = 931$). Patients with CKD-S by definition only developed GFR < 60 ml/min/1.73 m^2 after surgical intervention. The survival of patients with CKD-S approximates that of patients with no CKD even after surgery ($n = 2202$). **b**) Patients with CKD-S are heterogenous to some degree as those with new baseline GFR < 45 ml/min/1.73m^2 have reduced survival when compared to those with new baseline GFR > 45 ml/min/1.73 m^2. (From Wu et al. [32], Fig. 1, with permission oF John Wiley and Sons)

over 4000 patients who underwent surgical removal of a renal tumor with almost 10 years of median follow-up [30]. In these models, age, demographic factors, and important comorbidities were incorporated, in addition to relevant functional parameters, including preoperative GFR, GFR loss with surgery, and new baseline GFR. However, PN versus RN status was not utilized, because it carries too much potential bias related to selection processes, and there is often substantial overlap in the amount of function lost with these procedures. More specifically, challenging PNs can occasionally lead to considerable loss of GFR, while some RN for poorly functioning kidneys can be associated with minimal loss of function. Predictive algorithms were then developed for 5-year incidence of CKD or 10-year nonrenal cancer-related survival. As expected, the models confirm that a surgical intervention associated with about 10% loss of global function (as seen with a prototypical PN) correlated with substantially lower incidence of CKD when compared to an intervention associated with about 40% loss of global renal function (i.e., prototypical RN). However, the predictive models suggest that absolute differences in 10-year survival for these two interventions should be relatively small, in the range of 1–3%. For instance, for a 54-year-old with a preoperative GFR of 80 ml/min/1.73 m^2, 10-year survival was predicted to be 90% if prototypical PN was performed (loss of 10% of global function) versus 88% if a prototypical RN

was performed. In contrast, age and preoperative GFR were much stronger predictors of 10-year survival in this patient population. Preoperative GFR is a strong indicator of health status, as it reflects important comorbidities and their physiologic impact. This study suggests that interventions that on average save 90% versus 60% of the global renal function (i.e., PN versus RN) may not impact survival in a substantially divergent manner, at least in patients with relatively good preoperative renal function.

Similarly, Capitanio et al. in a large multicenter analysis of patients without preexisting CKD noted that even though PN is associated with lower risk of developing CKD (HR = 0.65, 95% CI 0.47–0.92), there was no significant difference in other-cause mortality on multivariable analysis (HR 0.8, 95% CI 0.67–1.40) during extended follow-up of 10–15 years [31]. These findings raise the possibility that optimal preservation of GFR may not be critically important in all patients. Stated another way, the more robust survival advantages of PN may be primarily limited to patients with preexisting CKD.

It is important to emphasize that while most patients with CKD-S have a good prognosis, there may be heterogeneity in this patient population that could affect management decisions. In particular, a recent study suggests that CKD-S patients with new baseline GFR < 45 ml/min/1.73 m^2 have significantly worse survival compared to those with GFR of 45–60 ml/min/1.73 m^2 [32]. In addition, survival of the latter group appeared to be very similar to patients who did not have CKD even after surgery. This suggests that if renal mass surgery is going to lead to new-onset CKD, it is best to avoid dropping the GFR below this critical threshold, and PN should thus be considered in some such patients.

In summary, the decision to perform PN versus RN in patients with a normal contralateral kidney remains complex and challenging [8]. A functional advantage for PN is clear and not subject to debate. However, the evidence suggesting a potential survival benefit of PN over RN in this setting is primarily driven by retrospective studies plagued with inherent selection biases. The single prospective randomized trial in this space failed to confirm a survival benefit of elective PN over RN [33]. A recent collaborative review of PN versus RN demonstrated increased perioperative morbidity and better renal function with PN, but a survival advantage again proved elusive when strict principles were applied, at least in the elective setting (Table 13.1d) [9].

Recent AUA guidelines address this issue in detail, recognizing ongoing overutilization of RN in the community setting and substantial controversies regarding the issue of PN versus RN [4]. The guidelines recommend consideration for RN whenever increased oncologic potential is suggested by increased tumor size, high tumor grade or unfavorable histology (if renal mass biopsy has been performed), or infiltrative or locally invasive appearance on imaging. Beyond this, the guidelines suggest that RN is then *preferred* if the following three criteria are *all* also satisfied: (1) high tumor complexity, such that PN would be challenging even in experienced hands, (2) there is no preexisting CKD or proteinuria, and (3) presence of a normal contralateral kidney that is likely to provide GFR > 45 ml/min/1.73 m^2 after intervention. If these specific criteria are *not* met,

then PN should be considered if feasible [4]. It is hoped that these guidelines will prove useful for the practicing urologist and will stimulate further research in this field.

Determinants of Functional Recovery After PN

In addition to the choice of PN versus RN, there are several factors that may affect the recovery of renal function after surgery for a renal tumor (Fig. 13.2). Preoperative factors are often related to patient or tumor characteristics and are usually non-modifiable. As already discussed, PN is preferred in imperative indications such as patients with preexisting CKD or a solitary kidney, and in these settings optimal functional recovery is of paramount importance. However, recovery of function after PN can be variable, and much work has been done to understand the determinants of functional recovery after this procedure. In this section we will focus on the roles of parenchymal mass preservation and ischemia type and duration as well as recent advances in this field.

Due to the highly vascular nature of the kidney, PN has traditionally required clamping of the renal vasculature to prevent blood loss and maintain a clear field of visualization during tumor resection. Several investigators have considered the potential impact that renal ischemia may have on the recovery of renal function, both short and long-term. Ischemia may impact the recovery process through

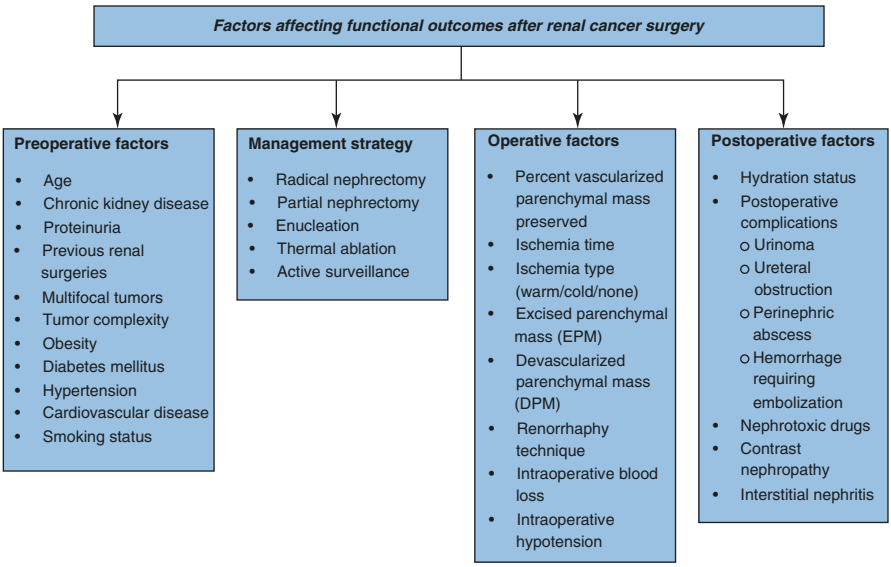

Fig. 13.2 Factors affecting functional outcomes after renal cancer surgery

several hypothesized mechanisms such as ischemia-reperfusion injury, constriction of renal arterioles, and renal tubular injury [6–8].

Cold Ischemia vs. Warm Ischemia

Hypothermia, typically through the use of ice slush, decreases cellular metabolism and has been proven to have a strongly protective effect with respect to ischemic renal injury. Previous experience with renal transplantation established that most kidneys recovery strongly and durably even after several hours of ischemia as long as hypothermia is utilized [6]. Hypothermia has traditionally been used for most cases of open PN and is now also being applied for minimally invasive cases at many centers. In a cohort of 662 patients, Yossepowitch and colleagues evaluated the impact of cold ischemia time on the percent change in GFR after surgery [34]. Longer duration of hypothermia was associated with increased risk of acute kidney injury (AKI) in the early postoperative period; however it was not a significant predictor of functional outcomes 1 year after surgery. Zhang and colleagues evaluated the impact of hypothermia in a more refined manner, including normalizing for parenchymal mass loss [35]. In a series of 277 PNs, a median recovery of 99% was noted when cold ischemia was used, suggesting that most nephrons make a complete recovery from the ischemic insult. Several other studies have confirmed these findings [6–8]. The general consensus is that the duration of hypothermia can be extended out 1–2 h if necessary, although in the short-term postoperative care can be complicated by AKI, as discussed below [6, 8].

Recovery from warm ischemia, while somewhat more variable, also appears to be relatively strong as long as prolonged durations of ischemia are avoided. In the series by Zhang [35], median functional recovery to level predicted by nephron mass loss was 91% for cases managed with warm ischemia, although limited durations of ischemia (<25–30 min) predominated in this series. Recovery from extended durations of warm ischemia has not been well studied and the threshold at which irreversible ischemic injury begins to occur remains controversial [6–8].

Impact of Parenchymal Mass Preservation and Ischemia Duration

One important early study in this domain evaluated a retrospective cohort of 362 patients undergoing PN in a solitary kidney with warm ischemia and reported that longer ischemia duration is associated with increased risk of AKI, need for dialysis, and new-onset CKD (Table 13.2a) [36]. Every minute increase in ischemia duration was associated with a 5% increased risk of AKI and a 6% increased risk of new-onset CKD. These findings popularized the concept that “every minute counts when

Table 13.2 Selective studies on determinants of renal function after partial nephrectomy

Study	Design	Main outcomes	Findings	Limitations/ perspective
(a) Studies without consideration of parenchymal mass preserved				
Yossepowitch O, et al., 2006 [34]	Retrospective review of patients undergoing PN with solitary kidney (n = 70) or bilateral functioning kidneys (n = 592)	Percentage change of GFR related to surgery	Longer hypothermia time associated with poor GFR recovery in early postoperative period but was not a significant predictor 1 year after PN	Parenchymal mass preserved not considered in multivariable analysis *Perspective*: Ischemia can lead to AKI, but ischemia duration did not impact ultimate GFR recovery in setting of hypothermia
Thompson RH, et al., 2010 [36]	Retrospective review of patients with solitary kidney (n = 362) undergoing PN with warm ischemia	ARF, acute-onset GFR <15, or new-onset GFR <30	Risk of new-onset CKD increased 6% with each minute of WIT, and risk of AKI increased 5% with each minute. Hence, "every minute counts"	Parenchymal mass preserved not incorporated into the analysis. *Perspective*: Findings about WIT potentially misleading because primary confounder (nephron mass loss) not incorporated
(b) Studies with subjective estimation of parenchymal mass preserved				
Lane BR, et al., 2011 [37]	Multicenter comparative study of PN in solitary kidney (n = 660) with warm or cold ischemia	AKI CKD	Preoperative GFR (quality) and % parenchyma preserved (quantity) associated with functional outcomes. Ischemia time did not correlate	Retrospective studies with subjective estimation of parenchymal mass preserved *Perspective*: Quantity and quality of parenchyma preserved are strong predictors of the functional outcomes after PN. Suggests that most nephrons recover from ischemia as long as hypothermia or limited warm is applied
Thompson RH, et al., 2012 [38]	Retrospective: solitary kidney (n = 362) undergoing PN with WIT. Repeat analysis: now incorporating subjective estimate of "quantity" factor	CKD	Percentage nephron mass preserved and preoperative GFR significantly associated with new-onset stage IV CKD. WIT lost statistical significance unless >25 min	

Table 13.2 (continued)

Study	Design	Main outcomes	Findings	Limitations/ perspective
(c) Studies with direct measurement of parenchymal mass preserved				
Song C, et al., 2011 [39]	Prospective:116 patients with 2 kidneys undergoing PN Ipsilateral renal function determined by DTPA scan	Determine course and factors affecting ipsilateral GFR recovery	Preoperative GFR, parenchymal mass loss, and collecting system repair associated with functional outcomes	Retrospective studies limited to only patients with data available for detailed functional analysis *Perspective*: Preoperative renal function (quality) and percent parenchyma preserved (quantity) are the primary predictors of ultimate renal function. Recovery from cold ischemia is very reliable and remains near complete even with prolonged cold ischemia. Recovery from warm ischemia is also relatively strong even out to 35 min (>90% when normalized by nephron mass preserved). The impact of more prolonged warm ischemia is not well studied
Mir C, et al., 2014 [40]	155 patients undergoing PN Renal volume determination by CT scan, MAG3 scan to estimated ipsilateral function	Recovery from ischemia: percent function saved/percent parenchyma saved	Parenchymal mass preserved is key factor for functional recovery. Recovery from ischemia most reliable with hypothermia	
Ginzburg S, et al., 2015 [42]	179 patients with bilateral kidneys underwent PN. CT estimated parenchymal volume preservation	Percent GFR preserved after surgery	Preoperative GFR and parenchymal mass preserved associated with functional outcomes 6 months after surgery	
Zhang Z., et al., 2016 [35]	Bilateral (194) and solitary (83) kidneys. Renal mass determination by CT, MAG3 for split renal function	Evaluate impact of type and duration of ischemia on functional recovery after PN	Recovery from hypothermia is near complete and remains strong (>96%) with prolonged hypothermia. Recovery from warm ischemia is also relatively strong to 35 min (>90%)	

(continued)

Table 13.2 (continued)

Study	Design	Main outcomes	Findings	Limitations/ perspective
(d) Studies with limited or zero ischemia during PN				
Thompson RH, et al., 2010 [44]	Retrospective: solitary kidneys having PN with no ischemia or warm ischemia	New-onset stage IV CKD	Warm ischemia associated with significantly increased risk of developing stage IV CKD	Potential selection bias, parenchymal mass preservation not taken into account *Perspective*: Reduced ischemia associated with better functional outcomes. However, minimal or zero ischemia cases may have been easier and thus associated with less parenchymal mass loss
Smith GL, et al., 2011 [45]	Single-center retrospective study comparing renal vascular clamping group with non-clamped group	Percent change in GFR at 1 year Complication rates	Non-clamped group had lower decrease in eGFR compared to vascular clamping group but had higher transfusion rates	
Desai MM, et al., 2014 [46]	Retrospective comparison (n = 121) of superselective PN versus main artery clamping	Perioperative complications Percent decrease in GFR	Superselective clamping had less decrease in percent GFR after PN and similar parenchymal volume preservation but had longer operative time and more need for transfusion	Potential selection bias, measurement of function early in the postoperative period when new baseline GFR not well defined *Perspective*: zero ischemia PN can be associated with higher blood loss although generally appears to be feasible. Current data suggests that zero ischemia PN may not provide significantly improved functional outcomes compared to clamped PN
Satkunasivam R, et al., 2015 [47]	Comparison of superselective clamping to non-clamped PN	Percent reduction in GFR and new-onset CKD stage >3 at 1 month	Percent GFR reduction was similar, however, new-onset CKD stage >3 occurred less frequently in non-clamped group	

Table 13.2 (continued)

Study	Design	Main outcomes	Findings	Limitations/ perspective
(e) Study evaluating histology and markers of renal tubular damage during renal ischemia				
Parekh D, et al., 2013 [48]	Prospective evaluation: renal histology and biomarkers before/during/ after renal ischemia. Included cases with prolonged ischemia	Renal histological changes, AKI biomarkers, and functional changes	Histologic changes less severe than animal models of renal ischemia Functional changes did not correlate with ischemia duration. Biomarkers did not suggest substantial ischemic damage	Biomarkers chosen may not have been optimal for this purpose. The implications of acute structural findings are not clear *Perspective*: Extended warm ischemia may not be as deleterious as previously thought although further studies are needed
(f) Review articles about factors associated with decline in renal function after PN				
Mir MC, et al., 2015 [6]	Review of evidence from 71 studies evaluating renal function after PN	Factors associated with loss of renal function after PN	Renal function decline after PN averages about 20% in the operated kidney. Preservation of nephron mass appears to be the main factor affecting functional recovery	Evidence synthesized primarily from retrospective studies *Perspective*: Amount of parenchymal mass preserved is primary determinant of renal function recovery after PN
Volpe A, et al., 2015 [7]	Collaborative review of 91 studies about the impact of renal ischemia on functional recovery after PN	Impact of renal ischemia on functional recovery after PN	Functional recovery after PN strongly correlates with nephron mass preserved. WIT is modifiable. Prolonged WIT can lead to reduced functional recovery	Available data suggest a potential benefit of keeping WIT<25 min, although the level of evidence to support this threshold is limited. Cold ischemia safely facilitates longer durations of ischemia

AKI acute kidney injury, *ARF* acute renal failure, *CKD* chronic kidney disease, *CT* computed tomography, *DPM* devascularized parenchymal mass, *DTPA* diethylenetriaminepentacetate, *EPM* excised parenchymal mass, *GFR* glomerular filtration rate, *MAG3* mercaptoacetyltriglycine, *PN* partial nephrectomy, *WIT* warm ischemia time

the renal hilum is clamped." However, this study did not incorporate the amount of parenchymal mass preserved into the analyses, thus potentially compromising the conclusions that could be drawn from this data.

Subsequently, in a nonrandomized comparative study, Lane and colleagues evaluated 660 PN performed in solitary kidneys where cold ischemia and warm ischemia were used in 300 and 360 cases, respectively [37]. At 3 months after PN, no significant difference in percent GFR decline was noted between the groups despite longer

ischemia times in the cold ischemia cohort. On initial multivariable analysis, preoperative GFR, increasing age, larger tumor size, and longer ischemia time were all significantly associated with functional recovery. However, when subjectively estimated amount of parenchyma preserved was incorporated into the analysis, it proved to be a very strong predictor of functional outcomes, and ischemia duration lost statistical significance. In the final analysis, only preoperative GFR (i.e., quality) and amount of parenchymal mass preserved (i.e., quantity) were significantly associated with the ultimate functional recovery after PN (Table 13.2b). This prompted a repeat analysis of the previous study of 362 solitary kidneys managed exclusively with warm ischemia, which suggested that "every minute counts" [38]. With updated analysis, percent of nephron mass preserved and preoperative GFR were significantly associated with functional outcomes, while ischemia duration proved to be insignificant, unless it was extended beyond 25 min [38]. In the process, nephron mass preservation was identified as the strongest predictor of functional outcomes after PN.

The findings of the above mentioned studies were further augmented with more accurate and direct estimation of parenchymal mass preserved using imaging studies (Table 13.2c) [35, 39–42]. In these studies the amount of vascularized parenchyma within the operated kidney was estimated from preoperative and postoperative CT scans using software or free-hand scripting with summation, and the percent of parenchyma preserved by the procedure was thus directly measured. Functional correlates were also obtained based on preoperative and postoperative serum creatinine-based estimates of global GFR complimented by split renal function from nuclear renal scans, when necessary [40]. As summarized in Table 13.2c, all such studies confirm a strong relationship between parenchymal mass saved and function saved in the operated kidney, confirming the primary importance of nephron mass preservation. Furthermore, these studies also support the importance of preoperative GFR for functional outcomes, because it defines the ceiling for recovery.

A more refined analysis of functional recovery after PN was recently reported by Dong and colleagues in a robust cohort of 401 patients, all of whom had detailed analysis of parenchymal mass and function saved specifically in the kidney exposed to ischemia [43]. Consistent with previous studies, function saved correlated strongly with parenchymal mass preservation. On multivariable analysis, ischemia type (warm) and duration both correlated significantly with functional recovery after controlling for nephron mass loss, while in many previous studies ischemia characteristics had not correlated in this manner. This study included substantially more patients with warm ischemia, and also more with prolonged duration of ischemia (>25–35 min), and thus facilitated a more refined perspective about the potential impact of ischemia. However, it is important to note that while ischemia correlated significantly with functional outcomes, the effects were rather marginal. On average, choice of warm rather than cold ischemia reduced the functional recovery only 7%, and each additional 10-min interval of warm ischemia reduced the functional recovery by only an additional 2.5%. Hence, a 40-min interval of warm ischemia would, on average, reduce the functional recovery in the ipsilateral kidney by only 17% [43]. By placing this field on a more scientific basis, these recent studies further support the importance of both quality and quantity with respect to

functional recovery after PN, and they also demonstrate real effects of ischemia, albeit marginal in impact.

Limited or Zero Ischemia PN: Real-world Test of Importance of Ischemia

Despite evidence showing that ischemia plays a limited role in the recovery of function after PN, several technical modifications have been made to reduce or eliminate exposure to ischemia. These modifications include early unclamping, selective vascular clamping, and zero ischemia approaches, and their feasibility and impact on functional recovery has been evaluated in several retrospective studies (Table 13.2d) [44–47]. In a cohort of patients with solitary kidneys, Thompson et al. compared the outcomes of off-clamp PN with clamped PN with warm ischemia [44]. Warm ischemia (median = 21 min) was associated with increased risk of developing new-onset stage IV CKD compared to off-clamp PN (HR 2.3, 95% CI 1.3–5.8). Other retrospective studies have reported similar findings; however, selection bias may be a contributing factor [6, 8]. Patients undergoing off-clamp PN are more likely to have small, peripheral tumors, and parenchymal mass loss is typically less in this setting. However, nephron mass preservation was not incorporated into these analyses, so definitive conclusions are difficult to draw.

Gill and colleagues have pushed forward with a variety of innovative approaches to reduce or eliminate ischemia [46, 47]. These techniques are feasible in hands of experienced surgeons and may provide benefit in the setting of severe preexisting CKD, where a patient may be on the verge of dialysis. However, zero or superselective clamping can be associated with increased blood loss and transfusion rates. Furthermore, these modifications are technically challenging and diffusion can be limited due to a steep learning curve [6, 7]. Beyond this, the logical question arises as to whether these technically complex modifications provide a significant functional advantage over the traditional clamped PN? Comparison of functional outcomes has failed to establish superiority of reduced ischemia approaches over traditional clamped PN. Global GFR preservation noted with zero/selective clamping has been in range of 86–92% (Table 13.2d), which is not substantially improved when compared to clamped PN [6–8, 43, 46].

Studies Evaluating Biomarkers and Histologic Changes During PN

A study by Parekh and colleagues also suggests that ischemia may not be as deleterious as previously thought [48]. This group studied a limited cohort of 40 patients and prospectively evaluated the renal histological and functional changes associated

with ischemia with duration up to 60 min during minimally invasive PN (Table 13.2e). Renal histological changes were less pronounced than previously noted in analogous animal studies and renal functional changes did not correlate with duration of ischemia. Furthermore, biomarkers of renal tubular injury also failed to correlate with functional outcomes [48]. This study suggests that the human kidney may tolerate prolonged ischemia better than previously thought; however, given the limitations of the analysis, further studies will be needed in this area.

Functional Recovery in Poorly Functioning Kidneys

Patients with poorly functioning kidneys pose a major challenge in the management of renal masses. Some have proposed that such kidneys may be more frail and thus less likely to recover from the ischemic insult. Mir and colleagues addressed this by evaluating four tiers of functional status within the operated kidney, namely, ipsilateral kidneys with GFR > 60 ml/min/1.73 m^2, GFR 45–60 ml/min/1.73 m^2, GFR 30–45 ml/min/1.73 m^2, or GFR < 30 ml/min/1.73 m^2 [41]. Recovery from ischemia was defined as percentage of GFR saved in the operated kidney normalized by percentage of parenchymal mass saved and would be 100% if all nephrons recovered completely from the ischemic insult. In a cohort of 155 patients, preoperative GFR status was not associated with recovery from ischemia, as it remained high (90–100%) in all of the cohorts. Kidneys with preoperative GFR < 30 ml/min/1.73 m^2 had median recovery from ischemia of 99% suggesting that even poorly functioning kidneys recover well from the ischemic insult, i.e., proportional to nephron mass preserved, as long as cold ischemia or limited warm ischemia is utilized [41].

Acute Kidney Injury After PN

Most studies in the literature have predominantly focused on new baseline GFR that is defined a few to several months after PN. However, acute changes in renal function within the immediate postoperative period could also be important and may play a role in establishing the new baseline GFR. In the general population, AKI due to medical etiologies, such as congestive heart failure, can predispose to CKD, but it is unknown if AKI due to surgical exposure to ischemia also predispose to CKD [8].

Zhang and colleagues addressed this by evaluating a cohort of patients with a solitary kidney undergoing PN to assess the incidence of AKI, risk factors for AKI, and impact of AKI on subsequent functional recovery [49]. One of the fundamental findings was that AKI as defined by conventional criteria (peak serum creatinine level (SCr) normalized by preoperative SCr) typically overestimated the incidence and degree of AKI, because it does not take into account nephron mass loss, which is the other major source of increased SCr in the early postoperative period. In this study the authors proposed a novel criteria for AKI after PN, whereby the peak SCr

is normalized by the projected peak SCr taking into account loss of nephron mass. In this manner the degree of AKI more accurately reflects the true impact of ischemia. On multivariable analysis, ischemia time correlated with increased degree of AKI. While increased degree of AKI by the proposed criteria correlated with reduced functional recovery, even patients with grade 3 AKI ultimately reached functional recovery levels of 88–90% [49].

Further work by Zhang and colleagues focused on studying AKI in patients with two kidneys, which is more complex because the contralateral kidney can mask functional events within the operated kidney [50]. To address this they developed a novel "spectrum score" whereby the peak postoperative SCr level is placed on a spectrum between two extreme scenarios. In the worst-case scenario, the operated kidney completely shuts down temporarily due to ischemic injury and renal function is entirely dependent on the contralateral kidney. Based on preoperative renal scans with split renal function, the projected worst-case peak SCr can be estimated. In the best-case scenario, the operated kidney does not experience or exhibit any ischemic injury, and changes in postoperative SCr levels are only influenced by nephron mass loss related to the surgery. Again, a projected peak SCr related to this best-case scenario can be estimated. The observed peak SCr level can then be placed on the spectrum between these two extreme values, on a scale from 0 to 100%, with the latter corresponding to the worst-case scenario. Four quartiles of spectrum score were defined as 0–25%, 26–50%, 51–75%, and 76–100%, and increased spectrum score correlated with ischemia type (warm worse than cold) and duration of ischemia. While increased spectrum score, analogous to increased degree of AKI, correlated significantly with reduced functional recovery, even patients with high spectrum score still ultimately demonstrated relative strong functional recovery (median = 83%) [50]. Further work is needed to understand the implications of AKI with respect to stability of renal function on a longitudinal basis.

Vascularized Nephron Mass: The Key to Functional Outcomes with PN

As outlined above, the quantity of vascularized parenchymal mass preserved has been established as the most important determinant of functional outcomes after PN, presuming that extended warm ischemia has been avoided [6–8]. Loss of vascularized nephron mass can be due to two primary sources (Fig. 13.3): (1) healthy parenchyma that is excised along with the mass (excised parenchymal mass, EPM) and (2) parenchyma that is devascularized during the reconstructive phase of the procedure (devascularized parenchymal mass, DPM).

Several studies have focused on technical modifications, such as "minimal-margin" PN or tumor enucleation (TE), to limit EPM [47, 51]. During TE blunt dissection is performed within the hypovascular plane along the pseudocapsule, potentially preserving more vascularized nephron mass. Current perspective about the role of TE in the management of localized kidney cancer is provided in

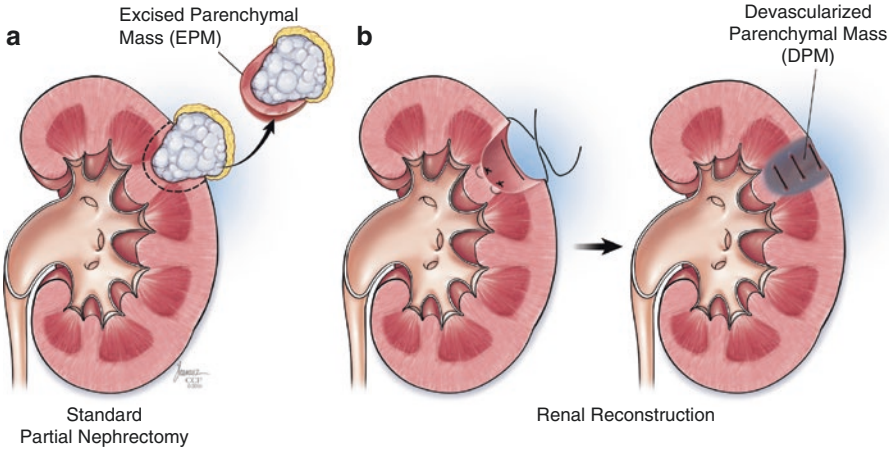

Fig. 13.3 Loss of nephron mass during partial nephrectomy (PN) is primarily due to excised parenchymal mass (EPM) or devascularized parenchymal mass (DPM), as illustrated in **a** and **b**, respectively. Renal reconstruction typically includes sutures placed into the base of the defect to address transected vessels and capsular re-approximation to reduce the risk of postoperative hemorrhage and urine leak. In the process a modest amount of parenchyma is devascularized. (From Dong et al. [52], with permission of Elsevier)

the recent AUA guidelines (see section on principles related to PN). In a recent study, median ipsilateral vascularized parenchymal mass preserved was 95% for TE and 84% for standard PN ($p < 0.001$), and median estimated global GFR preserved was 101% and 89% for TE and standard PN, respectively ($p < 0.001$). This study suggests that TE may provide marginally better functional outcomes than standard PN [51].

Another concept to minimize EPM is a minimal-margin approach to PN whereby wedge resection is prioritized rather than heminephrectomy, and this has been adopted at many centers. Dong and colleagues recently studied the impact of EPM and DPM in a cohort of 168 patients resected with a minimal-margin approach to PN [52]. Median EPM was 9 cm^3, representing only 5% of the preoperative ipsilateral parenchymal mass. In contrast, median DPM was 16 cm^3, representing 9% of the preoperative ipsilateral parenchymal mass. As expected, total loss of vascularized parenchymal mass correlated strongly with functional outcomes ($r = 0.64$, $p < 0.001$). DPM also correlated strongly with functional outcomes ($r = 0.55$, $p < 0.001$), while EPM failed to correlate. This suggests that loss of vascularized parenchymal mass predominantly occurs during the reconstructive phase of PN, and in this era of minimal-margin PN, the amount of nephron mass excised along with the tumor is of secondary importance. This emphasizes the need for precise ligation of transected vessels within the parenchymal defect, taking care to avoid inadvertent occlusion of adjacent branch arteries. Capsular closure should also be performed carefully to minimize devascularization, or this step can be omitted in some circumstances. TE may facilitate reduced DPM by precluding the need for capsular closure and reducing the need for parenchymal suturing [51].

Additional Surgical Considerations to Optimize Renal Function Preservation

Mir [6] and Volpe [7] comprehensively reviewed the factors associated with functional recovery after PN (Table 13.2f) and outline a number of practical measures or intraoperative maneuvers to minimize loss of function associated with the procedure. The most important modifiable factors associated with the decline in function after PN are suboptimal preservation of vascularized nephron mass and incomplete recovery from renal ischemia (Fig. 13.4).

In Fig. 13.4a, preventive measures to avoid irreversible ischemic injury are detailed. Among these, the most substantial experience has been with cold ischemia and the clinical experience in favor of hypothermia as a protective factor is robust. Surgical modifications to reduce exposure to global ischemia within the operated kidney have also shown promise, although further research is needed. In particular, it will be important to define which cohorts of patients should be considered for these approaches. Patients with severe preexisting CKD might benefit most from a zero ischemia approach, because any form of ischemia, even hypothermia, can increase the risk of AKI and potential need for dialysis in the early postoperative period [35]. Also, even with hypothermia, there can be some variability in recovery from ischemia, and in this setting complete avoidance of ischemia may be worth the increased complexity and possible risks of the procedure [35]. Several pharmacological agents have been investigated in an effort to prophylactically ameliorate the effects of ischemia. Mannitol has been used for this purpose for the past three to four decades, but a recent randomized trial of mannitol versus placebo failed to show any significant differences in functional recovery,

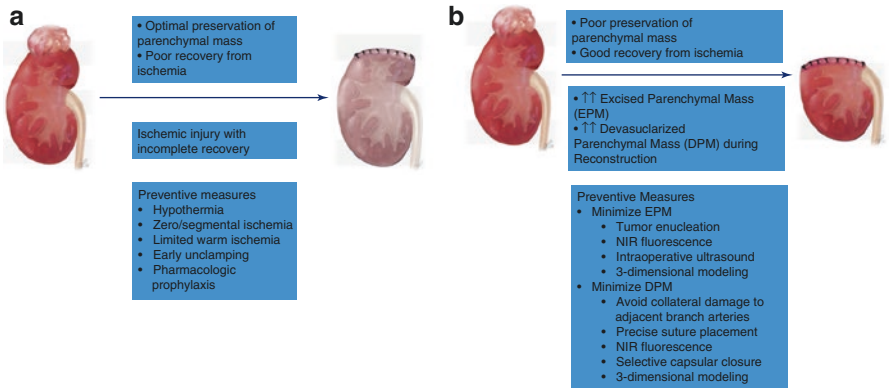

Fig. 13.4 Etiology of decline in renal function following partial nephrectomy and potential preventive measures. (**a**) Decline in function due to poor recovery from ischemia in the setting of optimal preservation of nephron mass. (**b**) Decline in function due to poor preservation of nephron mass in the setting of good recovery from ischemia. (From Mir et al. [6], Figs. 2, 3, with permission of Elsevier)

either short or long term [53]. Dopamine and fenoldopam have also been used in high-risk situations, such as solitary kidneys, to decrease the risk of AKI [54, 55]. However, randomized trials again failed to substantiate a benefit over placebo. Antioxidants including vitamins C and E have also been studied yet have not proven to be renoprotective [6]. In summary, the pharmacological agents investigated to date have not shown a protective effect against ischemic injury, and further research is needed [6].

As previously discussed, parenchymal mass preservation is of paramount importance for functional recovery from PN. Parenchymal mass preservation can be optimized by decreasing EPM and DPM and the practical measures to accomplish this are reviewed in Fig. 13.4b. The potential importance of TE or minimal-margin PN for reducing EPM was discussed above and such approaches may also minimize DPM by facilitating a more manageable reconstruction. Beyond this, advanced preoperative or intraoperative imaging, such as intraoperative ultrasound, near-infrared fluorescence, or three-dimensional modeling, may also be of use [56–58]. Information derived from such studies may help guide the resection allowing for more precise excision and strategic avoidance of branch arteries during reconstruction. For instance, adjacent branch arteries can be readily visualized with near-infrared fluorescence and by defining the edge of the tumor a more precise resection can be accomplished while still obtaining negative surgical margins. These imaging modalities are most useful for hilar or other endophytic tumors, but further research will be needed to explore their potential functional benefits.

Future Directions

Most studies on the implications of functional loss after renal mass surgery have follow-up that is limited to a decade or less. Studies with longer follow-up will be needed to determine the ultimate effect of functional loss on survival, which will be particularly important when managing younger patients. Also needed is a randomized trial of PN versus RN for larger renal masses, or other situations where oncologic potential is increased, such as infiltrative appearance on imaging or unfavorable histology on renal mass biopsy. In these settings optimal management is still controversial, in part related to concerns about selection biases [10]. Ideally such a trial would use overall survival as the primary endpoint and secondary outcomes could include functional stability, cardiovascular events, and cancer-related survival. The long-term implications of AKI after PN will also require further study, as some have hypothesized that nephrons that have been exposed to ischemic injury may be more frail during longitudinal follow-up [8]. Well-designed prospective studies will also be required to more fully understand the effects of EPM and DPM on functional outcomes after PN and to define procedural considerations to optimize outcomes with respect to both of these parameters [52].

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1): 7–30.
2. Pierorazio PM, Johnson MH, Patel HD, Sozio SM, Sharma R, Iyoha E, et al. Management of renal masses and localized renal cancer: systematic review and meta-analysis. J Urol. 2016;196(4):989–99.
3. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, et al. Guideline for management of the clinical T1 renal mass. J Urol. 2009;182(4):1271–9.
4. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA guideline. J Urol. 2017;198:520–9.
5. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296–305.
6. Mir MC, Ercole C, Takagi T, Zhang Z, Velet L, Remer EM, et al. Decline in renal function after partial nephrectomy: etiology and prevention. J Urol. 2015;193(6):1889–98.
7. Volpe A, Blute ML, Ficarra V, Gill IS, Kutikov A, Porpiglia F, et al. Renal ischemia and function after partial nephrectomy: a collaborative review of the literature. Eur Urol. 2015;68(1): 61–74.
8. Zabell JR, Wu J, Suk-Ouichai C, Campbell SC. Renal ischemia and functional outcomes following partial nephrectomy. Urol Clin North Am. 2017;44(2):243–55.
9. Kim SP, Campbell SC, Gill I, Lane BR, Van Poppel H, Smaldone MC, et al. Collaborative review of risk benefit trade-offs between partial and radical nephrectomy in the management of anatomically complex renal masses. Eur Urol. 2017;72(1):64–75.
10. Weight CJ, Miller DC, Campbell SC, Derweesh IH, Lane BR, Messing EM. The management of a clinical t1b renal tumor in the presence of a normal contralateral kidney. J Urol. 2013;189(4):1198–202.
11. Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol. 2011;59(4):543–52.
12. Lane BR, Campbell SC, Demirjian S, Fergany AF. Surgically induced chronic kidney disease may be associated with a lower risk of progression and mortality than medical chronic kidney disease. J Urol. 2013;189(5):1649–55.
13. Lane BR, Demirjian S, Derweesh IH, Takagi T, Zhang Z, Velet L, et al. Survival and functional stability in chronic kidney disease due to surgical removal of nephrons: importance of the new baseline glomerular filtration rate. Eur Urol. 2015;68(6):996–1003.
14. Gor R, Uzzo R, Li T, Haseebuddin M, Waingankar N, Ginzburg S, et al. Surgical chronic kidney disease appears to be a distinct subtype of chronic kidney disease based on mortality risks following renal surgery. J Urol. 2015;193:e975–6.
15. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA. 2015;313(8):837–46.
16. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. Nat Publ Gr. 2017;13:104–14.
17. Huang WC, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. Lancet Oncol. 2006;7(9):735–40.
18. Mashni JW, Assel M, Maschino A, Russo M, Masi B, Bernstein M, et al. New chronic kidney disease and overall survival after nephrectomy for small renal cortical tumors. Urology. 2015;86(6):1137–45.
19. Licht MR, Novick AC. Nephron sparing surgery for renal cell carcinoma. J Urol. 1993;149(1):1–7.

20. Herr HW. Partial nephrectomy for unilateral renal carcinoma and a normal contralateral kidney: 10-year followup. J Urol. 1999;161(1):33–4. discussion 34–5
21. Russo P, Goetzl M, Simmons R, Katz J, Motzer R, Reuter V. Partial nephrectomy: the rationale for expanding the indications. Ann Surg Oncol. 2002;9(7):680–7.
22. BC L, ML B, JC C, CM L, AL W, H Z. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. J Urol. 2004;171(3):1066–70.
23. Karellas ME, O'Brien MF, Jang TL, Bernstein M, Russo P. Partial nephrectomy for selected renal cortical tumours of ≥7 cm. BJU Int. 2010;106(10):1484–7.
24. Breau RH, Crispen PL, Jimenez RE, Lohse CM, Blute ML, Leibovich BC. Outcome of stage T2 or greater renal cell cancer treated with partial nephrectomy. J Urol. 2010;183(3): 903–8.
25. Kim SP, Thompson RH, Boorjian SA, Weight CJ, Han LC, Murad MH, et al. Comparative effectiveness for survival and renal function of partial and radical nephrectomy for localized renal tumors: a systematic review and meta-analysis. J Urol. 2012;188(1):51–7.
26. Tan H-J, Norton EC, Ye Z, Hafez KS, Gore JL, Miller DC. Long-term survival following partial vs radical nephrectomy among older patients with early-stage kidney cancer. JAMA. 2012;307(15):1629–35.
27. Weight CJ, Larson BT, Fergany AF, Gao T, Lane BR, Campbell SC, et al. Nephrectomy induced chronic renal insufficiency is associated with increased risk of cardiovascular death and death from any cause in patients with localized cT1b renal masses. J Urol. 2010;183(4): 1317–23.
28. Shuch B, Hanley J, Lai J, Vourganti S, Kim SP, Setodji CM, et al. Overall survival advantage with partial nephrectomy: a bias of observational data? Cancer. 2013;119(16):2981–9.
29. Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. Eur Urol. 2014;65(2):372–7.
30. Zabell J, Demirjian S, Campbell SC. MP59-15 long-term outcomes after renal cancer surgery: predictors of chronic kidney disease and non-renal cancer mortality. J Urol. 2017;197(4):e786–7.
31. Capitanio U, Terrone C, Antonelli A, Minervini A, Fiori C, Zegna L, et al. MP44-04 nephron-sparing surgery protects from chronic kidney disease relative to radical nephrectomy but does not impact on other-causes mortality: long-term (more than 10 years) survival and functional outcomes in patients with a T1A-T1B renal mass. J Urol. 2015;193(4):e527.
32. Wu J, Suk-Ouichai C, Dong W, Antonio EC, Derweesh IH, Lane BR, et al. Analysis of survival for patients with chronic kidney disease primarily related to renal cancer surgery. BJU Int. 2018;121(1):93–100.
33. Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, et al. A prospective randomized EORTC intergroup phase 3 study comparing the complications of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. Eur Urol. 2007;51(6):1606–15.
34. Yossepowitch O, Eggener SE, Serio A, Huang WC, Snyder ME, Vickers AJ, et al. Temporary renal ischemia during nephron sparing surgery is associated with short-term but not long-term impairment in renal function. J Urol. 2006;176(4):1339–43.
35. Zhang Z, Zhao J, Velet L, Ercole CE, Remer EM, Mir CM, et al. Functional recovery from extended warm ischemia associated with partial nephrectomy. Urology. 2016;87:106–13.
36. Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, et al. Every minute counts when the renal hilum is clamped during partial nephrectomy. Eur Urol. 2010;58(3):340–5.
37. Lane BR, Russo P, Uzzo RG, Hernandez AV, Boorjian SA, Thompson RH, et al. Comparison of cold and warm ischemia during partial nephrectomy in 660 solitary kidneys reveals predominant role of nonmodifiable factors in determining ultimate renal function. J Urol. 2011;185(2):421–7.

38. Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, et al. Renal function after partial nephrectomy: effect of warm ischemia relative to quantity and quality of preserved kidney. Urology. 2012;79(2):356–60.
39. Song C, Park S, Jeong IG, Hong JH, Park HK, Kim C-S, et al. Followup of unilateral renal function after laparoscopic partial nephrectomy. J Urol. 2011;186(1):53–8.
40. Mir MC, Campbell RA, Sharma N, Remer EM, Li J, Demirjian S, et al. Parenchymal volume preservation and ischemia during partial nephrectomy: functional and volumetric analysis. Urology. 2013;82(2):263–9.
41. Mir MC, Takagi T, Campbell RA, Sharma N, Remer EM, Li J, et al. Poorly functioning kidneys recover from ischemia after partial nephrectomy as well as strongly functioning kidneys. J Urol. 2014;192(3):665–70.
42. Ginzburg S, Uzzo R, Walton J, Miller C, Kurz D, Li T, et al. Residual parenchymal volume, not warm ischemia time, predicts ultimate renal functional outcomes in patients undergoing partial nephrectomy. Urology. 2015;86(2):300–6.
43. Dong W, Wu J, Suk-Ouichai C, Caraballo Antonio E, Remer EM, Li J, et al. Ischemia and functional recovery from partial nephrectomy: refined perspectives. Eur Urol Focus. 2017; https://doi.org/10.1016/j.euf.2017.02.001.
44. Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, et al. Comparison of warm ischemia versus no ischemia during partial nephrectomy on a solitary kidney. Eur Urol. 2010;58(3):331–6.
45. Smith GL, Kenney PA, Lee Y, Libertino JA. Non-clamped partial nephrectomy: techniques and surgical outcomes. BJU Int. 2011;107(7):1054–8.
46. Desai MM, de Castro Abreu AL, Leslie S, Cai J, Huang EY-H, Lewandowski P-M, et al. Robotic partial nephrectomy with superselective versus main artery clamping: a retrospective comparison. Eur Urol. 2014;66(4):713–9.
47. Satkunasivam R, Tsai S, Syan S, Bernhard J-C, de Castro Abreu AL, Chopra S, et al. Robotic unclamped "minimal-margin" partial nephrectomy: ongoing refinement of the anatomic zero-ischemia concept. Eur Urol. 2015;68(4):705–12.
48. Parekh DJ, Weinberg JM, Ercole B, Torkko KC, Hilton W, Bennett M, et al. Tolerance of the human kidney to isolated controlled ischemia. J Am Soc Nephrol. 2013;24(3):506–17.
49. Zhang Z, Zhao J, Dong W, Remer E, Li J, Demirjian S, et al. Acute kidney injury after partial nephrectomy: role of parenchymal mass reduction and ischemia and impact on subsequent functional recovery. Eur Urol. 2016;69(4):745–52.
50. Zhang Z, Zhao J, Dong W, Aguilar Palacios D, Remer EM, Li J, et al. Acute ipsilateral renal dysfunction after partial nephrectomy in patients with a contralateral kidney: Spectrum score to unmask ischemic injury. Eur Urol. 2016;70(4):692–8.
51. Dong W, Gupta GN, Blackwell RH, Wu J, Suk-Ouichai C, Shah A, et al. Functional comparison of renal tumor enucleation versus standard partial nephrectomy. Eur Urol Focus. 2017;3:437.
52. Dong W, Wu J, Suk-Ouichai C, Caraballo Antonio E, Remer E, Li J, et al. Devascularized parenchymal mass associated with partial nephrectomy: predictive factors and impact on functional recovery. J Urol. 2017;198(4):787–94.
53. Spaliviero M, Power NE, Murray KS, Sjoberg DD, Benfante NE, Bernstein ML, et al. Intravenous mannitol versus placebo during partial nephrectomy in patients with normal kidney function: a double-blind, clinically-integrated, randomized trial. Eur Urol. 2017; 16:e369.
54. O'Hara JF, Mahboobi R, Novak SM, Bonilla AM, Mascha EJ, Fergany AF, et al. Fenoldopam and renal function after partial nephrectomy in a solitary kidney: a randomized, blinded trial. Urology. 2013;81(2):340–6.
55. O'Hara JF, Hsu THS, Sprung J, Cywinski JB, Rolin HA, Novick AC. The effect of dopamine on renal function in solitary partial nephrectomy surgery. J Urol. 2002;167(1):24–8.

56. Kaczmarek BF, Sukumar S, Petros F, Trinh Q-D, Mander N, Chen R, et al. Robotic ultrasound probe for tumor identification in robotic partial nephrectomy: initial series and outcomes. Int J Urol. 2013;20(2):172–6.
57. Bjurlin MA, Gan M, McClintock TR, Volpe A, Borofsky MS, Mottrie A, et al. Near-infrared fluorescence imaging: emerging applications in robotic upper urinary tract surgery. Eur Urol. 2014;65(4):793–801.
58. Ahmadi H, Liu J-J. 3-D imaging and simulation for nephron sparing surgical training. Curr Urol Rep. 2016;17(8):58.

Chapter 14
Pre-surgical Treatment of Renal Cell Carcinoma

Shivashankar Damodaran and E. Jason Abel

Introduction

Pre-surgical therapy is a general term referring to any treatment administered prior to surgery. In contrast, neoadjuvant therapy refers to the use of pre-surgical treatments in patients for whom surgical management may be curative. Since patients with metastatic renal cell carcinoma (RCC) are unlikely to be cured, the term pre-surgical therapy is most appropriate when discussing the treatment of patients with locally advanced or metastatic RCC.

Multiple rationales exist for the use of pre-surgical therapy in patients with RCC. These include:

- To enable surgery of unresectable tumors
- To downsize tumors such that partial nephrectomy can be performed instead of radical nephrectomy
- To facilitate minimally invasive surgery
- To decrease the extent of tumor thrombus, thereby enabling a less complex surgical approach
- To treat micrometastatic disease
- To theoretically "prime" the immune system
- To use tumor response to pre-surgical treatment as a litmus test to select patients who may benefit from surgery

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Among these rationales, the use of pre-surgical therapies to reduce the size and complexity of primary tumors is perhaps the most straightforward. However, for this approach to be advantageous, pre-surgical treatments must produce substantial and reliable primary tumor responses with acceptable toxicity. For healthy patients with small localized tumors, contemporary series of nephrectomy and partial nephrectomy report minimal morbidity and mortality [1, 2]. As such, pre-surgical therapies are unlikely to improve outcomes for patients with localized tumors who can already be treated surgically with low morbidity. However, one third of RCC patients have locally advanced or metastatic disease at presentation [3], and more extensive surgery is typically required, thus increasing the risk for surgical morbidity. It is in this patient population where pre-surgical therapy has been most extensively studied.

One group of RCC patients who potentially stand to benefit from pre-surgical therapy are those with venous tumor invasion, as surgical morbidity for nephrectomy with tumor thrombectomy is considerably higher than a typical nephrectomy and morbidity substantially increases with the level of inferior vena cava (IVC) thrombus [4–6]. In a contemporary multi-institutional series of patients with RCC and IVC invasion, the perioperative mortality and major complication rate was reported to be 10% and 34%, respectively [7]. Tumors that invade directly into adjacent structures also require more extensive surgical resection including occasional removal of other organs, increasing the risk for perioperative complications. Nephrectomy for tumors invading adjacent organs is associated with substantial morbidity and poor survival in patients with positive surgical margins or metastatic disease [8–11]. Similarly, for the 15–20% of patients who present with metastatic RCC [12], cytoreductive surgery may improve survival, but patient selection remains critical [13]. Patients with metastatic RCC have a limited life expectancy [14] and a rationale for pre-surgical therapy exists if morbidity can be decreased or selection for surgery can be improved.

Historical Pre-surgical Therapies

Pre-surgical Chemotherapy

Data from phase I and phase II trials revealed early on that only a small minority of patients with metastatic RCC will be responsive to cytotoxic chemotherapy [15]. In light of this, investigations into the potential benefits of pre-surgical chemotherapy for RCC are scarce.

Radiation Therapy

Preoperative radiation therapy (RT) has been investigated in patients with high-risk RCC [16–20]. In a single-center study of patients with recurrent or residual kidney cancer following nephrectomy, preoperative RT of 4.5–5.0 Gy was given followed

by aggressive surgical de-bulking and intraoperative irradiation (1.0–2.5 Gy) [16]. Four of 8 patients (50%) with clear cell RCC were free of disease at 29 months. Prospective randomized studies, however, have failed to show a survival advantage with RT in the pre-surgical setting [17–20]. More specifically, in a randomized trial of 88 patients comparing pre-surgical RT plus nephrectomy versus nephrectomy alone, 5-year survival rates of 47% and 63% were observed, respectively [18]. Similarly, in a prospective study from Rotterdam, there was no overall survival advantage to preoperative RT versus upfront surgery [19]. RT dose in this study was 30 Gy in 15 sessions and a follow-up study using a higher dose of RT showed no additional benefit [20].

Cytokine Therapy

Prior to the development of modern targeted therapeutic agents, the cytokines interleukin-2 (IL-2) and interferon-α (INF-α) were commonly used for the treatment of metastatic RCC. Although effective at prolonging survival in a subset of patients with metastatic disease, these agents have been found to have little impact on the primary tumors of patients treated prior to cytoreductive nephrectomy [21–24]. Because of this, interest in the use of preoperative cytokine therapy has waned. Additionally, with the publication of two randomized phase III trials that reported improved overall survival with upfront cytoreductive nephrectomy followed by INF-α, the standard treatment sequence of upfront surgery followed by systemic therapy was established [25, 26].

Pre-surgical Renal Artery Embolization

Selective occlusion of the renal artery prior to surgery may reduce neovascularity from large tumors or shrink tumor thrombus, potentially facilitating surgery and potentially result in less perioperative blood loss. From an immunological viewpoint, angioinfarction also releases tumor antigens stimulating a potentially beneficial immune response [27, 28]. In a retrospective analysis of 100 cases, preoperative angioembolization was found to reduce operative time and need for blood transfusion [29]. In a retrospective study that compared 118 patients matched for sex, age, stage, tumor size, and tumor grade to 116 patients who underwent surgery alone, a 5- and 10-year survival benefit was seen (62% and 47% versus 35% and 23%) [30]. However, a large series of 225 patients treated with preoperative angioembolization before radical nephrectomy and tumor thrombectomy demonstrated deleterious effects of angioembolization with increased operative time, transfusion requirements, and increased perioperative mortality [31]. Collectively, these potential risks outweigh benefits of routine angioembolization for most patients.

Use of Targeted Therapies in the Pre-surgical Setting

Since 2005, the United States Food and Drug Administration has approved a multitude of agents for the treatment of metastatic RCC. This includes the multitarget tyrosine kinase inhibitors sorafenib, sunitinib, pazopanib, axitinib, and cabozantinib, as well as the anti-VEGF-A antibody bevacizumab [32–37]. These agents work to slow tumor progression by inhibiting angiogenesis. Other targeted agents approved for the treatment of metastatic RCC include temsirolimus and everolimus, which are inhibitors of the mammalian target of rapamycin (mTOR) [38, 39]. Additionally the immune checkpoint inhibitor nivolumab, a monoclonal antibody targeted against programmed death receptor-1 (PD-1), was recently approved for the second-line treatment of metastatic RCC [40].

In 2008, van der Veldt et al. reported a series of 22 patients who were treated pre-surgically with the tyrosine kinase inhibitor sunitinib [41]. In 17 patients who had imaging available for response evaluation, 12 (70.6%) patients had stable disease, 4 (23.5%) had a partial response, and 1 (5.9%) had disease progression. A larger retrospective study evaluated 168 patients with metastatic RCC with the primary tumor in situ treated with targeted therapies including sunitinib, sorafenib, bevacizumab, erlotinib, pazopanib, bevacizumab + erlotinib, and bevacizumab + chemotherapy [42]. The authors found a median reduction in tumor diameter of 7.1% (interquartile range from –14% to –0.11%), with partial responses in 6% of patients.

Multiple small prospective clinical trials have been conducted to investigate the potential benefits of pre-surgical therapy in patients with RCC (summarized in Table 14.1). In a phase II trial to assess the feasibility of pre-surgical bevacizumab, 23 patients were treated with a combination of bevacizumab + erlotinib and 27 were treated with bevacizumab alone for 8 weeks [43]. Nephrectomy was performed for 42 patients (84%) and deferred for patients with disease progression or worsening performance status. Pre-surgical treatment demonstrated similar efficacy to postsurgical treatment with median overall survival of 25.4 months; however, there was a higher rate of delayed wound healing in pre-surgical treatment group.

In a phase II trial evaluating the utility of preoperative sorafenib in stage II or higher RCC, 93% of patients had stable disease, 6% patients had a partial response, and none progressed during preoperative treatment [44]. In a multicenter retrospective review to assess feasibility of sunitinib therapy prior to nephron-sparing surgery involving 14 tumors in 12 patients with clear cell RCC, 4 (35%) had a partial response and 10 (71%) had stable disease [45]. In another study aimed to evaluate safety and clinical response to sunitinib administered prior to nephrectomy, 1 (5%) patient had a partial response and 16 (80%) patients had stable disease [46]. In a combined analysis of two phase II trials to assess safety and efficacy of sunitinib prior to planned nephrectomy in patients with metastatic clear cell RCC, 5 of 52 (10%) patients achieved a partial response, while 12 (24%) had progression of disease at the time of surgery [47]. In a phase II trial of 28 patients with unresectable RCC treated with sunitinib, 7 (25%) had a partial response and 13 (45%) underwent subsequent nephrectomy [48].

Table 14.1 Summary of primary tumor responses from clinical trials evaluating pre-surgical therapy for renal cell carcinoma

Study	Agent	No. of patients	M1 (%)	ccRCC (%)	Median diameter reduction (%)	PR+ CR (%)
Jonasch et al. (2009) [43]	Bevacizumab	50	100	100	NR	0
Cowey et al. (2010) [44]	Sorafenib	30	44	70	9.6	7
Zhang et al. (2015) [83]	Sorafenib	18	39	83	20[a]	22
Van der Veldt et al. (2008) [41]	Sunitinib	22	100	95	31	18
Silberstein et al. (2010) [45]	Sunitinib	12	42	100	21[a]	28
Hellenthal et al. (2010) [46]	Sunitinib	20	20	100	12[a]	5
Powles et al. (2011) [47]	Sunitinib	66	100	100	12	6
Rini et al. (2012) [48]	Sunitinib	28	66	76	22	37
Lane et al. (2015) [93]	Sunitinib	72	40	89	18	19
Rini et al. (2015) [49]	Pazopanib	25	0	100	26	36
Powles et al. (2016) [51]	Pazopanib	104	100	100	14	13
Karam et al. (2014) [50]	Axitinib	24	0	100	28	46

M1 metastatic, *PR* partial response, *CR* complete response
[a]Indicates mean reduction in diameter

Prospective phase II studies with newer generation targeted therapies have suggested slightly higher response rates in primary tumors. Pre-surgical pazopanib demonstrated partial responses in 36% of patients with localized clear cell RCC [49]. Similarly, another clinical trial evaluating pre-surgical axitinib in patients with locally advanced nonmetastatic clear cell RCC demonstrated partial responses and stable disease in 46% and 54% of patients, respectively [50]. Lower response rates were observed for patients with metastatic RCC treated with pazopanib, with only 13% of patients demonstrating a partial response with the primary tumor in situ [51].

For patients with metastatic RCC, the optimal timing of cytoreductive surgery relative to administration of targeted agents remains in question [52]. The SURTIME trial (ClinicalTrials.gov identifier NCT01099423) is an international phase III randomized study that was designed to address this question by comparing the survival of patients with metastatic RCC treated with upfront cytoreductive nephrectomy followed by sunitinib versus pre-surgical sunitinib followed by nephrectomy. This study was closed with an accrual of 99 patients with results expected to be reported in 2018. The Clinical Trial to Assess the Importance of

Nephrectomy or CARMENA trial (ClinicalTrials.gov identifier NCT00930033) is a French randomized phase III trial that will compare overall survival in patients treated with cytoreductive nephrectomy followed by sunitinib versus patients treated nonsurgically with sunitinib alone. Enrollment began in 2009 with a target accrual of 576 patients and a study completion date of 2020. Data from this trial may lend further insights into the optimal use of surgery and systemic therapy in patients with metastatic RCC.

In the future, pre-surgical administration of immune checkpoint inhibitors may have a role in the treatment of RCC, although data is still lacking for these agents. A phase I study is currently underway to analyze the safety and feasibility of preoperative nivolumab in patients with nonmetastatic stage II–IV clear cell RCC (ClinicalTrials.gov identifier NCT02575222). Results from this study are expected in 2019. Looking beyond safety and feasibility, the PROSPER trial is a phase III study designed to examine if the addition of perioperative nivolumab to radical or partial nephrectomy can prolong recurrence-free survival in patients with locally advanced RCC (ClinicalTrials.gov identifier: NCT03055013). Patients in the intervention arm of this trial will receive a combination of pre-surgical and adjuvant nivolumab. Results for this study are expected in 2022.

Discussion of RCC Patients Most Likely to Benefit from Pre-surgical Therapy

Unresectable Primary Tumor

Surgery for primary tumors that invade adjacent organs can be morbid and outcomes are poor unless negative surgical margins can be achieved [8–11]. The use of systemic therapy to facilitate surgery for unresectable tumors is a primary advantage for pre-surgical treatment and this approach has been reported by several authors [48, 53–56]. In a retrospective analysis of 19 unresectable RCC primary tumors with adjacent organ or vascular invasion treated with sunitinib, 4 (21%) were felt to have had achieved adequate cytoreduction to be deemed resectable [55]. In a similar series of tumors invading adjacent organs or in close proximity to vital structures, 3 out of 10 (33%) tumors were judged to be resectable after therapy [54]. In a phase II study involving 30 patients with unresectable RCC, 13 (45%) patients underwent nephrectomy following treatment with sunitinib [48]. Similar findings were demonstrated in a multi-institutional study of 14 unresectable patients with metastatic RCC, with 4 (28%) patients judged to be operable after targeted therapy [56].

Multiple explanations exist for the variability seen among studies using pre-surgical therapy to enable surgery in otherwise unresectable tumors. First, the definition of “unresectable” varies considerably among surgeons, and therefore conversion from unresectable to resectable is a difficult endpoint to rigorously study

in a clinical trial. In addition, truly dramatic responses to therapy are rare [42] and the choice of agent may impact outcomes [50]. Similarly, the overall disease burden may affect primary tumor response. Although there are limitations to these data, the potential benefit is considerable for pre-surgical therapy in otherwise inoperable renal tumors with invasion of adjacent organs.

RCC with Tumor Thrombus

Approximately 10% of cases of RCC will present with invasion of the renal vein or inferior vena cava (IVC) [4]. The extent or level of venous invasion greatly increases surgical complexity and risk for complications [6, 7]. Thus, it stands to reason that pre-surgical therapies capable of reducing the level of a tumor thombus would decrease perioperative morbidity from tumor thrombectomy, especially if cardiopulmonary bypass is no longer necessary [57]. In several case reports, targeted therapies have produced dramatic responses in this manner, increasing enthusiasm for pre-surgical approaches in the management of locally advanced RCC [58–62]. However, the responses that were demonstrated in cases reports were not reproduced in larger series [63, 64]. More specifically, a study of 25 patients with level 2 or higher IVC tumor thrombi treated with pre-surgical targeted therapy demonstrated that dramatic responses are rare [64]. Height, diameter, and level of thrombus were measured radiographically and used as endpoints for the study. Patients were treated with sunitinib ($n = 12$), bevacizumab ($n = 9$), temsirolimus ($n = 3$), and sorafenib ($n = 1$). Only three patients (12%) had a decrease in thrombus level, while 1 (4%) patient had an increase in thrombus level, and 21 (84%) did not have any change in the thrombus level. None of the patients had a modification of surgical approach as a result of the response to the targeted therapy.

Bigot et al. [63] reported another retrospective series of 14 patients with tumor thrombus who were treated with pre-surgical sunitinib or sorafenib. After therapy, six patients (43%) had a measurable decrease in the thrombus size, six (42%) had no change in size, and two cases (14%) progressed. The authors concluded that preoperative use of tyrosine kinase inhibitors produced a minimal reduction in the thrombus size, which did not modify subsequent surgical therapy. Kwon et al. [65], however, did find slightly more encouraging results in a retrospective study of patients with RCC and thrombus treated with pre-surgical targeted therapy. In their cohort of 22 patients, 18 (82%) received sunitinib and 4 (18%) received sorafenib as neoadjuvant targeted therapy. The authors used the Choi criteria [66] to evaluate tumor response, which defines partial response as >10% decrease in one-dimensional tumor size or >15% decrease in the maximal attenuation on X-ray computed tomography (CT). Nine patients (40.9%) demonstrated a partial response and had a longer survival than patients who had stable disease. In a multivariate analysis, response by the Choi criteria was the only significant predictor of overall survival.

Given that rarity of responses in tumor thrombus well as the risk of progression during therapy [67], pre-surgical treatment with currently available agents is

unlikely to benefit otherwise healthy patients without metastatic disease. However, certain patients with metastatic RCC and tumor thrombus may have very poor expectations for overall survival despite treatment with upfront nephrectomy and systemic therapy. In a multi-institutional study that looked at overall survival in metastatic RCC with venous tumor thrombus treated with cytoreductive nephrectomy, IVC thrombus above the diaphragm, poor risk group, systemic symptoms, and sarcomatoid dedifferentiation were associated with poor overall survival [68]. Patients with very limited life expectancy may benefit from pre-surgical clinical trials if the benefit of future systemic agents outweighs the risk of deferring surgery.

Metastatic Renal Cell Carcinoma

The prognosis of patients with metastatic RCC remains poor, with a median overall survival of slightly less than 2 years [69, 70]. Although upfront cytoreductive nephrectomy remains part of the standard treatment paradigm, the selection of patients for surgery is critical [71]. Contemporary population-based studies have estimated that only 36–46% of patients with metastatic RCC are treated with cytoreductive nephrectomy [72, 73]. Clinical and pathological variables [13] as well as prognostic risk stratification tools [74] are currently used to identify patients who are most likely to benefit from cytoreductive nephrectomy. Response to systemic therapy, however, may also enable selection of patients, providing a "litmus test" for patients likely to benefit cytoreductive nephrectomy [43, 75].

Survival from metastatic RCC is exceptionally variable and a subset of patients will rapidly progress despite maximum therapy [14, 76]. Proponents of upfront systemic therapy for metastatic RCC argue that patient selection for surgery will be improved if therapeutic response is used as a selection criterion for cytoreductive nephrectomy [52]. Using this approach, surgery can be avoided in the subset of patients who progress and quickly succumb to their disease despite targeted therapy. Disease prognosis could then be estimated based on initial treatment response. Of note, Heng et al. [77] found in an analysis of 1056 patients treated with anti-VEGF agents for RCC that 26% of patients had progressive disease as their best response to therapy. The median overall survival of these patients was 6.8 months compared to 29 months in patients who had either stable disease or responded to systemic therapy. Importantly, the poor overall survival in this subset was not predicted by known risk stratification systems, with only 39% of patients being considered poor risk by the widely used International Metastatic Renal Cell Carcinoma Database Criteria.

The potential for selecting patients for cytoreductive nephrectomy based on response to upfront systemic therapy was demonstrated in a phase II clinical trial of patients with metastatic RCC treated with upfront bevacizumab prior to surgery [43]. Of the 50 patients in the final analysis, 42 (84%) were treated with cytoreductive surgery after restaging following 8 weeks of systemic therapy and 8 patients did not undergo cytoreductive nephrectomy, with 6 (12%) patients showing clinical or

radiographic progression. In another study of 75 patients with metastatic RCC who were treated with sunitinib with the primary tumor in situ, it was found that patients who had a ≥10% response in their primary tumor within the first 60 days of treatment had a median overall survival of 30 months as compared to 16 months for less favorable responders [75]. In a single-arm phase II trial involving 104 metastatic RCC patients treated with 12–14 weeks of pre-surgical pazopanib therapy, 63 (61%) patients underwent subsequent nephrectomy and 13 patients progressed on pazopanib therapy. These patients had poor overall and progression-free survival implying pre-surgical systemic therapy can be used as a litmus test for choosing patients for subsequent surgery.

Enabling Partial Nephrectomy for Complex Tumors

For patients with small renal tumors, partial nephrectomy is the preferred treatment option because of the importance of preserving renal function [78, 79]. Thus, there is a potential benefit for pre-surgical therapy if treatment increases the feasibility of partial nephrectomy by shrinking tumors and enabling nephron preservation. This benefit can be potentially most impactful in patients who have a solitary functioning kidney.

In a multicenter retrospective analysis of 12 patients with 14 biopsy proven clear cell RCCs who were preoperatively treated with sunitinib, the authors observed that all tumors had a decrease in size, with a mean reduction in maximum diameter of 1.5 cm (21.1%) [45]. Additionally, nephron-sparing surgery was achievable in all 14 kidneys. In a phase II trial of nonmetastatic RCC patients treated with preoperative axitinib, Karam et al. observed partial responses in 11 (46%) patients with a median reduction in tumor diameter of 28% [50]. The authors subsequently performed a retrospective analysis of data from this trial in which five urological surgeons were independently surveyed as to whether pre-surgical systemic treatment facilitated performance of partial nephrectomy [80]. The authors observed a decrease in the median R.E.N.A.L. nephrometry score from 11 to 10 following treatment with axitinib. In addition, all five reviewers agreed that only five patients required treatment with a radical nephrectomy following treatment. In comparison, the five reviewers felt that eight patients required a radical nephrectomy prior to treatment, suggesting a change in surgical approach to partial nephrectomy was possible in a subset of patients.

Enabling Minimally Invasive Surgery

Reducing morbidity by utilizing minimally invasive approaches is another possibility for patients following pre-surgical therapy. However, like unresectable tumors, the ability to perform minimally invasive approaches is a poor endpoint for clinical trials since this definition varies widely among surgeons [81]. As such, the ability to

facilitate minimally invasive surgery has not been studied as a primary endpoint and few data are available to analyze. In the phase II trial of pre-surgical axitinib for patients with T2–T3b tumors, 5 out of 24 (21%) had minimally invasive surgery following treatment [50]. If reliable and dramatic responses are demonstrated with newer systemic agents, this approach may be studied further as a method to decease perioperative morbidity.

Safety of Pre-surgical Targeted Therapy

Since many targeted therapies also inhibit pathways that are involved in wound healing, the safety of pre-surgical therapy remains a concern. An early clinical trial evaluating pre-surgical treatment with bevacizumab in patients with colorectal cancer reported higher complication rates with pre-surgical treatment [82]. Similarly, a pre-surgical study of bevacizumab in patients with metastatic RCC demonstrated higher rates of wound dehiscence and delayed wound healing compared to historical controls (20.9% versus 2%; $p < 0.001$) [43]. However, data with tyrosine kinase inhibitors appears to be more favorable. For example, patients treated with sorafenib have not shown associated complications with delayed wound healing, dehiscence, or excessive bleeding [83]. Likewise, a pre-surgical clinical trial with axitinib reported only one patient (4.2%) with a superficial wound healing complication [50]. In a study of 173 patients with metastatic RCC comparing pre-surgical systemic treatment to upfront cytoreductive surgery, 90 days complication rate, multiple complications, and wound complications were higher, but major complication rates (≥Clavien 3) were not increased with pre-surgical therapy [84]. Many of the patients with wound complications were treated with pre-surgical bevacizumab, which has a significantly longer half- life (17 days) as compared to sunitinib (4 days) [85] and pazopanib (31 h) [86]. Current recommendations are to discontinue bevacizumab for 30 days prior to surgery and not restart for at least 30 days postoperatively [87].

Duration of Therapy

The optimal duration of pre-surgical treatment is unknown but depends on several factors including the rationale for treatment and strength of response to an individual agent. In order to shrink tumors to facilitate surgery, pre-surgical treatment should maximize responses in the shortest possible time. Tumors that respond to pre-surgical therapy undergo extensive vascular remodeling that decreases tumor size, which generally has been observed within the first two cycles of therapy [88]. The median duration of therapy in contemporary studies of sunitinib was two cycles, with each cycle including 4 weeks of therapy with 50 mg daily followed by 2 weeks off [89, 90]. The duration of sorafenib therapy ranged from 33 to 96 days, and for

pazopanib it was from 8 to 14 weeks [90]. Therefore, a short course of therapy with radiological monitoring of tumor response is critical for timing of surgery following pre-surgical therapy. After treatment, patients should be scheduled for surgery as soon as possible because the risk of rapid tumor regrowth and progression after stopping therapy [91, 92].

Conclusions

Although there are no large randomized clinical trials demonstrating benefit of pre-surgical therapy for patients with RCC, there is a potential for benefit in well-selected patients treated with targeted agents. Large complex tumors that are judged to be unresectable may shrink during pre-surgical treatment and facilitate surgery. Additionally, response to pre-surgical therapy may facilitate nephron-sparing surgery or conversion from an open to minimally invasive surgical approach. Likewise, patients with metastatic RCC may benefit from upfront systemic therapy as a litmus test to judge the potential benefit from cytoreductive nephrectomy. Most studies with pre-surgical targeted agents have demonstrated the safety of this approach, with slightly increased risk for wound complications. However, dramatic responses are uncommon, and the possibility of progression while on therapy must be considered. Clinical use of pre-surgical therapy should continue to be investigated especially in RCC patients who have the strongest rationale for treatment including unresectable primary tumors and metastatic disease. Ultimately, additional clinical trials are needed in this arena.

References

1. Pierorazio PM, Johnson MH, Patel HD, Sozio SM, Sharma R, Iyoha E, et al. Management of renal masses and localized renal cancer: systematic review and meta-analysis. J Urol. 2016;196(4):989–99.
2. Berg WT, Tomaszewski JJ, Yang H, Corcoran A. Complications of renal surgery. Urol Clin North Am. 2017;44(2):275–88.
3. Psutka SP, Leibovich BC. Management of inferior vena cava tumor thrombus in locally advanced renal cell carcinoma. Ther Adv Urol. 2015;7(4):216–29.
4. Blute ML, Leibovich BC, Lohse CM, Cheville JC, Zincke H. The Mayo Clinic experience with surgical management, complications and outcome for patients with renal cell carcinoma and venous tumour thrombus. BJU Int. 2004;94(1):33–41.
5. Zargar-Shoshtari K, Sharma P, Espiritu P, Kurian T, Pow-Sang JM, Mangar D, et al. Caval tumor thrombus volume influences outcomes in renal cell carcinoma with venous extension. Urol Oncol. 2015;33(3):112.e23–9.
6. Abel EJ, Wood CG, Eickstaedt N, Fang JE, Kenney P, Bagrodia A, et al. Preoperative pulmonary embolism does not predict poor postoperative outcomes in patients with renal cell carcinoma and venous thrombus. J Urol. 2013;190(2):452–7.
7. Abel EJ, Thompson RH, Margulis V, Heckman JE, Merril MM, Darwish OM, et al. Perioperative outcomes following surgical resection of renal cell carcinoma with inferior vena

cava thrombus extending above the hepatic veins: a contemporary multicenter experience. Eur Urol. 2014;66(3):584–92.
8. Borregales LD, Kim DY, Staller AL, Qiao W, Thomas AZ, Adibi M, et al. Prognosticators and outcomes of patients with renal cell carcinoma and adjacent organ invasion treated with radical nephrectomy. Urol Oncol. 2016;34(5):237.e19–26.
9. Kassouf W, Sanchez-Ortiz R, Tamboli P, Jonasch E, Merchant MM, Spiess PE, et al. Cytoreductive nephrectomy for T4NxM1 renal cell carcinoma: the M.D. Anderson Cancer Center experience. Urology. 2007;69(5):835–8.
10. Karellas ME, Jang TL, Kagiwada MA, Kinnaman MD, Jarnagin WR, Russo P. Advanced-stage renal cell carcinoma treated by radical nephrectomy and adjacent organ or structure resection. BJU Int. 2009;103(2):160–4.
11. Margulis V, Sanchez-Ortiz RF, Tamboli P, Cohen DD, Swanson DA, Wood CG. Renal cell carcinoma clinically involving adjacent organs: experience with aggressive surgical management. Cancer. 2007;109(10):2025–30.
12. Thorstenson A, Bergman M, Scherman-Plogell AH, Hosseinnia S, Ljungberg B, Adolfsson J, et al. Tumour characteristics and surgical treatment of renal cell carcinoma in Sweden 2005-2010: a population-based study from the national Swedish kidney cancer register. Scand J Urol. 2014;48(3):231–8.
13. Abel EJ, Wood CG. Cytoreductive nephrectomy for metastatic RCC in the era of targeted therapy. Nat Rev Urol. 2009;6(7):375–83.
14. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27(34):5794–9.
15. Yagoda A, Petrylak D, Thompson S. Cytotoxic chemotherapy for advanced renal cell carcinoma. Urol Clin North Am. 1993;20(2):303–21.
16. Frydenberg M, Gunderson L, Hahn G, Fieck J, Zincke H. Preoperative external beam radiotherapy followed by cytoreductive surgery and intraoperative radiotherapy for locally advanced primary or recurrent renal malignancies. J Urol. 1994;152(1):15–21.
17. Parashar B, Patro KC, Smith M, Arora S, Nori D, Wernicke AG. Role of radiation therapy for renal tumors. Semin Interv Radiol. 2014;31(1):86–90.
18. Juusela H, Malmio K, Alfthan O, Oravisto KJ. Preoperative irradiation in the treatment of renal adenocarcinoma. Scand J Urol Nephrol. 1977;11(3):277–81.
19. van der Werf-Messing B. Proceedings: carcinoma of the kidney. Cancer. 1973;32(5):1056–61.
20. van der Werf-Messing B, van der Heul RO, Ledeboer RC. Renal adenocarcinoma; a prospective therapy study in Rotterdam. Ned Tijdschr Geneeskd. 1980;124(31):1298–303.
21. Spencer WF, Linehan WM, Walther MM, Haas GP, Lotze MT, Topalian SL, et al. Immunotherapy with interleukin-2 and alpha-interferon in patients with metastatic renal cell cancer with in situ primary cancers: a pilot study. J Urol. 1992;147(1):24–30.
22. Wagner JR, Walther MM, Linehan WM, White DE, Rosenberg SA, Yang JC. Interleukin-2 based immunotherapy for metastatic renal cell carcinoma with the kidney in place. J Urol. 1999;162(1):43–5.
23. Robertson CN, Linehan WM, Pass HI, Gomella LG, Haas GP, Berman A, et al. Preparative cytoreductive surgery in patients with metastatic renal cell carcinoma treated with adoptive immunotherapy with interleukin-2 or interleukin-2 plus lymphokine activated killer cells. J Urol. 1990;144(3):614–7.
24. Baird AD, Woolfenden KA, Desmond AD, Fordham MV, Parsons KF. Outcome and survival with nonsurgical management of renal cell carcinoma. BJU Int. 2003;91(7):600–2.
25. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001;345(23):1655–9.

26. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet. 2001;358(9286):966–70.
27. Bakke A, Gothlin JH, Haukaas SA, Kalland T. Augmentation of natural killer cell activity after arterial embolization of renal carcinomas. Cancer Res. 1982;42(9):3880–3.
28. Nakano H, Nihira H, Toge T. Treatment of renal cancer patients by transcatheter embolization and its effects on lymphocyte proliferative responses. J Urol. 1983;130(1):24–7.
29. Schwartz MJ, Smith EB, Trost DW, Vaughan ED Jr. Renal artery embolization: clinical indications and experience from over 100 cases. BJU Int. 2007;99(4):881–6.
30. Zielinski H, Szmigielski S, Petrovich Z. Comparison of preoperative embolization followed by radical nephrectomy with radical nephrectomy alone for renal cell carcinoma. Am J Clin Oncol. 2000;23(1):6–12.
31. Subramanian VS, Stephenson AJ, Goldfarb DA, Fergany AF, Novick AC, Krishnamurthi V. Utility of preoperative renal artery embolization for management of renal tumors with inferior vena caval thrombi. Urology. 2009;74(1):154–9.
32. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356(2):125–34.
33. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2): 115–24.
34. Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet. 2007;370(9605):2103–11.
35. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061–8.
36. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011;378(9807):1931–9.
37. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2016;17(7):917–27.
38. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356(22):2271–81.
39. Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008;372(9637):449–56.
40. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373(19):1803–13.
41. van der Veldt AA, Meijerink MR, van den Eertwegh AJ, Bex A, de Gast G, Haanen JB, et al. Sunitinib for treatment of advanced renal cell cancer: primary tumor response. Clin Cancer Res. 2008;14(8):2431–6.
42. Abel EJ, Culp SH, Tannir NM, Matin SF, Tamboli P, Jonasch E, et al. Primary tumor response to targeted agents in patients with metastatic renal cell carcinoma. Eur Urol. 2011;59(1): 10–5.
43. Jonasch E, Wood CG, Matin SF, Tu SM, Pagliaro LC, Corn PG, et al. Phase II presurgical feasibility study of bevacizumab in untreated patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(25):4076–81.
44. Cowey CL, Amin C, Pruthi RS, Wallen EM, Nielsen ME, Grigson G, et al. Neoadjuvant clinical trial with sorafenib for patients with stage II or higher renal cell carcinoma. J Clin Oncol. 2010;28(9):1502–7.
45. Silberstein JL, Millard F, Mehrazin R, Kopp R, Bazzi W, DiBlasio CJ, et al. Feasibility and efficacy of neoadjuvant sunitinib before nephron-sparing surgery. BJU Int. 2010;106(9):1270–6.

46. Hellenthal NJ, Underwood W, Penetrante R, Litwin A, Zhang S, Wilding GE, et al. Prospective clinical trial of preoperative sunitinib in patients with renal cell carcinoma. J Urol. 2010;184(3):859–64.
47. Powles T, Kayani I, Blank C, Chowdhury S, Horenblas S, Peters J, et al. The safety and efficacy of sunitinib before planned nephrectomy in metastatic clear cell renal cancer. Ann Oncol. 2011;22(5):1041–7.
48. Rini BI, Garcia J, Elson P, Wood L, Shah S, Stephenson A, et al. The effect of sunitinib on primary renal cell carcinoma and facilitation of subsequent surgery. J Urol. 2012;187(5):1548–54.
49. Rini BI, Plimack ER, Takagi T, Elson P, Wood LS, Dreicer R, et al. A phase II study of pazopanib in patients with localized renal cell carcinoma to optimize preservation of renal parenchyma. J Urol. 2015;194(2):297–303.
50. Karam JA, Devine CE, Urbauer DL, Lozano M, Maity T, Ahrar K, et al. Phase 2 trial of neoadjuvant axitinib in patients with locally advanced nonmetastatic clear cell renal cell carcinoma. Eur Urol. 2014;66(5):874–80.
51. Powles T, Sarwar N, Stockdale A, Sarker SJ, Boleti E, Protheroe A, et al. Safety and efficacy of pazopanib therapy prior to planned nephrectomy in metastatic clear cell renal cancer. JAMA Oncol. 2016;2(10):1303–9.
52. Margulis V, Wood CG. Cytoreductive nephrectomy in the era of targeted molecular agents: is it time to consider presurgical systemic therapy? Eur Urol. 2008;54(3):489–92.
53. Thomas AA, Rini BI, Stephenson AJ, Garcia JA, Fergany A, Krishnamurthi V, et al. Surgical resection of renal cell carcinoma after targeted therapy. J Urol. 2009;182(3):881–6.
54. Bex A, van der Veldt AA, Blank C, van den Eertwegh AJ, Boven E, Horenblas S, et al. Neoadjuvant sunitinib for surgically complex advanced renal cell cancer of doubtful resectability: initial experience with downsizing to reconsider cytoreductive surgery. World J Urol. 2009;27(4):533–9.
55. Thomas AA, Rini BI, Lane BR, Garcia J, Dreicer R, Klein EA, et al. Response of the primary tumor to neoadjuvant sunitinib in patients with advanced renal cell carcinoma. J Urol. 2009;181(2):518–23.
56. Kim SH, Seo SI, Lee HM, Choi HY, Jeon SH, Lee HL, et al. A prospective multicenter trial of the efficacy and tolerability of neoadjuvant sunitinib for inoperable metastatic renal cell carcinoma. J Korean Med Sci. 2016;31(12):1983–8.
57. Nguyen HG, Tilki D, Dall'Era MA, Durbin-Johnson B, Carballido JA, Chandrasekar T, et al. Cardiopulmonary bypass has no significant impact on survival in patients undergoing nephrectomy and level III-IV inferior vena cava thrombectomy: multi-institutional analysis. J Urol. 2015;194(2):304–8.
58. Shuch B, Riggs SB, LaRochelle JC, Kabbinavar FF, Avakian R, Pantuck AJ, et al. Neoadjuvant targeted therapy and advanced kidney cancer: observations and implications for a new treatment paradigm. BJU Int. 2008;102(6):692–6.
59. Di Silverio F, Sciarra A, Parente U, Andrea A, Von Heland M, Panebianco V, et al. Neoadjuvant therapy with sorafenib in advanced renal cell carcinoma with vena cava extension submitted to radical nephrectomy. Urol Int. 2008;80(4):451–3.
60. Harshman LC, Srinivas S, Kamaya A, Chung BI. Laparoscopic radical nephrectomy after shrinkage of a caval tumor thrombus with sunitinib. Nat Rev Urol. 2009;6(6):338–43.
61. Karakiewicz PI, Suardi N, Jeldres C, Audet P, Ghosn P, Patard JJ, et al. Neoadjuvant sutent induction therapy may effectively down-stage renal cell carcinoma atrial thrombi. Eur Urol. 2008;53(4):845–8.
62. Robert G, Gabbay G, Bram R, Wallerand H, Deminiere C, Cornelis F, et al. Case study of the month. Complete histologic remission after sunitinib neoadjuvant therapy in T3b renal cell carcinoma. Eur Urol. 2009;55(6):1477–80.
63. Bigot P, Fardoun T, Bernhard JC, Xylinas E, Berger J, Roupret M, et al. Neoadjuvant targeted molecular therapies in patients undergoing nephrectomy and inferior vena cava thrombectomy: is it useful? World J Urol. 2014;32(1):109–14.

64. Cost NG, Delacroix SE Jr, Sleeper JP, Smith PJ, Youssef RF, Chapin BF, et al. The impact of targeted molecular therapies on the level of renal cell carcinoma vena caval tumor thrombus. Eur Urol. 2011;59(6):912–8.
65. Kwon T, Lee JL, Kim JK, You D, Jeong IG, Song C, et al. The Choi response criteria for inferior vena cava tumor thrombus in renal cell carcinoma treated with targeted therapy. J Cancer Res Clin Oncol. 2014;140(10):1751–8.
66. Choi H, Charnsangavej C, Faria SC, Macapinlac HA, Burgess MA, Patel SR, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. J Clin Oncol. 2007;25(13):1753–9.
67. Bex A, Van der Veldt AA, Blank C, Meijerink MR, Boven E, Haanen JB. Progression of a caval vein thrombus in two patients with primary renal cell carcinoma on pretreatment with sunitinib. Acta Oncol. 2010;49(4):520–3.
68. Abel EJ, Spiess PE, Margulis V, Master VA, Mann M, Zargar-Shoshtari K, et al. Cytoreductive nephrectomy for renal cell carcinoma with venous tumor thrombus. J Urol. 2017;198(2):281–8.
69. Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 2013;14(2):141–8.
70. Hanna N, Sun M, Meyer CP, Nguyen PL, Pal SK, Chang SL, et al. Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: a National Cancer Data Base Study. J Clin Oncol. 2016;34(27):3267–75.
71. Fallick ML, McDermott DF, LaRock D, Long JP, Atkins MB. Nephrectomy before interleukin-2 therapy for patients with metastatic renal cell carcinoma. J Urol. 1997;158(5):1695.
72. Tsao CK, Small AC, Moshier EL, Gartrell BA, Wisnivesky JP, Sonpavde G, et al. Trends in the use of cytoreductive nephrectomy in the United States. Clin Genitourin Cancer. 2012;10(3):159–63.
73. Minnillo BJ, Zhu H, Maurice MJ, Abouassaly R. Trends in cytoreductive nephrectomy in the eras of immuno and targeted therapy. J Clin Oncol. 2014;32(4):472.
74. Culp SH, Tannir NM, Abel EJ, Margulis V, Tamboli P, Matin SF, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? Cancer. 2010;116(14):3378–88.
75. Abel EJ, Culp SH, Tannir NM, Tamboli P, Matin SF, Wood CG. Early primary tumor size reduction is an independent predictor of improved overall survival in metastatic renal cell carcinoma patients treated with sunitinib. Eur Urol. 2011;60(6):1273–9.
76. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol. 2002;20(1):289–96.
77. Heng DY, Mackenzie MJ, Vaishampayan UN, Bjarnason GA, Knox JJ, Tan MH, et al. Primary anti-vascular endothelial growth factor (VEGF)-refractory metastatic renal cell carcinoma: clinical characteristics, risk factors, and subsequent therapy. Ann Oncol. 2012;23(6):1549–55.
78. Campbell S, Uzzo RG, Allaf ME, Bass EB, Cadeddu JA, Chang A, et al. Renal mass and localized renal cancer: AUA guideline. J Urol. 2017;198(3):520–9.
79. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol. 2015;67(5):913–24.
80. Karam JA, Devine CE, Fellman BM, Urbauer DL, Abel EJ, Allaf ME, et al. Variability of interobserver agreement on feasibility of partial nephrectomy before and after neoadjuvant axitinib for locally advanced renal cell carcinoma (RCC): independent analysis from a phase II trial. BJU Int. 2016;117(4):629–35.
81. Best SL, Blute M Jr, Lane B, Abel EJ. Surgical treatment of 4-10 cm renal-cell carcinoma: a survey of the lions and gazelles. J Endourol. 2017;31(S1):S43–S7.

82. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol. 2003;21(1):60–5.
83. Zhang Y, Li Y, Deng J, Ji Z, Yu H, Li H. Sorafenib neoadjuvant therapy in the treatment of high risk renal cell carcinoma. PLoS One. 2015;10(2):e0115896.
84. Chapin BF, Delacroix SE, Culp SH, Gonzalez GMN, Tannir NM, Jonasch E, et al. Safety of presurgical targeted therapy in the setting of metastatic renal cell carcinoma. Eur Urol. 2011;60(5):964–71.
85. Bhat S. Role of surgery in advanced/metastatic renal cell carcinoma. Indian J Urol. 2010;26(2):167–76.
86. Hurwitz HI, Dowlati A, Saini S, Savage S, Suttle AB, Gibson DM, et al. Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res. 2009;15(12):4220–7.
87. Abel EJ, Matin SF. Cytoreductive nephrectomy in the age of systemic therapy, AUA update series 2015, vol. 24. Linthicum: American Urological Association; 2015.
88. Flaherty KT, Rosen MA, Heitjan DF, Gallagher ML, Schwartz B, Schnall MD, et al. Pilot study of DCE-MRI to predict progression-free survival with sorafenib therapy in renal cell carcinoma. Cancer Biol Ther. 2008;7(4):496–501.
89. Kondo T, Hashimoto Y, Kobayashi H, Iizuka J, Nishikawa T, Nakano M, et al. Presurgical targeted therapy with tyrosine kinase inhibitors for advanced renal cell carcinoma: clinical results and histopathological therapeutic effects. Jpn J Clin Oncol. 2010;40(12):1173–9.
90. Schrader AJ, Steffens S, Schnoeller TJ, Schrader M, Kuczyk MA. Neoadjuvant therapy of renal cell carcinoma: a novel treatment option in the era of targeted therapy? Int J Urol. 2012;19(10):903–7.
91. Johannsen M, Florcken A, Bex A, Roigas J, Cosentino M, Ficarra V, et al. Can tyrosine kinase inhibitors be discontinued in patients with metastatic renal cell carcinoma and a complete response to treatment? A multicentre, retrospective analysis. Eur Urol. 2009;55(6):1430–8.
92. Vasudev NS, Reynolds AR. Anti-angiogenic therapy for cancer: current progress, unresolved questions and future directions. Angiogenesis. 2014;17(3):471–94.
93. Lane BR, Derweesh IH, Kim HL, O'Malley R, Klink J, Ercole CE, et al. Presurgical sunitinib reduces tumor size and may facilitate partial nephrectomy in patients with renal cell carcinoma. Urologic Oncology. 2015;33(3):112.e15–21.

Chapter 15
Adjuvant Therapy for High-Risk Renal Cell Carcinoma

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Introduction

Renal cell carcinoma (RCC) is the 13th most common malignancy worldwide, contributing to more than 129,000 annual deaths [1, 2]. At initial presentation, 75% of patients will be diagnosed with localized disease [3]. While stage I tumors are largely curable with surgical resection alone, up to 40% of patients with stage II–III RCC who undergo surgical extirpation will progress to metastatic disease [4, 5]. Additionally, the 5-year survival rate of patients with locoregional lymph node involvement at the time of nephrectomy is quite poor at <30% [6, 7]. A number of pre- and postoperative nomograms have been developed to identify individuals with localized or locally advanced RCC who are at high risk for disease recurrence [7–9].

In an effort to improve the outcomes of patients with RCC, there has been considerable interest in exploring the use of postoperative adjuvant therapies in patients with high-risk localized or locally advanced RCC. In this chapter, we summarize the history and development of adjuvant therapies for RCC. These therapies have been categorized by subtype of intervention.

Cytokines and Other Historic Forms of Immunotherapy

The cytokines interleukin-2 (IL-2) and interferon alpha (IFN-α) have long been used for the treatment of metastatic RCC, with 5–10% of appropriately selected patients showing a complete response to therapy [10]. However, these agents come

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with significant side effects including capillary leak and cytokine release syndromes [11]. To date, trials evaluating IL-2 and IFN-α in the adjuvant setting have not showed any survival benefit [12–14]. More specifically, a study by Pizzocaro et al. that randomized 247 patients with high-risk localized or locally advanced RCC to adjuvant IFN-α versus observation found no difference in disease-free survival (DFS) or overall survival (OS) [12]. Additionally, a study by the Eastern Cooperative Oncology Group that randomized 283 patients to IFN-α versus observation failed to meet its primary end point of improving 5-year OS [13]. Looking to improve upon outcomes of trials with IFN-α monotherapy, the German Cooperative Renal Carcinoma Chemo-immunotherapy Group initiated a randomized trial to evaluate the efficacy of the combination of IL-2, IFN-α, and 5-fluorouracil versus observation [14]. In this study, the investigators found no improvement in DFS with the combination regiment and similar to the Eastern Cooperative Oncology Group study [13] found that OS was favored in controls. In light of the significant side effects associated with cytokine therapy, as well as the lack of oncologic benefit observed across trials, IL-2 and IFN-α have been abandoned as adjuvant therapies for patients with RCC.

Other immune-based approaches have also been studied in the adjuvant setting. For example, Galligioni et al. randomized 120 patients with stage I to III RCC to receive autologous irradiated tumor cells mixed with bacillus Calmette-Guerin (BCG) following surgical resection [15]. The authors found that after a median follow-up of 61 months, 5-year DFS was 63% for the treated patients and 72% for control with no statistical difference in 5-year OS (69% and 78%, respectively). Another study by Jocham et al. explored the efficacy of Reniale, a autologous vaccine of tumor cells incubated with IFN-γ [16]. In this study, 558 patients with pT2-3b N0-3 M0 tumors were randomized to either vaccine or standard of care treatment. Initial findings were promising with 5-year progression-free survival of 77.4% in the vaccine group and 67.8% in the control ($p = 0.02$). However, there were several notable concerns regarding the trial including a non-blinded design, large post-randomization dropout, and an unbalanced distribution of patient with non-clear cell histology. A follow-up report by the same group in 2006 failed to show any OS benefit [17]. Another autologous vaccine known as Vitespen has been studied as an adjuvant treatment for RCC [18]. In a phase 3 randomized trial, 728 patients received either adjuvant Vitespen, comprised of the tumor-derived heat shock protein gp96 peptide complex, or observation only. At a median follow-up of 1.9 years, the vaccine showed no difference in the recurrence rate between the groups. A meta-analysis by Scherr et al. considered all three adjuvant vaccine-based therapies and did not find any improvement in DFS [19].

One final study worthy of mention is the recently reported ARISER trial [20]. In this study investigators explored the efficacy of the monoclonal antibody girentuximab in patients with high-risk localized or node-positive RCC following surgical resection. Unique to this drug is the mechanism of cell kill, which is based on antibody-dependent cellular cytotoxicity against cells expressing the RCC marker carbonic anhydrase IX. In this phase 3 trial of 864 patients stratified by risk groups, the authors found that there was no clear benefit of adjuvant girentuximab versus pla-

cebo for DFS (HR 0.97 85% CI 0.79–1.18) or OS (HR 0.99 95% CI 0.74–1.32) [20]. It should be noted that further examination of the data showed that patients with higher CAIX expression had an improvement in DFS of 21 months; however, this observation did not reach the conventional level of statistical significance (HR 0.75 95% CI 0.55–1.04 $p = 0.08$). This detail, though, may become important especially as future biomarkers and molecular criteria become a focal point for patient selection.

In summary, conventional immunotherapeutic approaches including IL-2, IFN-α, cancer vaccines, and monoclonal antibodies have been largely unsuccessful as forms of adjuvant therapy for RCC.

Hormonal and Radiation Therapy

Studies have shown significant expression of the estrogen and androgen receptors in RCC tissue specimens [21]. This has prompted some to explore the use of hormone-directed therapies for the treatment of RCC. This approach, however, has been unsuccessful in the adjuvant setting. More specifically, in a prospective randomized multicenter study comparing adjuvant medroxyprogesterone acetate as treatment for 1 year versus observation alone in 136 patients following radical nephrectomy, the authors found no significant difference in relapse rate after a median follow-up of 5 years [22]. Additionally, the authors observed an unacceptably high complication rate with this approach.

Radiotherapy plays an important role in the palliation of patients with locally advanced or metastatic RCC, specifically for treating hematuria and painful bony metastases [23]. However, the use of radiation for the primary treatment of RCC is not routinely performed due to the radioresistant nature of this malignancy when treated with conventional fractionation [24]. Despite this, radiation therapy has been evaluated in the adjuvant setting for treatment of RCC. In one prospective randomized study, 72 patients underwent either observation or treatment with 50 Gy in 20 fractions to the kidney and bilateral lymph nodes [25]. The authors observed no difference in the rate of cancer relapse; however, they found a significant rate of adverse events, with radiation-related complications resulting in the deaths of 19% of treated patients.

Modern Vascular-Targeted Therapies

The role of vascular-targeted therapies in RCC traces back to the discovery of the von Hippel-Lindau tumor suppressor gene (*VHL*) – a gene that is near universally lost in cases of clear cell RCC – and its integral role in the pathophysiology of tumor angiogenesis [26]. A number of vascular-targeted therapies have since been approved for the treatment of metastatic RCC. First-line agents include the tyrosine

kinase inhibitors (TKIs), which bind to and inhibit the vascular endothelial growth factor (VEGF) receptor and platelet-derived growth factor receptors, thereby reducing the tumor-driven angiogenesis needed for growth. Likewise, inhibitors of mammalian target of rapamycin, a related but different class of drug, have showed efficacy in the second-line setting [27].

This newer class of targeted agents has quickly supplanted cytokines as the mainstay of treatment for patients with metastatic RCC. As such, these agents have been explored in the adjuvant setting for patients with high-risk localized RCC. The first study to be published evaluating vascular-targeted therapies in this context was the ASSURE trial [28]. In brief, ASSURE randomized 1,943 patients with intermediate- to high-risk localized RCC defined by the Integrated Staging System [8] in a 1:1:1 fashion to adjuvant sunitinib, sorafenib, or placebo. This study showed no differences in terms of DFS or OS for either treatment arm. Of note, the authors did observe a high rate of treatment discontinuation (26%) due to excessive toxicity, despite allowing for treatment dose reductions.

A second study evaluating adjuvant TKI therapy for patients with high-risk RCC was the S-TRAC trial [29]. In this study 615 patients with intermediate- to high-risk RCC were randomized 1:1 to adjuvant sunitinib or placebo. Unlike ASSURE, this trial showed a significant improvement in DFS in the sunitinib arm (median 6.8 years versus 5.6 years, HR 0.76 95% CI 0.59–0.98, $p = 0.03$). The authors did note, however, that these benefits were at the cost of a higher rate of toxic events from the TKI.

The discordant findings of the ASSURE and S-TRAC trials have garnered considerable attention with many pointing to differences in trial design and conduct to explain the differences in findings [30, 31]. For example, one frequently cited area of discrepancy between the two trials lies in the baseline characteristics of enrolled patients. More specifically, S-TRAC enrolled patients with a minimum of pT3a disease, whereas ASSURE allowed for patients with pT1b tumors as well as high-grade pT1a RCC. Additionally, the S-TRAC study only enrolled patients with clear cell RCC, while ASSURE had no restriction based on tumor histology. This difference is of considerable importance because non-clear cell RCCs are not typically driven by derangements in the VHL gene and therefore are less responsive to therapies targeting angiogenesis [32]. Likewise, the two studies employed different dose reduction strategies, with the S-TRAC trail allowing reductions only to 37.5 mg/day for sunitinib versus a lower 25 mg/day dose reduction in the ASSURE trial. With these differences in mind, the authors of the ASSURE trial performed a secondary analysis of their study with a subset of patients that more closely approximated the population enrolled in S-TRAC [33]. This analysis, which was restricted to patients with clear cell histology and pT3-4, or node-positive disease, found no improvement in DFS or OS. Although this study does provide a better comparison to the S-TRAC results, it was not powered to detect differences in this subgroup and violates the tenants of randomized trial design and so must be interpreted with caution.

In addition to ASSURE and S-TRAC, there are other ongoing trials investigating targeted therapies in patients with RCC in the adjuvant therapy. These include the

SORCE trial (sorafenib vs. placebo, ClinicalTrials.gov identifier NCT00492258), the ATLAS trial (axitinib vs. placebo, ClinicalTrials.gov identifier NCT01599754), and the EVEREST trial (everolimus vs. placebo, Clinical Trials.gov identifier NCT01120249). Notably, another trial known as PROTECT (ClinicalTrials.gov identifier NCT01235962) which evaluated adjuvant pazopanib has been completed and reported in abstract form to not meet its primary end point [34].

Checkpoint Inhibitor Therapy

Perhaps the most exciting class of cancer therapeutic agents are drugs targeting immune checkpoint molecules such as the programmed cell death 1 (PD-1) receptor and its ligand PDL-1 [35, 36]. For patients with metastatic RCC, the monoclonal antibody targeting PDL-1 known as nivolumab was recently approved in the second-line setting. In a randomized trial this drug was compared to everolimus and demonstrated an improved OS by 5.4 months with significantly fewer side effects [36]. Naturally, checkpoint inhibitors are being evaluated as adjuvant therapies for high-risk localized RCC. While no trial in the adjuvant setting has been completed with these agents, two are ongoing and are worthy of mention: the PROSPER trial evaluating nivolumab (ClinicalTrials.gov identifier NCT03055013) and the IMmotion010 trial evaluating atezolizumab (an antibody against PDL-1; ClinicalTrials.gov identifier NCT03024996). Simply beyond receiving different drugs targeting the PD-1-PDL-1 axis, it is important to highlight several important factors regarding study designs between these two trials. More specifically, in the PROSPER trial patients will receive both neoadjuvant and adjuvant nivolumab, whereas INmotion010 is purely an adjuvant design. The authors of PROSPER argue that checkpoint inhibitors require high level of tumor antigen to be present before surgery in order to prime the immune system and therefore a neoadjuvant administration of drug is required to see an effect on the primary outcome of OS. We look forward to the results of these novel trials that will undoubtedly provide crucial information regarding the efficacy of checkpoint inhibitors in the perioperative setting for patients with high-risk localized RCC.

Conclusions

Despite a great clinical need for effective adjuvant therapies for patients with high-risk localized RCC, there is currently a paucity of data to support the routine use of available agents such as cytokines and TKIs following surgical resection. Although the S-TRAC trial does suggest potential benefit for the use of adjuvant sunitinib in patients with high-risk tumors, conflicting results from the ASSURE and PROTECT trials have called the use of TKIs in the adjuvant setting into question. Ongoing trials evaluating other targeted agents may provide further clarity on the role of

targeted agents in the adjuvant setting. Additionally, trials evaluating checkpoint inhibitors are of particularly promising given the activity of nivolumab in the metastatic setting.

References

1. Ljungberg B, Campbell SC, Choi HY, Jacqmin D, Lee JE, Weikert S, et al. The epidemiology of renal cell carcinoma. Eur Urol. 2011;60:615–21.
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods, and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):359–86.
3. Kane CJ, Mallin K, Rithcey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. Cancer. 2008;113:78–83.
4. Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radial or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin North Am. 2003;30:843–52.
5. Eggener SE, Yossepowitch O, Pettus JA, Snyder ME, Motzer RJ, Russo P. Renal cell carcinoma recurrence after nephrectomy for localized disease: predicting survival from time of recurrence. J Clin Oncol. 2006;24(19):3101–6.
6. Pantuck AJ, Zisman A, Dorey F, Caho DH, Han KR, Said J. Renal cell carcinoma with retroperitoneal lymph nodes: role of lymph node dissection. J Urol. 2003;169(9):2076–83.
7. Terrone C, Cracco C, Porpiglia F, Bollito E, Scoffone C, Poggio M. Reassessing the current TNM lymph node staging for renal cell carcinoma. Eur Urol. 2006;49:324–31.
8. Sorbellini M, Kattan MW, Snyder ME, Reuter V, Motzer R, Goetzl M, et al. A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. J Urol. 2005;173:48–51.
9. Parker WP, Cheville JC, Frank I, Zaid HB, Lohse CM, Boorjian SA, et al. Application of the stage, size, grade, and necrosis (SSIGN) score for clear cell renal cell carcinoma in contemporary patients. Eur Urol. 2017;71(4):665–73.
10. Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. Cancer J Sci Am. 2000;6:55–7.
11. Yang JC, Sherry RM, Steinberg SM, Topalian SL, Schwartzentruber DJ, Hwu P, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol. 2003;21(16):3127–32.
12. Pizzocaro G, Piva L, Colavita M, Ferri S, Artusi R, Boracchi P, et al. Interferon adjuvant to radical nephrectomy in Robson stages II and III renal cell carcinoma: a multicentric randomized study. J Clin Oncol. 2001;19(2):425–31.
13. Messing EM, Manola J, Wilding G, Propert K, Fleischmann J, Crawford ED, et al. Phase III study of interferon alfa-NL as adjuvant treatment for resectable renal cell carcinoma. J Clin Oncol. 2003;21(7):1214–22.
14. Atzpodien J, Schmitt E, Gertenbach U, Fornara P, Heynemann H, Maskow A, et al. Adjuvant treatment with interluekin2 and interferon alpha based chemoimmunotherapy in renal cell carcinoma post tumor nephrectomy: results of a prospectively randomized trial of the German Cooperative Renal Cell Carcinoma Chemoimmunotherapy Group. Br J Cancer. 2005;92(5):843–6.
15. Galligioni E, Quaia M, Merlo A, Carbone A, Spada A, Farvaro D, et al. Adjuvant immunotherapy treatment of renal cell carcinoma patients with autologous tumor cells and bacillus Calmette-Guerin: a five-year result of a prospective randomized study. Cancer. 1996;77(12):2560–6.
16. Jocham D, Richter A, Hoffmann L, Iwig K, Fahlenkamp D, Zakrewski G, et al. Adjuvant autologous renal tumor cell vaccine and risk of tumor progression in patients with renal

cell carcinoma after radial nephrectomy: phase III, randomized controlled trial. Lancet. 2004;363(9409):594–9.
17. Van Poppel H, Joniau S, Van Gool SW. Vaccine therapy in patients with renal cell carcinoma. Eur Urol. 2009;55:1333–44.
18. Wood C, Srivastava P, Bukowski R, Lacombe L, Gorelov AI, Gorelov S, et al. An adjuvant autologous therapeutic vaccine (HSPPC-96; Vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicenter, open-label, randomized phase III trial. Lancet. 2008;372(9633):145–54.
19. Scherr AJ, Lima JP, Sasse EC, Lima CS, Sasse AD. Adjuvant therapy for locally advanced renal cell cancer: a systematic review with meta-analysis. BMC Cancer. 2011;11(115):1–7.
20. Chamie K, Donin NM, Klopfer P, Bevan P, Fall B, Wilhelm O, et al. Adjuvant weekly girentuximab following nephrectomy for high-risk renal cell carcinoma: the ARISER randomized clinical trial. JAMA Oncol. 2017;3(7):913–20.
21. Karr JP, Pontes JP, Schneider S, Sandberg JP, Murphy JP. Clinical aspect of steroid hormone receptors in human renal cell carcinoma. J Surg Oncol. 1983;23(2):117–24.
22. Pizzocaro G, Piva L, Di Fronzo G, Giongo A, Cozzoli A, Dormia E, et al. Adjuvant medroxyprogesterone acetate to radical nephrectomy in renal cancer: 5 year prospective randomized study. J Urol. 1987;138(6):1379–81.
23. Fossa SD, Kjolseth I, Lund G. Radiotherapy of metastases from renal cancer. Eur Urol. 1982;138(6):1379–81.
24. Campbell SP, Song DY, Pierorazio PM, Allaf ME, Gorin MA. Stereotactic ablative radiotherapy for the treatment of clinically localized renal cell carcinoma. J Oncol. 2015;2015:547143.
25. Kjaer M, Iversen P, Hvidt V, Bruun W, Skaarup P, Hansen JB, et al. A randomized trial of postoperative radiotherapy versus observation in stage II and III renal adenocarcinoma, a study by the Copenhagen renal cancer study group. Scand J Urol Nephrol. 1987;21(4):285–9.
26. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. Lancet. 2009;373(9669):1119–32.
27. Buti S, Leonetti A, Dallatomasina A, Bersanelli M. Everolimus in the management of metastatic renal cell carcinoma: an evidence-based review of its place in therapy. Core Evid. 2016;11:23–36.
28. Haas NB, Manola J, Uzzo RG, Flaherty KT, Wood CG, Kane C, et al. Adjuvant Sunitinib or Sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): a double-blind, placebo-controlled, randomized, phase 3 trial. Lancet. 2016;387(10032):2008–16.
29. Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant Sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med. 2016;375(23):2246–54.
30. Porta C, Chiellino S. ASSURE vs. STRAC: conflicting results of adjuvant treatments for kidney cancer in the era of targeted agents and genomics. Ann Transl Med. 2016;4:1–5.
31. Gyawal B, Ando Y. Adjuvant sunitinib for high risk resected renal cell carcinoma: a meta-analysis of ASSURE and STRAC trials. Ann Oncol. 2017;28(4):898–9.
32. Bellmunt J, Dutcher J. Targeted therapies and the treatment of non-clear cell renal cell carcinoma. Ann Oncol. 2013;24(7):1730–40.
33. Haas NB, Manola J, Dutcher JP, Flaherty KT, Uzzo RG, Atkins MB, et al. Adjuvant treatment for high risk clear cell renal cancer: updated results of a high-risk subset of the ASSURE randomized trial. JAMA Oncol. 2017;3(9):1249–52.
34. Motzer RJ, Haas NB, Donskov F, Gross-Goupil M, Varlamov S, Kopyltsov E, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (PROTECT). J Clin Oncol. 2017;35(15_suppl):4507.
35. Alme AK, Karir BS, Faltas BM, Drake CG. Blocking immune checkpoints in prostate, kidney, and urothelial cancer: an overview. Urol Oncol. 2016;34(4):171–81.
36. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373:1803–13.

Chapter 16
Posttreatment Surveillance for Renal Cell Carcinoma

Karan Arora and Sarah P. Psutka

Introduction

Following the treatment of renal cell carcinoma (RCC), 20–38% of patients with localized tumors will experience disease progression [1, 2]. The most common sites of recurrence are pulmonary (52–64%) and osseous (9–15%), in addition to the pancreas (3–7%), liver (5–11%), distant lymph nodes (4–7%), brain (7%), adrenal gland (10%), and other sites (3–33%) [3]. Local recurrences to the renal fossa, ipsilateral adrenal gland, and regional lymph nodes are relatively rare, occurring in 0.8–3.6% of patients [4–7]. Prompt recognition of recurrence and progression of RCC is proposed to be of benefit in cases of local recurrence, as the most effective treatment appears to include locally directed therapy (i.e., cytoreductive surgery or ablation) which is more easily administered to less extensive foci of disease [4]. It is worth noting, however, that although early detection of asymptomatic metastatic RCC is thought to be worthwhile, the degree of clinical benefit remains to be determined.

Overall the 5-year recurrence-free survival for RCC ranges from 41.9% to 97.8% [3]. While the highest degree of risk for recurrence appears to be within the first 5 years following treatment, this risk varies substantially according to both disease characteristics such as stage and grade and treatment-related factors including surgical approach, utilization of nephron-sparing strategies, and surgical margin status [8, 9]. Additionally, time to recurrence varies between different anatomical

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locations. For example, the median time to pulmonary, osseous, and brain metastases for a pT2 RCC are 31, 24, and 11 months, respectively [8].

Posttreatment surveillance for recurrences is a cornerstone of the management of patients with RCC and is based on the premise that identification of both local and distant asymptomatic recurrences can permit the prompt initiation of treatment of relapses, with the goal of improving cancer-specific survival. Furthermore, posttreatment surveillance permits early detection of renal function deterioration and timely referral to nephrology as indicated. The rationale for surveillance for RCC relapse after initial definitive treatment is therefore to permit timely initiation of treatment, with the goal of extending survival.

In this chapter, we review published risk stratification tools for patients with RCC who have undergone surgical treatment. In addition, we summarize and compare contemporary posttreatment surveillance guidelines. Finally, we evaluate the limitations of contemporary guidelines as well as identify challenges in optimizing posttreatment surveillance.

Risk Prognostication: Assessing Risk of Relapse at the Time of Treatment

As noted, the risk of relapse following treatment varies considerably according to tumor biology, patient-specific, and treatment-related factors. Recommendations regarding the intensity of posttreatment surveillance vary according to risk prognostication, underscoring the importance of accurately characterizing a patient's risk for relapse at the time when a surveillance strategy is undertaken.

Tumor-specific Prognostic Factors

Tumor Size

Among patients with small renal masses (i.e., <4 cm in diameter), there is conflicting evidence regarding whether tumor size is associated with malignant versus benign histology [10, 11]. However, there is a strong association between increasing tumor size and risk of RCC recurrence. Among patients with localized RCC who have undergone extirpation, local recurrence-free survival and metastasis-free survival decreases significantly with each 1 cm in size of the tumor [12].

Tumor Stage

The American Joint Commission on Cancer tumor-node-metastasis (TNM) staging system is the universally accepted system utilized to describe RCC, incorporating tumor size as well as the extent of local infiltration and distant lymphatic and metastatic involvement to characterize the anatomic extent of the disease [13]. Validation

studies of earlier versions of the TNM system for kidney tumors [14, 15] have resulted in refinements of prior version, leading to the current iteration which includes a subclassification within T2 cancers based on a tumor size cutoff of 10 cm (T2a ≤ 10 cm and T2b > 10 cm), inclusion of both perirenal fat involvement and renal vein tumor thrombus in the T3a stratum, and classification of patients with ipsilateral adrenal disease T4 cancer. Independent validation of this system has been performed in large retrospective single- and multi-institutional cohorts [16, 17]. The estimated 10-year cancer-specific survival for patients treated with either radical or partial nephrectomy according to the primary tumor classifications using the updated TNM staging system was 96%, 80%, 66%, 55%, 36%, 26%, 25%, and 12% for pT1a, pT1b, pT2a, pT2b, pT3a, pT3b, pT3c, and pT4, respectively [17].

Collecting System Invasion

Invasion of the renal collecting system by RCC is independently associated with an increased risk of RCC recurrence [18]. A meta-analysis of 17 pooled studies demonstrated a 2.3-fold increased risk of RCC in patients with collecting system invasion and increased risk of cancer-specific mortality, especially in patients with stage T1-2 cancers, leading the authors to suggest that RCC patients with urinary collecting system invasion may warrant more intense surveillance following treatment [18].

Tumor Grade

The Fuhrman nuclear grading system was first described in 1982 and up until recently was widely used for the grading of RCC [19]. In this system, a nuclear grade of 1 to 4 is assigned according to a combination of nuclear size, irregularity, and nucleolar prominence. Fuhrman nuclear grade is independently associated with increased risk of recurrence [20–22]. There are, however, several limitations to the Fuhrman grading system including challenges related to incorporating the three scored components into a single grade and the fact that nuclear atypia is frequently noted in indolent chromophobe tumors. In light of these limitations, the International Society of Urological Pathology (ISUP) now recommends that grading should be based solely on nucleolar prominence and only be applied to cases of clear cell and papillary RCC [23].

Histologic Subtypes of Renal Cell Carcinoma

As mentioned in earlier chapters in this book, RCC is comprised of multiple distinct histologic variants, each of which is associated with variable metastatic potential and oncologic outcomes. The most common subtype is clear cell RCC (75%), followed by papillary RCC (10%), chromophobe RCC (5%), clear cell papillary RCC (1–4%), collecting duct RCC (1%), and rare variants such as Xp11 translocation tumors and mucinous tubular and spindle cell tumors [24]. In a contemporary population-based series of 17,605 surgically treated RCC patients, Keegan et al.

observed that the prevalence of advance disease at diagnosis (pT3/pT4, N1, or M1) varied considerably between the histologic variants: 28% of patients with clear cell RCC compared to 82.8% of patients with sarcomatoid, 55.7% of collecting duct, 17.6% of papillary, and 16.9% of patients with chromophobe RCC. On multivariable analysis, compared to clear cell RCC, chromophobe histology was associated with decreased all-cause mortality, while collecting duct and sarcomatoid histology were independently associated with increased mortality (HR 2.97 and 2.26, respectively) [25].

Other Histologic Features Associated with Increased Risk of Posttreatment Relapse

Microvascular invasion (MVI) is another pathologic feature that is associated with risk of RCC recurrence [23, 26, 27]. Dall'Oglio and colleagues demonstrated that the 5-year disease-free survival was 27.2% (95% confidence interval [CI] 14.9–50.3%) for patients with MVI compared to 87.1% (95% CI 79–95%) for patients without MVI in a retrospective series of 230 patients [28]. In a large meta-analysis including nearly 15,000 patients, MVI was found to be independently associated with a 2.7-fold increased risk of local recurrence (HR = 2.75, 95% CI 1.97–3.83), a 1.6-fold increase in the risk of metastasis (HR = 1.62, 95% CI 1.095–2.40), and 2.1-fold increase in the risk of cancer-specific mortality (HR = 2.09, 95% CI 1.53–2.86) [27].

Sarcomatoid differentiation describes an aggressive and highly lethal variant of RCC [29]. These tumors are characterized by spindle-like cells with high cellularity and cellular atypia and comprise approximately 5% of cases of RCC [30]. In a series of 206 patients with sarcomatoid RCC, nearly half of patients presented with synchronous metastatic disease and 70% of those without metastases at the time of surgery developed distant relapse [31].

Lymphovascular invasion (LVI) is identified in 5–20% of patients with RCC, with a higher prevalence among cases of locally advanced disease (pT3–pT4) [32]. Patients with organ-confined RCC found to have LVI has been observed to have similar oncologic outcomes to patients with locally advanced tumors [32].

Coagulative tumor necrosis is associated with adverse clinicopathologic and molecular features in RCC [23, 33] and is associated with increased risk of disease recurrence and cancer-specific death [22, 34, 35]. The most recent ISUP recommendations included the statement that, for clear cell RCC, the presence or absence of tumor necrosis should be included in routine pathology reports given its association with oncologic outcomes [23]. Conversely, there is conflicting evidence regarding the prognostic utility of necrosis in nonclear cell histologies; thus this recommendation is not applied to all RCC morphotypes [36].

Prognostic Nomograms and Risk Scores

Several risk models incorporating a variety of prognostic factors have been developed to further improve the postsurgical risk stratification of patients with RCC [21, 33, 35–41].

One example of a risk stratification tool is the *Cindolo Recurrence Risk Formula* [37], which generates a risk of tumor recurrence on the basis of tumor size at the time of treatment and the presence or absence of symptoms related to the tumor at diagnosis. A score is generated according to the formula [1.28 × presentation (asymptomatic, 0; symptomatic, 1) + 0.13 × clinical size]. For scores ≤1.2, the 5-year disease-free survival was 93% compared to 68% for a score > 1.2 [37].

Another risk stratification tool is the *Kattan nomogram* which incorporates histologic subtype, tumor size, 2002 TNM classification, and the presence or absence of symptoms [38]. The predictive accuracy of this nomogram has subsequently been validated in contemporary practice using the 2010 TNM staging system [39].

The *Leibovich prognosis score* (PROG score) [40] estimates the risk of progression to metastatic RCC after radical nephrectomy. This algorithm utilizes pathological T stage (pT1–pT4), regional lymph node spread (pNx-pN2; 2002 TNM criteria), tumor size (<10 or ≥10 cm), nuclear grade (1–4), and presence of histological tumor necrosis (yes or no). After scoring, patients can be stratified into three risk groups: low (0–2), intermediate (3–5), and high (≥6), with a 5-year metastasis-free survival rates of 97.1%, 73.8%, and 31.2%, respectively.

The *Mayo Clinic SSIGN score* [22] is another validated prognostication system that predicts cancer-specific survival for patients with clear cell RCC after radical nephrectomy. This system utilizes the same features as the Leibovich algorithm to assess survival except for the inclusion of metastasis: the pathological T stage (pT1-pT4), regional lymph node spread (pNx-pN2), M stage (pM0 or pM1; 2002 TNM criteria), tumor size (<5 or ≥5 cm), nuclear grade (1–4), and presence of histological tumor necrosis (yes or no). Patients with a SSIGN score of 0–1, 5, and ≥10 have 5-year cancer-specific survivals of 99.4%, 65.4%, and 7.4%, respectively. Zigeuner and colleagues provided evidence for the external validation of the SSIGN score through a retrospective multivariate analysis of 1862 patients [41]. Recently, Parker and colleagues validated the SSIGN score in a contemporary cohort of surgically treated RCC patients, confirming that the c-index was preserved across 3600 patients treated with radical nephrectomy from 1970 to 1998 (the development cohort) and those treated with either radical or partial nephrectomy from 1999 to 2010 [35]. The authors observed that the c-index was preserved across the three cohorts (*c*-index = 0.82, 0.84, and 0.82, respectively) [35].

The *Karakiewicz nomogram* [42] was developed using data from 2530 patients treated with either radical or partial nephrectomy for renal cortical tumors. The nomogram incorporates the 2002 TNM stages, tumor size, Fuhrman grade, histologic subtype, local symptoms, age, and sex to generate predictions for cancer-specific survival. This nomogram was externally validated in an additional 1422 patients, demonstrating 88.8% accuracy at 10 years [42].

The University of California Los Angeles Integrated Staging System (UISS) [41] is a prognostication system that predicts overall survival in patients with any histological subtype of kidney cancer after surgical resection. Patients are stratified into five categories (I–V) based upon the TNM staging system (1997 TNM criteria), Eastern Cooperative Oncology Group (ECOG) performance status, and Fuhrman grade. Risk groups are further differentiated based upon local versus metastatic disease. Patients categorized as UISS I, II, III, IV, and V have a 5-year overall survival rate of 94%, 67%, 39%, 23%, and 0%, respectively. The UISS algorithm can be broadly used to assess treatment outcomes, determine the need for adjuvant therapy, and assess eligibility for future clinical trials [1, 43, 44].

Treatment-Associated Factors

Oncologic Outcomes Following Partial vs. Radical Nephrectomy vs. Thermal Ablation

For pT1a renal cortical tumors (<4 cm, confined to the kidney), management strategies include partial nephrectomy (PN), radical nephrectomy (RN), thermal ablation, or active surveillance [44, 45]. The comparative effectiveness of definitive treatments has focused predominantly on cancer-specific survival, renal function preservation, and comparison of complications rates [46], while, at this time, there is relatively limited data available regarding patient-reported quality of life outcomes. A recent meta-analysis regarding the management of localized kidney cancer concluded that, regarding oncologic outcomes, comparisons of RN versus PN demonstrated relatively equivalent oncologic outcomes for T1a, T1b, and T2 tumors [46]. In contrast, when comparing PN to thermal ablation, this analysis found a higher local recurrence rate with ablation. However, when repeat treatment for residual tumor following initial thermal ablation was taken into account, there was no significant difference in recurrence risks between PN and thermal ablation.

Positive Surgical Margins

Among patients treated with PN, the prognostic implications of *positive surgical margins* are a subject of debate. Following PN, positive surgical margins are detected in 1.7–10% of patients [47–49]. In a population-based sample, positive surgical margins have been associated with increased all-cause mortality following PN (HR = 1.34, 95% CI 1.01, 1.78) [49]. Similarly, in a large multi-institutional cohort of 1240

patients with a median follow-up of only 33 months, positive surgical margins were associated with a twofold increase in the risk of local recurrence [48]. However, when these results were stratified into high risk (pT2–pT3; Fuhrman grades III–IV) versus low-risk disease (pT1, Fuhrman grades I–II), positive surgical margins were associated with increased risk of local relapse among high-risk patients, but not those with low-risk disease on multivariable analysis (HR = 7.48, 95% CI 2.75–20.34 vs. HR = 0.62, 95% CI 0.08–4.7). Conversely, a multicenter Korean study of 1831 patients with a median follow-up of 32.5 months did not identify any difference in local recurrence-free survival on the basis of positive margin status [47].

Positive surgical margins following RN are reported in 0.8–2.3% of cases [22, 50, 51] and are associated with a risk of local recurrence of 3.5–6.3% [52]. Approximately 4% of patients with positive surgical margins have been observed to ultimately develop metastases; however, surgical margin status has not been found to be independently associated with metastasis-free survival or cancer-specific survival after adjusting for other relevant confounding factors [53, 54].

At this time, guidelines from both the American Urological Association (AUA) [45] and Eastern Association of Urology (EAU) [44] acknowledge the potential for increased risk of RCC relapse in the setting of positive margins and recommend that these patients be surveilled according to the high-risk protocols.

With respect to vascular margin status, while gross tumor at the vein margin may be identified in up to 32% of patients treated with RN [52, 55], microscopic disease at the vascular margin is reported in 18.4% of cases with venous tumor thrombus [55, 56]. Abel and colleagues reviewed a series of 256 patients with RCC and venous tumor thrombus and identified local recurrence in only 2 patients (0.8%) [55]. On multivariable analysis, the authors reported that positive vascular margins were independently associated with an increased risk of local recurrence, but not with systemic recurrence or cancer-specific mortality. Similar findings have been reported by Liu and colleagues who noted that, among patients with venous tumor thrombus, the risk of relapse following nephrectomy is most strongly associated with the degree of the tumor thrombus extent, while the positive vascular margins were not associated with either disease progression or survival [56].

Summary of Established Surveillance Guideline Statements

Posttreatment surveillance is a fundamental component in the treatment and care of patients with RCC. Appropriate surveillance allows urologists to assess for local or distant recurrence, postoperative complications, and renal function. Established guidelines from the AUA [45], Canadian Urological Association (CUA) [57], EAU [44], and National Comprehensive Cancer Network (NCCN) [58] all emphasize the importance of posttreatment surveillance but with minor variations (i.e., imaging modalities, surveillance timeline, risk stratification, etc.). What follows is a summary of the most current recommendations for posttreatment surveillance of RCC from each governing body as of the writing of this text. Table 16.1 provides a summary of the various schedules of examinations recommended by each guideline committee.

Table 16.1 Summary of the recommended surveillance schedules following treatment of localized renal cell carcinoma by guidelines committee

Guideline statement (last updated)	Risk group/treatment approach	Recommended testing	Months after treatment									
			3	6	12	18	24	30	36	48	60	72
AUA (2013)[c]	***Thermal ablation***[d]	*History and physical examination*[a]	X	X	X		X		X	X	X[o]	
		Laboratories[b]	X	X	X		X		X	X	X[o]	
		Chest surveillance			XR		XR		XR	XR	XR	
		Abdominal surveillance	CT or MRI	CT or MRI	CT or MRI		CT or MRI		CT or MRI	CT or MRI	CT or MRI[o]	
	Low-risk (pT1 Nx-0) Partial nephrectomy	*History and physical examination*[a]	X				X		X[o]			
		Laboratories[b]	X				X		X[o]			
		Chest surveillance	XR				XR		XR[o]			
		Abdominal surveillance	Baseline CT or MRI within 3–12 months				CT, MRI, or US[p]		CT, MRI, or US[o,p]			
	Low-risk (pT1 Nx-0) Radical nephrectomy	*History and physical examination*[a]	X				X		X[o]			
		Laboratories[b]	X				X		X[o]			
		Chest surveillance	XR				XR		XR[o]			
		Abdominal surveillance	Baseline CT or MRI				CT, MRI, or US[p]		CT, MRI, or US[o,p]			
	Moderate/high risk (pT2–pT4 Nx-0, pT1–pT3 N1, pT)	*History and physical examination*[a]	X		X	X	X	X	X	X	X[o]	
		Laboratories[b]	X		X	X	X	X	X	X	X[o]	
		Chest surveillance	CT or MRI		XR/CT	XR/CT	XR/CT	XR/CT	XR/CT	XR/CT	XR/CT[o]	
		Abdominal surveillance	Baseline CT or MRI		CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US[o]	

Guideline statement (last updated)	Risk group/treatment approach	Recommended testing	Months after treatment									
			3	6	12	18	24	30	36	48	60	72
CUA (2008)[e,f]	***pT1***	*History and physical examination*			X		X		X	X	X	X[o]
		Laboratories[h]			X		X		X	X	X	X[o]
		Chest surveillance			XR		XR		XR	XR	XR	XR[o]
		Abdominal surveillance (partial nephrectomy)	CT[p]		US		US		US	US	US	US
		Abdominal surveillance (radical nephrectomy)					CT or US				CT or US[o]	
	pT2	*History and physical examination*		X	X		X		X	X	X	X[o]
		Laboratories[h]		X	X		X		X	X	X	X[o]
		Chest surveillance		XR	XR	XR	XR	XR	XR	XR	XR	XR[o]
		Abdominal surveillance			CT or US				CT or US		CT or US[o]	
	pT3	*History and physical examination*		X	X		X		X	X	X	X[o]
		Laboratories[h]		X	X		X		X	X	X	X[o]
		Chest surveillance		XR	XR	XR	XR	XR	XR	XR	XR	XR[o]
		Abdominal surveillance		CT	CT	CT	CT		CT	CT	CT	CT[r]
	pTany N1	*History and physical examination*	X	X	X		X		X	X	X	X[g]
		Laboratories[h]	X	X	X		X		X	X	X	X[g]
		Chest surveillance	XR	XR	XR	XR	XR	XR	XR	XR[f]	XR[f]	XR[g]
		Abdominal surveillance	CT	CT	CT	CT	CT		CT	CT	CT	CT[g]

(continued)

Table 16.1 (continued)

Guideline statement (last updated)	Risk group/treatment approach	Recommended testing	Months after treatment									
			3	6	12	18	24	30	36	48	60	72
EAU (2016)[i]	***Low risk (radical nephrectomy or partial nephrectomy only)***	*History and physical examination[j]*										
		Laboratories[j]										
		Chest surveillance			CT				CT		Ct[q]	
		Abdominal surveillance		US	CT		US		CT	US	Ct[q]	
	Intermediate risk (radical/partial nephrectomy, thermal ablation)	*History and physical examination[j]*										
		Laboratories[j]										
		Chest surveillance		CT	CT		CT			CT	CT[r]	
		Abdominal surveillance		CT	CT		CT		US	CT	CT[r]	
	High risk (radical/partial nephrectomy, thermal ablation)	*History and physical examination[j]*										
		Laboratories[j]										
		Chest surveillance		CT	CT		CT		CT	CT	CT[r]	
		Abdominal surveillance		CT	CT		CT		CT	CT	CT[r]	

Guideline statement (last updated)	Risk group/treatment approach	Recommended testing	Months after treatment									
			3	6	12	18	24	30	36	48	60	72
NCCN (2016)[l]	***Thermal ablation***	*History and physical examination*		X	X	X	X		X	X	X	
		Laboratories[m]		X	X	X	X		X	X	X	
		Chest surveillance			XR or CT		XR or CT		XR or CT	XR or CT	XR or CT	
		Abdominal surveillance	CT or MRI		CT, MRI, or US		CT, MRI, or US		CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	
	pT1 Nx-0 Partial nephrectomy	*History and physical examination*		X	X		X		X	X	X	
		Laboratories[m]		X	X		X		X	X	X	
		Chest surveillance			XR or CT		XR or CT		XR or CT[o]			
		Abdominal surveillance	CT, MRI, or US			CT, MRI, or US[p]		CT, MRI, or US[o,p]				
	pT1 Nx-0 Radical nephrectomy	*History and physical examination*		X	X		X		X	X	X	
		Laboratories[m]		X	X		X		X	X	X	
		Chest surveillance			XR or CT		XR or CT		XR or CT[o]			
		Abdominal surveillance	CT, MRI, or US[o]									
	pT2–pT3 Nx-0 or pT1–pT3 N1 or pT4 Nx-1 Radical nephrectomy	*History and physical examination*[n]	X	X	X	X	X	X	X	X[o]		
		Laboratories[m]	X	X	X	X		X	X	X[o]		
		Chest surveillance[n]	XR or CT		XR or CT	XR or CT	XR or CT	XR or CT	XR or CT	XR or CT	XR or CT[o]	
		Abdominal surveillance[n]	CT or MRI		CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US	CT, MRI, or US[o]	

(continued)

Table 16.1 (continued)

XR chest X-ray, *CT* computed tomography, *US* abdominal ultrasound

[a]History and physical exam directed at detecting progression or metastases

[b]Basic laboratories to include BUN/creatinine, UA, estimated glomerular filtration rate. Complete blood count, lactate dehydrogenase, liver function tests, alkaline phosphatase, and calcium to be used at the discretion of the physician. The AUA guidelines stipulate that progressive renal insufficiency should prompt referral to nephrology

[c]Pelvic imaging, spine MRI, bone scan to be performed as clinically indicated

[d]The panel recommends against further radiographic imaging for any patients with pathologically confirmed benign histology before or at the time of treatment and have radiographic confirmation of treatment effect and no complications

[e]Recommendations for follow-up after partial nephrectomy or radical nephrectomy only. No recommendations given for follow-up after thermal ablation

[f]Chest X-ray may be alternated with chest CT

[g]Annual surveillance is recommended to continue

[h]Laboratory studies include complete blood count, serum chemistries, and liver function tests

[i]Risk stratification utilizing one of the multifactor prognostic nomograms discussed in section "Treatment-Associated Factors". Surveillance includes evaluation of renal function and cardiovascular risk

[j]There is no commentary in the most recent update to the EAU recommendations regarding the frequency of non-imaging-based surveillance including clinic visits or laboratory examinations

[k]Optional after radical nephrectomy only

[l]Pelvic CT or MRI, CT or MRI of the head, MRI of the spine, bone scan as clinically indicated

[m]Comprehensive metabolic panel with other tests as indicated

[n]Every 3–6 months for 3 years and then annually for years 4 and 5

[o]Ongoing follow-up at the physician's discretion

[p]Optional after baseline

[q]Patients to be discharged

[r]Follow-up thereafter every 2 years

American Urological Association (AUA)

The AUA guidelines regarding follow-up for clinically localized renal neoplasms were most recently updated in 2013 [45]. These guidelines provide recommendations for follow-up stratified according disease stage and the treatment modality undertaken. Each individual guideline is graded according to the strength of underlying evidence (from highest to lowest) as a standard, recommendation, option, clinical principle, or expert opinion.

The AUA specifies that patients undergoing follow-up for treated or observed renal cortical tumors should be followed with a history and physical examination that is directed toward identifying signs and symptoms of metastatic spread or local recurrence. Standard laboratories recommended include blood urea nitrogen and creatinine to assess renal function as well as urine analysis. The guidelines specify that additional laboratory evaluations such as a complete blood count, lactate dehydrogenase, liver function tests, and calcium level should also be considered and utilized at the discretion of the treating physician. In terms of optimal imaging for relapses in the chest, the AUA preferentially recommends chest X-ray (CXR) rather than X-ray computed tomography (CT) due to a lower rate of false-positive and benign findings that may result in unnecessary invasive evaluation.

The AUA makes the recommendation that patients with progression of renal insufficiency on follow-up evaluations should be referred for consultation by nephrology. Adjunct studies including bone scan and neurologic cross-sectional imaging (i.e., CT or magnetic resonance imaging [MRI]) are only recommended in the setting of symptoms suggestive of metastases to the bone (e.g., elevated alkaline phosphatase, bone pain, and/or findings of bony neoplasm on other surveillance studies) or central nervous system (e.g., acute neurological signs or symptoms), respectively. Additionally, it is the expert opinion of the AUA guideline panel that positron emission tomography should not be utilized in the follow-up of RCC at this time due to lacking data regarding the sensitivity and specificity of this imaging modality in this setting. Finally, the AUA currently recommends against the routine use of molecular biomarkers in posttreatment RCC surveillance due to a lack of clear clinical benefit at this time.

Canadian Urologic Association (CUA)

The CUA guidelines were last published in 2008 for surveillance following PN or RN for RCC, with an expected update pending at the time of this writing [57]. Follow-up according to the CUA guidelines is stratified by pathologic tumor stage. The guidelines specify that CXR should be the standard imaging modality for evaluation of pulmonary relapse. The authors stipulate that chest CT may be performed instead; however, they cite insufficient evidence to suggest a benefit for universal

preferential use of chest CT over CXR. With respect to abdominal imaging, the panel recommends utilization of CT of the abdomen, however, patients with pT1 or pT2 RCC may also be followed with abdominal ultrasound (US). As recommended by the AUA guidelines, CT of the head and bone scan are only reserved for situations where symptoms are suggestive of brain or osseous relapse. The routine laboratory panel recommended by the CUA includes a complete blood count, serum chemistry panel, and liver function tests. Finally, the CUA panel recommends surveillance out to 6 years following definitive treatment.

European Association of Urology (EAU)

The EAU guidelines [44] differ from the prior guideline statements in that they recommend risk stratification into low-, intermediate-, and high-risk disease according to available clinical risk stratification models such as those detailed earlier. No preference, however, is given to any specific model. Contrary to the other guideline statements, the EAU cite evidence regarding the poor sensitivity of CXR for detecting small pulmonary metastases [44, 59] and therefore specify CT as the preferred imaging modality for relapse in the chest. MRI of the chest is recommended as an alternative to minimize radiation exposure. Similar to the recommendations put forth by the AUA panel, the EAU guidelines advise against the routine use of positron emission tomography and bone scintigraphy due to limited sensitivity and specificity. In terms of duration of follow-up, the EAU recommends that low-risk patients may be discharged from surveillance at 5 years after definitive treatment, whereas patients with intermediate- and high-risk disease, or any patient treated with thermal ablation, are recommended to undergo continued surveillance on a biennial basis.

National Cancer Control Network (NCCN)

The NCCN guidelines are stratified by disease stage and treatment modality [58], with a surveillance framework that is similar to the recommendations proposed by the AUA. The NCCN reiterates that no single follow-up plan is appropriate for every patient and therefore recommends modification of follow-up according to the treating physician's judgment. Recommendations are made up to 5 years following treatment; however, due to the potential for relapse after 5 years [60], the NCCN recommends consideration of follow-up after 5 years according to clinician discretion.

With respect to which imaging studies are recommended, the NCCN guidelines state that CT of the abdomen with or without pelvic CT and CXR are considered essential baseline studies [58]. In terms of screening for metastases, pulmonary imaging is mandated. While the panel acknowledges that chest CT is more accurate than CXR for the assessment of pulmonary metastases, the guidelines do not give preference to one modality over the other.

Review of Guidelines, Stratified by Tumor Stage/Risk Category and Treatment Modality

Low-Risk Patients (pT1 N0/x) Following Surgical Resection (RN or PN)

For clinically localized disease, the majority of the guidelines recommend less intensive postoperative surveillance due to the decreased risk of recurrence [44, 45, 57, 58]. The AUA guidelines [45] specify that for low-risk patients (pT1, N0, Nx) treated with PN or RN, an initial physical examination with basic laboratory studies should be performed at 6 months posttreatment and then annually for 3 years. Baseline abdominal imaging (CT or MRI) is recommended within 3–12 months after surgery. While patients treated with PN are recommended to undergo further abdominal imaging (US, CT, or MRI) annually for 3 years, additional abdominal imaging after RN is recommended at the discretion of the physician. Chest imaging is recommended annually for 3 years to assess for pulmonary metastases.

The CUA [57] specifies that surveillance following PN or RN for T1 RCC should include a history and physical exam and labs including complete blood count, chemistries, liver function tests, and CXR on an annual basis. For pT1 lesions treated with RN, abdominal imaging in the form of either CT or abdominal ultrasound, with consideration for alternating the two, is recommended at 2 years and 5 years. For pT1 lesions treated with PN, the panel gives the option of obtaining a CT at 3 months to assess the residual disease and gives consideration to the option of annual abdominal US.

For patients with low-risk disease treated surgically with PN or RN, the EAU [44] recommendations include US of the kidneys and renal fossa at 6 months, followed by alternating CT of the chest, abdomen, and pelvis with US on an annual basis until 5 years following treatment, at which time the patients are discharged from further surveillance.

The NCCN [58] recommendations following surgery for T1 RCC are similar, including a history and physical and comprehensive metabolic panel every 6 months for the first 2 years and then annually through year 5. Abdominal imaging using US, CT, or MRI is recommended within 3–12 months of PN and annually for 3 years.

Intermediate to High Risk (pT2-pT4, N0, Nx or any Stage, N1) Following Surgical Resection

For intermediate- to high-risk patients treated with RN, more intensive surveillance is recommended due to the increased risk of both local recurrence and development of systemic metastases [44, 45, 57, 58]. The AUA [45] and NCCN [58] recommend a postoperative history and physical exam and basic laboratories every 6 months for 3 years and then yearly for years 4 and 5 after surgery. Baseline chest and abdominal cross-sectional imaging (CT or MRI) is recommended within the first 3–6 months. Surveillance imaging (US, CXR, CT, or MRI of the abdomen) is obtained every 6 months for 3 years and then annually until year 5. After 5 years, further imaging

may be performed at the discretion of the physician and should be performed if symptoms are suggestive of recurrence or metastatic spread.

The CUA guidelines [57] similarly recommend a CXR every 6 months, extending out to 6 years, but recommend lower-intensity abdominal surveillance, recommending either CT or abdominal US at 1, 3, and 5 years for T2 tumors. For T3 tumors, cross-sectional imaging (CT or MRI) is favored and recommended every 6 months through year 2 and then at years 4 and 6. Finally, for patients with node-positive disease, CXR and CT of the abdomen are recommended every 6 months through 6 years following surgery.

For patients with clinically risk-stratified high-risk disease, the EAU recommends CT of the chest/abdomen and pelvis at 6 months and 12 months, then yearly until 5 years, and every other year thereafter [44]. Among patients with intermediate-risk disease, the panel cites the option of ultrasound rather than CT at year 3.

Follow-Up After Thermal Ablation

Relapse following thermal ablation is reported in 2–10% of patients [45, 46, 61]. The AUA guideline panel [45] adopted a standardized definition of post-thermal ablation "treatment failure or local recurrence." This is defined as a visually enlarging neoplasm or new nodularity in the same area of prior treatment and may be identified by enhancement of the renal mass on posttreatment imaging with contrast or failure of the renal mass to regress in size over time, as well as by new satellite, nodules along the port-site or needle track, or a biopsy-proven recurrence.

Follow-up after thermal ablation otherwise follows a similar schedule to that recommended for after PN for low-risk disease, extended out to 5 years. Specifically, the panel recommends a history and physical exam, labs, and cross-sectional abdominal imaging (CT or MRI) at 3 and 6 months to determine treatment success and then annually for surveillance for 5 years and thereafter according to the clinician's assessment of individualized patient risk.

Importantly, it is a central tenant of the AUA recommendations that all patients under consideration for ablation undergo a biopsy prior to treatment to confirm that the renal cortical mass represents an RCC [45]. However, for patients who were treated with thermal ablation for a pathologically confirmed benign tumor, with radiographic evidence of treatment success without evidence of treatment complications, no further radiologic assessment is recommended. The panel provided expert opinion that patients with treatment failure within 6 months should be offered the alternatives of observation, repeat treatment, or definitive surgical extirpation and that any evidence of recurrence within an ablated neoplasm should prompt consideration of biopsy.

The EAU guidelines specify that patients with RCC treated with thermal ablation should be followed according to the regimens specified for either intermediate- or high-risk disease [44]. According to these guidelines, high-risk patients should be surveilled with CT or MRI of the chest, abdomen, and pelvis at 6 months and then

yearly for 5 years, while intermediate-risk patients may substitute US for cross-sectional imaging at year 3. After 5 years, patients are recommended to undergo CT or MRI of the chest, abdomen, and pelvis every 2 years, indefinitely.

Evaluation of the Available Guidelines for Surveillance After Definitive Treatment for RCC

Limitations of the Available Guideline Statements

In the guideline statements from the AUA, CUA, EAU, and NCCN, it is acknowledged that no single follow-up regimen can be considered universally appropriate. This is echoed by the European Society for Medical Oncology (ESMO) which advocates for a follow-up strategy that incorporates both patient- and disease-specific risk factors and possible treatment options that may be employed in the setting of potential relapse [62].

In 2014, Stewart and colleagues evaluated the ability of the available AUA and NCCN surveillance guidelines to identify local and systemic relapse following surgical treatment for M0 RCC in 3651 patients from a single center [60]. With a median follow-up of 9 years, the authors observed recurrences in 1088 (29.8%) patients. The 2014 NCCN recommendations had recently been updated prior to the study, adopting a similar risk-adapted surveillance strategy, similar to the 2013 AUA recommendations. If the then-contemporary 2014 NCCN guidelines were followed, 742 recurrences (68.2%) would have been detected. Similarly, the 2013 AUA guidelines would have identified 728 (66.9%) of recurrences (Fig. 16.1). In the same paper, the authors presented a comparison of the relative costs of the two guideline-

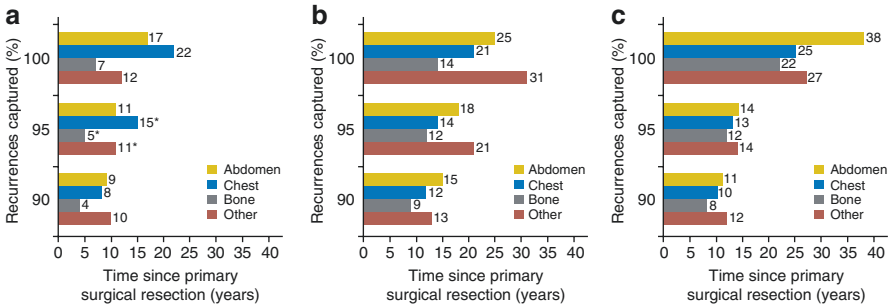

Fig. 16.1 Total duration of surveillance required to capture 90%, 95%, and 100% of recurrences stratified by the American Urological Association risk groups and recurrence locations: (**a**) low risk after partial nephrectomy, (**b**) low risk after radical nephrectomy, and (**c**) moderate/high risk. (*) Estimated duration of surveillance as a result of the few recurrences in these groups. (From Stewart et al. [60]. Reprinted with permission. ©(2018) American Society of Clinical Oncology. All rights reserved)

based surveillance strategies compared to a continued surveillance strategy that would have captured 95% of all recurrences. For example, for a patient with a pT1 renal mass treated with PN, complete surveillance as recommended by the NCCN in 2014 would have resulted in 2014 Medicare costs totaling $2131.52 compared to $1738.31 if the 2013 AUA guidelines were followed. However, to capture 95% of all recurrences, surveillance costs would be estimated to total $9856.82. Importantly, these costs did not include indirect costs such as clinic visits, lost wages related to time away from work for the patient or their family members. These findings led the authors to call for improved surveillance algorithms, balancing both patient benefit and health-care costs.

Radiation-Related Harms with Surveillance

In addition to taking the health-care costs into consideration when evaluating surveillance protocols, the potential harms of more intensive surveillance must also be considered. While intensive surveillance may capture more recurrences over time, the potential harm of the cumulative radiation dose incurred must be considered and should be discussed with patients as part of the shared decision-making around recommending an optimal surveillance strategy. As discussed in the 2013 AUA guidelines [45], the carcinogenic potential of relative low-dose (<100 mSv) radiation is extrapolated from analysis of the survival of Japanese survivors of the atomic bomb exposed to intermediate (>100 mSv). These extrapolations rely on the linear no-threshold model, which assumes that there is risk for biological damage (increase in the risk of carcinogenesis) at any dose of radiation [63]. For reference, the average CXR is associated with an estimated radiation dose of <0.1 mSv, compared to 1–10 mSv for abdominal CT without contrast or abdominal radiograph and 10–100 mSv for abdominal CT scans with and without contrast. At this point, there is indirect evidence demonstrating increased risk of developing cancer following exposure to low levels of radiation at doses that would be expected with the surveillance CT scans recommended in the guidelines discussed herein [64]. This increasing understanding of the potential risks associated with CT scanning has generated new low radiation dose scanning protocols and increasing reliance on imaging modalities that do not utilize ionizing radiation [65]. As stated in the 2013 AUA guidelines, “it is prudent to limit the use of CT to clinical indications in which the benefit is felt to outweigh the risks” [45].

In addition to radiation exposure, both CT and MRIs administered with contrast involve risks related to hypersensitivity and allergies, as well as potential complications in patients with renal insufficiency. Capogrosso and colleagues demonstrated a lacking consensus regarding surveillance due to clinician heterogeneity in post-treatment follow-up and imaging modalities [66]. The authors recommend that a standardized evidence-based protocol is still needed with a goal of limiting radiation exposure, minimizing unnecessary costs, and ensuring early detection of tumor recurrence.

The Guidelines in Practice

When real-world evaluations of surveillance patterns and uptake of the various guideline strategies are undertaken considerable variation is noted. For example, Sohn and colleagues identified 7603 patients treated for RCC in the Surveillance, Epidemiology, and End Results database and reported on both adherence to the AUA surveillance guidelines as well as the association between more intensive surveillance and oncologic outcomes [67]. Dividing patients into relatively abbreviated follow-up periods of only 15 (short) and 30 (intermediate) months, the authors noted that more than 40% of the patients in the short follow-up cohort did not undergo any chest imaging. Similarly, more than 50% of the intermediate interval cohort did not undergo chest imaging and over 30% of all patients did not undergo any surveillance imaging following definitive treatment. The authors also assessed whether compliance with the AUA guidelines was associated with cancer-specific survival and noted that adherence to imaging follow-up per the AUA guidelines was not associated with improved outcomes compared to no imaging at all.

Alternative Surveillance Strategies

Indeed, it is challenging to demonstrate a survival benefit related to the intensity of post-RCC surveillance. As noted above, survival is ultimately the product of disease-specific, patient-specific, and both initial and salvage treatment-related factors, which may manifest differently within a single patient. Furthermore, lead-time bias, which results in a lengthening of apparent survival simply related to earlier detection of recurrences, confounds assessment of the relative benefit of more intensive surveillance strategies.

As such, no one follow-up strategy can be recommended over any other due to the paucity of comparative studies pitting surveillance strategies against one another. Furthermore, and perhaps more importantly, there are limited data to support the fact that treatment of asymptomatic recurrences captured on surveillance confers a survival benefit compared to treatment of recurrences detected related to symptoms alone. In some patients, metastatic RCC may be asymptomatic with a relatively indolent course. Park and colleagues reported on outcomes in 58 patients in whom first-line systemic therapy for metastatic RCC was deliberately deferred, with a median time to progression in 12.4 months [68]. Systemic therapy was ultimately initiated at the time of progression after a period of active surveillance, with objective response rates to systemic therapy that were similar to historical controls. Additionally, in a prospective phase 2 trial, Rini and colleagues demonstrated that treatment-naïve, asymptomatic patients with metastatic RCC can undergo active surveillance prior to beginning system therapy in 48 patients [69]. The authors found that increasing numbers of the International Metastatic Database Consortium adverse risk factors and a greater number of metastatic sites were associated with a

shorter period of surveillance. Conversely, in an assessment of RCC retroperitoneal recurrence size after surgical treatment, Thomas and colleagues observed that the maximal diameter of the retroperitoneal recurrence was independently associated with risk of cancer mortality, suggesting the potential benefit of earlier detection of relapse among patients who were candidates for cytoreductive surgery [70].

Alternative surveillance strategies have been proposed to meet the objective of improving the efficiency and efficacy of posttreatment surveillance, incorporating different risk-stratifying algorithms including factors such as DNA ploidy, tumor size, and stage [71]. Lam and colleagues proposed an alternate strategy using the UISS nomogram for risk stratification, including stage, Fuhrman grade, and performance status [72]. Alternatively, Siddiqui and colleagues recommended incorporation of histologic subtype in risk stratification [73].

Williamson and colleagues proposed a surveillance protocol that unifies recommendations from the existing guideline statements from the AUA, CUA, EAU, and NCCN [74]. Briefly, the authors recommend that following treatment (RN, PN, or thermal ablation) for low-risk/T1 renal tumors, follow-up should be initiated at 3 months with a history and physical exam, CT, and labs. Then patients may be followed by yearly US or CT through 3 years with a final US or CT at 5 years. For chest surveillance, the authors recommend annual CXR with a chest CT at 3 and 5 years. For intermediate- and high-risk disease, the authors propose a baseline abdominal CT at 3 months, and then alternating abdominal US with CT at 6 months, and then every 6 months for 3 years, and annually for years 4 and 5. For chest surveillance, it was proposed that CXR and chest CT could be alternated at the same intervals as the abdominal imaging.

Ultimately, however, these strategies and the available existing guidelines might be considered to fall short in that they do not account for patient-specific risk stratification and the competing risks of noncancer morbidity. Specifically, there are no recommendations for how clinical guidelines should be modified for a specific patient according to his or her comorbidity burden, age, or other patient-specific factors that a physician might wish to weigh when considering how to personalize a surveillance strategy.

To address this knowledge gap, Stewart-Merrill and colleagues developed a novel surveillance schedule incorporating the changing risk of site-specific cancer relapse over time stratified by disease stage, age, and comorbidity [9]. According to this strategy, a patient's risk of RCC recurrence, stratified by pathologic stage, and relapse site is presented graphically in the context of their risk of non-RCC death stratified by age and Charlson comorbidity index (Fig. 16.2). This methodology permits assessment of the individualized point at which a patient's competing risks of non-RCC death exceed the risk of recurrence, at which point, further surveillance may be considered to have relatively limited benefit. Table 16.2 presents comparisons of the durations of the variable risk-stratified individualized surveillance durations. To date, however, this protocol has yet to be externally validated or compared to the current recommended guidelines.

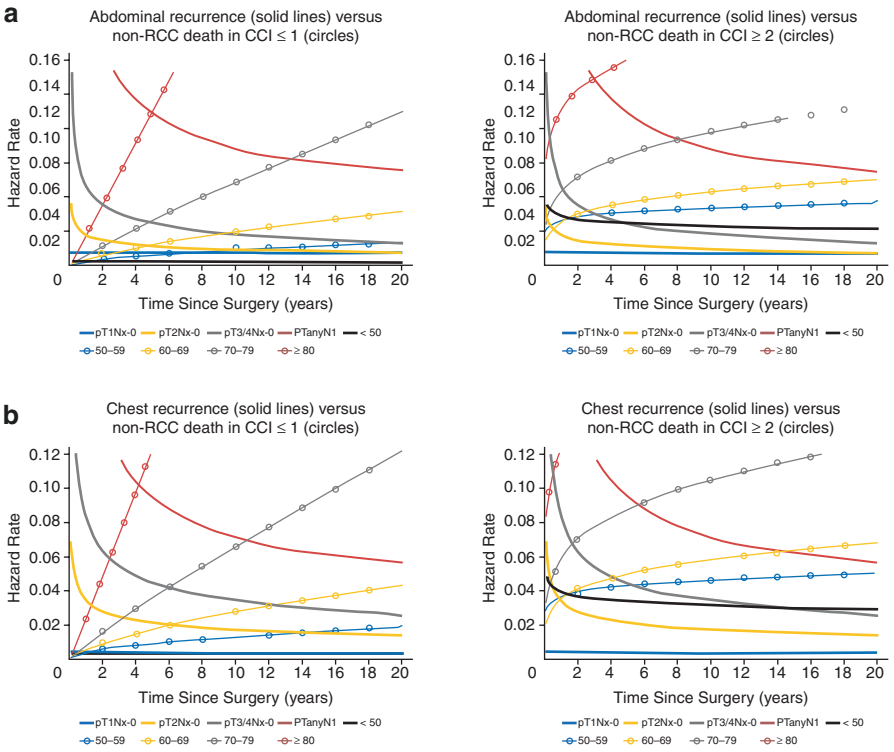

Fig. 16.2 Weibull models illustrating the time points at which the risk of non-RCC death exceeds the risk of recurrence. Decreasing hazard rates of recurrence over time are stratified by stage and relapse location (solid lines; [**a**] abdomen, [**b**] chest, [**c**] bone, and [**d**] other sites) . These are compared to increasing hazard rates of non-RCC death over time stratified by age and Charlson Comorbidity Index (CCI) groups (circles; 1 or 2). Age-, CCI-, stage-, and relapse location-specific time points (in years) were estimated when risk of non-RCC death exceeded the risk of recurrence. (From Stewart-Merrill et al. [9]. Reprinted with permission. ©(2018) American Society of Clinical Oncology. All rights reserved)

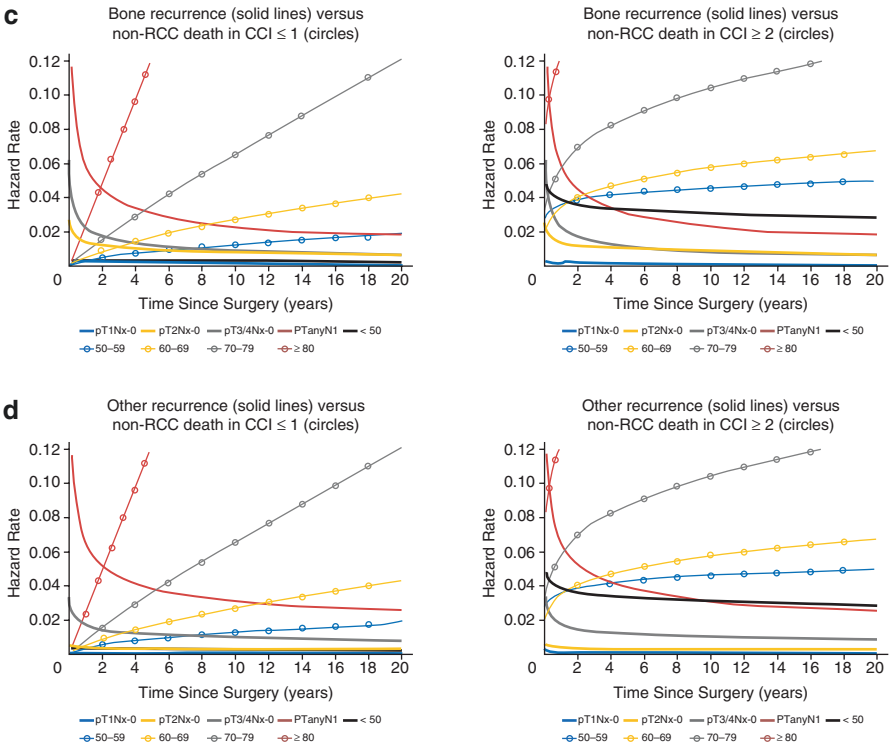

Fig. 16.2 (continued)

Conclusions

At the present time, there are multiple guidelines available to direct posttreatment surveillance of RCC. However, considerable variation exists between these recommendations. A patient's posttreatment risk of relapse may vary considerably with factors related to tumor biology, the individual patient, and mode of treatment. Prognostic multivariable nomograms and models may be helpful in assessing a patient's individual risk of local relapse and oncologic outcomes, which can then guide a physician in defining the most appropriate surveillance strategy for a patient. Contemporary surveillance guidelines proposed by the AUA, CUA, EAU, and NCCN are consistent in their goal of ensuring early relapse recognition; however, they differ regarding patient risk stratification methodology, surveillance frequency, and imaging modalities utilized. At the time of writing this chapter, there is no consensus in terms of recommending one strategy for posttreatment surveillance over another. While more intense surveillance may permit earlier identification of relapses, increased frequency and duration of surveillance may be associated with greater harm from cumulative radiation exposure, potential direct and indirect health-care costs, and quality of life impact for the patient. Ultimately, optimization of posttreatment surveillance requires

Table 16.2 Age-, Charlson Comorbidity Index-, and relapse location-specific time points at which the risk of death from causes other than renal cell carcinoma exceeds the risk of recurrence of renal cell carcinoma in years

		Time point in years by age group (years) and Charlson comorbidity index at which the risk of non-RCC death exceeds the risk of RCC recurrence after surgical treatment									
		< 50 years		*50–59 years*		*60–69 years*		*70–79 years*		*≥80 years*	
Stage group	**Relapse location**	*CCI ≤ 1*	*CCI ≥ 2*	*CCI ≤ 1*	*CCI ≥ 2*	*CCI ≤ 1*	*CCI ≥ 2*	*CCI ≤ 1*	*CCI ≥ 2*	*CCI ≤ 1*	*CCI ≥ 2*
pT1 Nx-0	*Abdomen*	>20	–	7	–	2.5	–	1.5	–	0.5	–
	Chest	>20	–	1	–	1	–	0.5	–	–	–
	Bone	0.5	–	0.5	–	0.5	–	0.5	–	0.5	–
	Other	–	–	–	–	–	–	–	–	–	–
pT2 Nx-0	*Abdomen*	>20	0.5	10.5	0.5	5	0.5	2.5	0.5	1	–
	Chest	>20	0.5	14	1	6	1	3	0.5	1.5	–
	Bone	>20	–	6.5	–	3	–	1.5	–	1	–
	Other	>20	–	2.5	–	2	–	0.5	–	0.5	–
pT3/pT4 Nx-0	*Abdomen*	>20	5	19.5	3	9	2.5	5	1.5	2	0.5
	Chest	>20	14	>20	5.5	12.5	4.5	6	1.5	2.5	1
	Bone	>20	0.5	7.5	0.5	4	0.5	2.5	0.5	1.5	–
	Other	>20	0.5	10	0.5	5.5	0.5	2	0.5	1	–
pTany N1	*Abdomen*	>20	>20	>20	>20	>20	>20	13	8	5	3
	Chest	>20	>20	>20	>20	>20	14	10.5	5.5	4.5	2
	Bone	>20	4.5	20	3	9	2.5	4.5	1	2	0.5
	Other	>20	>20	>20	10.5	13	4.5	6.5	2	2.5	1

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Abbreviations: *CCI* Charlson Comorbidity Index

Dash mark "—" represents that the risk of non-RCC death exceeded the risk of recurrence starting at 30 days following surgery, which may be suggestive of the fact that surveillance may not be indicated in these situations

shared decision-making between the patient and the physician. Future work is needed to improve risk stratification strategies and to better understand the risks and benefits of varying approaches to posttreatment surveillance.

References

1. Zisman A, Pantuck AJ, Wieder J, Chao DH, Dorey F, Said JW, et al. Risk group assessment and clinical outcome algorithm to predict the natural history of patients with surgically resected renal cell carcinoma. J Clin Oncol. 2002;20:4559–66.
2. Kuczyk MA, Anastasiadis AG, Zimmermann R, Merseburger AS, Corvin S, Stenzl A. Current aspects of the surgical management of organ-confined, metastatic, and recurrent renal cell cancer. BJU Int. 2005;96:721–7.
3. Speed JM, Trinh QD, Choueiri TK, Sun M. Recurrence in localized renal cell carcinoma: a systematic review of contemporary data. Curr Urol Rep. 2017;18(2):15.
4. Psutka SP, Heidenreich M, Boorjian SA, Bailey GC, Cheville JC, Stewart-Merrill SB, et al. Renal fossa recurrence after nephrectomy for renal cell carcinoma: prognostic features and oncological outcomes. BJU Int. 2016;119(1):116–27.
5. Bruno JJ 2nd, Snyder ME, Motzer RJ, Russo P. Renal cell carcinoma local recurrences: impact of surgical treatment and concomitant metastasis on survival. BJU Int. 2006;97:933–8.
6. Schrodter S, Hakenberg OW, Manseck A, Leike S, Wirth MP. Outcome of surgical treatment of isolated local recurrence after radical nephrectomy for renal cell carcinoma. J Urol. 2002;167:1630–3.
7. Margulis V, McDonald M, Tamboli P, Swanson DA, Wood CG. Predictors of oncological outcome after resection of locally recurrent renal cell carcinoma. J Urol. 2009;181:2044–51.
8. Adamy A, Chong KT, Chade D, Costaras J, Russo G, Kaag MG, et al. Clinical characteristics and outcomes of patients with recurrence 5 years after nephrectomy for localized renal cell carcinoma. J Urol. 2011;185:433–8.
9. Stewart-Merrill SB, Thompson RH, Boorjian SA, Psutka SP, Lohse CM, Cheville JC, et al. Oncologic surveillance after surgical resection for renal cell carcinoma: a novel risk-based approach. J Clin Oncol. 2015;33:4151–7.
10. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. J Urol. 2003;170:2217–20.
11. Klatte T, Patard JJ, de Martino M, Bensalah K, Verhoest G, de la Taille A, et al. Tumor size does not predict risk of metastatic disease or prognosis of small renal cell carcinomas. J Urol. 2008;179:1719–26.
12. Crispen PL, Boorjian SA, Lohse CM, Sebo TS, Cheville JC, Blute ML, et al. Outcomes following partial nephrectomy by tumor size. J Urol. 2008;180:1912–7.
13. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al. AJCC cancer staging manual. 8th ed. New York: Springer International Publishing; 2017.
14. Ficarra V, Schips L, Guille F, Li G, De La Taille A, Prayer Galetti T, et al. Multiinstitutional European validation of the 2002 TNM staging system in conventional and papillary localized renal cell carcinoma. Cancer. 2005;104:968–74.
15. Frank I, Blute ML, Leibovich BC, Cheville JC, Lohse CM, Zincke H. Independent validation of the 2002 American Joint Committee on cancer primary tumor classification for renal cell carcinoma using a large, single institution cohort. J Urol. 2005;173:1889–92.
16. Novara G, Ficarra V, Antonelli A, Artibani W, Bertini R, Carini M, et al. Validation of the 2009 TNM version in a large multi-institutional cohort of patients treated for renal cell carcinoma: are further improvements needed? Eur Urol. 2010;58:588–95.
17. Kim SP, Alt AL, Weight CJ, Costello BA, Cheville JC, Lohse C, et al. Independent validation of the 2010 American Joint Committee on Cancer TNM classification for renal cell carcinoma: results from a large, single institution cohort. J Urol. 2011;185:2035–9.

18. Chen L, Li H, Gu L, Ma X, Li X, Zhang F, et al. Prognostic role of urinary collecting system invasion in renal cell carcinoma: a systematic review and meta-analysis. Sci Rep. 2016;6:21325.
19. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982;6:655–63.
20. Brookman-May S, May M, Shariat SF, Xylinas E, Stief C, Zigeuner R, et al. Features associated with recurrence beyond 5 years after nephrectomy and nephron-sparing surgery for renal cell carcinoma: development and internal validation of a risk model (PRELANE score) to predict late recurrence based on a large multicenter database (CORONA/SATURN Project). Eur Urol. 2013;64:472–7.
21. Zucchi A, Novara G, Costantini E, Antonelli A, Carini M, Carmignani G, et al. Prognostic factors in a large multi-institutional series of papillary renal cell carcinoma. BJU Int. 2012;109:1140–6.
22. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol. 2002;168:2395–400.
23. Delahunt B, Cheville JC, Martignoni G, Humphrey PA, Magi-Galluzzi C, McKenney J, et al. The International Society of Urological Pathology (ISUP) grading system for renal cell carcinoma and other prognostic parameters. Am J Surg Pathol. 2013;37:1490–504.
24. Muglia VF, Prando A. Renal cell carcinoma: histological classification and correlation with imaging findings. Radiol Bras. 2015;48:166–74.
25. Keegan KA, Schupp CW, Chamie K, Hellenthal NJ, Evans CP, Koppie TM. Histopathology of surgically treated renal cell carcinoma: survival differences by subtype and stage. J Urol. 2012;188:391–7.
26. Nguyen DP, Vertosick EA, Corradi RB, Vilaseca A, Benfante NE, Touijer KA, et al. Histological subtype of renal cell carcinoma significantly affects survival in the era of partial nephrectomy. Urol Oncol. 2016;34:259.e1–8.
27. Huang H, Pan XW, Huang Y, Xu DF, Cui XG, Li L, et al. Microvascular invasion as a prognostic indicator in renal cell carcinoma: a systematic review and meta-analysis. Int J Clin Exp Med. 2015;8:10779–10,792.
28. Dall'Oglio MF, Ribeiro-Filho LA, Antunes AA, Crippa A, Nesrallah L, Goncalves PD, et al. Microvascular tumor invasion, tumor size and Fuhrman grade: a pathological triad for prognostic evaluation of renal cell carcinoma. J Urol. 2007;178:425–8.
29. Keskin SK, Msaouel P, Hess KR, Yu KJ, Matin SF, Sircar K, et al. Outcomes of patients with renal cell carcinoma and sarcomatoid dedifferentiation treated with nephrectomy and systemic therapies over three decades: comparison between the cytokine (1987–2005) and the targeted therapy (2006–2015) eras. J Urol. 2017;198(3):530–7.
30. Shuch B, Bratslavsky G, Linehan WM, Srinivasan R. Sarcomatoid renal cell carcinoma: a comprehensive review of the biology and current treatment strategies. Oncologist. 2012;17:46–54.
31. Costello BA, Zhang B, Lohse CM, Boorjian SA, Cheville JC, Leibovich BC, et al. Outcomes of patients with sarcomatoid renal cell carcinoma: the Mayo Clinic experience. J Clin Oncol. 2013;31(6_suppl):359. https://doi.org/10.1200/jco.2013.31.6_suppl.359.
32. Belsante M, Darwish O, Youssef R, Bagrodia A, Kapur P, Sagalowsky AI, et al. Lymphovascular invasion in clear cell renal cell carcinoma – association with disease-free and cancer-specific survival. Urol Oncol. 2014;32(30):e23–8.
33. Lam JS, Shvarts O, Said JW, Pantuck AJ, Seligson DB, Aldridge ME, et al. Clinicopathologic and molecular correlations of necrosis in the primary tumor of patients with renal cell carcinoma. Cancer. 2005;103:2517–25.
34. Leibovich BC, Cheville JC, Lohse CM, Zincke H, Frank I, Kwon ED, et al. A scoring algorithm to predict survival for patients with metastatic clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. J Urol. 2005;174:1759–63. discussion 1763
35. Parker WP, Cheville JC, Frank I, Zaid HB, Lohse CM, Boorjian SA, et al. Application of the stage, size, grade, and necrosis (SSIGN) score for clear cell renal cell carcinoma in contemporary patients. Eur Urol. 2017;71:665–73.

36. Peckova K, Martinek P, Pivovarcikova K, Vanecek T, Alaghehbandan R, Prochazkova K, et al. Cystic and necrotic papillary renal cell carcinoma: prognosis, morphology, immunohistochemical, and molecular-genetic profile of 10 cases. Ann Diagn Pathol. 2017;26:23–30.
37. Cindolo L, de la Taille A, Messina G, Romis L, Abbou CC, Altieri V, et al. A preoperative clinical prognostic model for non-metastatic renal cell carcinoma. BJU Int. 2003;92:901–5.
38. Kattan MW, Reuter V, Motzer RJ, Katz J, Russo P. A postoperative prognostic nomogram for renal cell carcinoma. J Urol. 2001;166:63–7.
39. Veeratterapillay R, Rakhra S, El-Sherif A, Johnson M, Soomro N, Heer R. Can the Kattan nomogram still accurately predict prognosis in renal cell carcinoma using the revised 2010 tumor-nodes-metastasis reclassification? Int J Urol. 2012;19:773–6.
40. Leibovich BC, Blute ML, Cheville JC, Lohse CM, Frank I, Kwon ED, et al. Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer. 2003;97:1663–71.
41. Zigeuner R, Hutterer G, Chromecki T, Imamovic A, Kampel-Kettner K, Rehak P, et al. External validation of the Mayo Clinic stage, size, grade, and necrosis (SSIGN) score for clear-cell renal cell carcinoma in a single European centre applying routine pathology. Eur Urol. 2010;57:102–9.
42. Karakiewicz PI, Briganti A, Chun FK, Trinh QD, Perrotte P, Ficarra V, et al. Multi-institutional validation of a new renal cancer-specific survival nomogram. J Clin Oncol. 2007;25:1316–22.
43. Zisman A, Pantuck AJ, Dorey F, Said JW, Shvarts O, Quintana D, et al. Improved prognostication of renal cell carcinoma using an integrated staging system. J Clin Oncol. 2001;19:1649–57.
44. Ljungberg B, Albiges L, Bensalah K, Bex A, Giles RH, Hora M, et al. EAU guidelines: renal cell carcinoma. Eur Urol. 2017;
45. Donat SM, Diaz M, Bishoff JT, Coleman JA, Dahm P, Derweesh IH, et al. Follow-up for clinically localized renal neoplasms: AUA guideline. J Urol. 2013;190:407–16.
46. Pierorazio PM, Johnson MH, Patel HD, Sozio SM, Sharma R, Iyoha E, et al. Management of renal masses and localized renal cancer: systematic review and meta-analysis. J Urol. 2016;196(4):989–99.
47. Kang HW, Lee SK, Kim WT, Yun SJ, Lee SC, Kim WJ, et al. Surgical margin does not influence recurrence rate in pT1 clear cell renal cell carcinoma after partial nephrectomy: a multicenter study. J Surg Oncol. 2016;114:70–4.
48. Shah PH, Moreira DM, Okhunov Z, Patel VR, Chopra S, Razmaria AA, et al. Positive surgical margins increase risk of recurrence after partial nephrectomy for high risk renal tumors. J Urol. 2016;196:327–34.
49. Maurice MJ, Zhu H, Kim SP, Abouassaly R. Reexamining the association between positive surgical margins and survival after partial nephrectomy in a large American cohort. J Endourol. 2016;30:698–703.
50. Pierorazio PM, Hyams ES, Lin BM, Mullins JK, Allaf ME. Laparoscopic radical nephrectomy for large renal masses: critical assessment of perioperative and oncologic outcomes of stage T2a and T2b tumors. Urology. 2012;79:570–5.
51. Lau WK, Blute ML, Weaver AL, Torres VE, Zincke H. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. Mayo Clin Proc. 2000;75:1236–42.
52. Alemozaffar M, Filson CP, Master VA. The importance of surgical margins in renal cell and urothelial carcinomas. J Surg Oncol. 2016;113:316–22.
53. Yossepowitch O, Bjartell A, Eastham JA, Graefen M, Guillonneau BD, Karakiewicz PI, et al. Positive surgical margins in radical prostatectomy: outlining the problem and its long-term consequences. Eur Urol. 2008;55(1):87–99.
54. Bensalah K, Pantuck AJ, Rioux-Leclercq N, Thuret R, Montorsi F, Karakiewicz PI, et al. Positive surgical margin appears to have negligible impact on survival of renal cell carcinomas treated by nephron-sparing surgery. Eur Urol. 2010;57:466–71.
55. Abel EJ, Carrasco A, Karam J, Tamboli P, Delacroix S, Vaporciyan AA, et al. Positive vascular wall margins have minimal impact on cancer outcomes in non-metastatic RCC patients with tumor thrombus. BJU Int. 2014;114(5):667–73.

56. Liu NW, Wren JD, Vertosick E, Lee JK, Power NE, Benfante NE, et al. The prognostic impact of a positive vascular margin on pT3 clear cell renal cell carcinoma. J Urol. 2016;195:264–9.
57. Kassouf W, Siemens R, Morash C, Lacombe L, Jewett M, Goldenberg L, et al. Follow-up guidelines after radical or partial nephrectomy for localized and locally advanced renal cell carcinoma. Can Urol Assoc J. 2009;3:73–6.
58. Motzer RJ, Jonasch E, Agarwal N, Bhayani S, Bro WP, Chang SS, et al. NCCN clinical practice guidelines in oncology: kidney cancer version 2.2017. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. 2016.
59. Doornweerd BH, de Jong IJ, Bergman LM, Ananias HJ. Chest X-ray in the follow-up of renal cell carcinoma. World J Urol. 2014;32:1015–9.
60. Stewart SB, Thompson RH, Psutka SP, Cheville JC, Lohse CM, Boorjian SA, et al. Evaluation of the National Comprehensive Cancer Network and American Urological Association renal cell carcinoma surveillance guidelines. J Clin Oncol. 2014;32(36):4059–65.
61. Thompson RH, Atwell T, Schmit G, Lohse CM, Kurup AN, Weisbrod A, et al. Comparison of partial nephrectomy and percutaneous ablation for cT1 renal masses. Eur Urol. 2015;67:252–9.
62. Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v58–68.
63. Brenner DJ, Elliston CD. Estimated radiation risks potentially associated with full-body CT screening. Radiology. 2004;232:735–8.
64. Board on Radiation Effects Research Division on Earth and Life Sciences National Research Council of the National Academics. Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2. Washington, D.C.: National Academies Press; 2006.
65. Mileto A, Nelson RC, Paulson EK, Marin D. Dual-energy MDCT for imaging the renal mass. Am J Roentgenol. 2015;204:W640–7.
66. Capogrosso P, Capitanio U, La Croce G, Nini A, Salonia A, Montorsi F, et al. Follow-up after treatment for renal cell carcinoma: the evidence beyond the guidelines. Eur Urol. 2016;272:272–81.
67. Sohn W, Graves AJ, Tyson MD, O'Neil B, Chang SS, Ni S, et al. An empiric evaluation of the effect of variation in intensity of followup for surgically treated renal neoplasms on cancer specific survival. J Urol. 2017;197:37–43.
68. Park I, Lee JL, Ahn JH, Lee DH, Lee KH, Jeong IG, et al. Active surveillance for metastatic or recurrent renal cell carcinoma. J Cancer Res Clin Oncol. 2014;140:1421–8.
69. Rini BI, Dorff TB, Elson P, Rodriguez CS, Shepard D, Wood L, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol. 2016;17:1317–224.
70. Thomas AZ, Adibi M, Borregales LD, Hoang LN, Tamboli P, Jonasch E, et al. Surgical management of local retroperitoneal recurrence of renal cell carcinoma after radical nephrectomy. J Urol. 2015;194:316–22.
71. Ljungberg B, Alamdari FI, Rasmuson T, Roos G. Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. BJU Int. 1999;84:405–11.
72. Lam JS, Shvarts O, Leppert JT, Pantuck AJ, Figlin RA, Belldegrun AS. Postoperative surveillance protocol for patients with localized and locally advanced renal cell carcinoma based on a validated prognostic nomogram and risk group stratification system. J Urol. 2005;174:466–72. discussion 472; quiz 801
73. Siddiqui SA, Frank I, Cheville JC, Lohse CM, Leibovich BC, Blute ML. Postoperative surveillance for renal cell carcinoma: a multifactorial histological subtype specific protocol. BJU Int. 2009;104:778–85.
74. Williamson TJ, Pearson JR, Ischia J, Bolton DM, Lawrentschuk N. Guideline of guidelines: follow-up after nephrectomy for renal cell carcinoma. BJU Int. 2016;117:555–62.

Chapter 17
Cytoreductive Nephrectomy and Metastasectomy for Renal Cell Carcinoma

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Introduction

Renal cell carcinoma (RCC) is one of the most common cancers in the United States with an estimated 63,000 new cases diagnosed in 2017 [1]. Over the last several decades, there has been a rise in the incidence of RCC, and this is largely attributable to an increase in the incidental detection of localized tumors on cross-sectional imaging [2]. Despite this migration toward lower stage disease, nearly 30% of patients present with metastases at the time of initial diagnosis [3]. Historically, patients with disseminated disease have a poor prognosis with an estimated 5-year survival rate of less than 8% [4].

Surgery remains the cornerstone of treatment for patients with clinically localized RCC; however, up to 25% of those undergoing nephrectomy for localized disease will develop metastases [5]. Primary landing sites for metastatic RCC (mRCC) are the lung, lymph nodes, bone, liver, adrenal glands, and brain [3]. RCC is resistant to treatment with conventional chemotherapy, and until the last decade, systemic treatment was limited to cytokine immunotherapy [6]. Based on the results of two prospective randomized trials, cytoreductive nephrectomy (CN) prior to immunotherapy had been the accepted treatment paradigm for mRCC [7, 8]. The advent of targeted molecular therapies (TMT) has rapidly changed the treatment of this disease over the last decade. Additionally, more recently there has been a resurgence of interest in immunotherapy that has led to the development of novel immune

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checkpoint inhibitors such as nivolumab, which is now approved as a second-line therapy for mRCC [9]. With the rapidly changing landscape of systemic therapies for mRCC, the question remains as to the role and timing of CN and metastasectomy in combination with newer agents. In this chapter, we aim to provide historical context as well as clinical evidence for the use of CN and metastasectomy in the treatment of mRCC.

Rationale for Cytoreductive Nephrectomy

While the management of mRCC requires a multidisciplinary approach, the surgical removal of the renal primary tumor, known as a CN, remains one of the cornerstones of treatment. Historically, CN had been reserved for the palliation of those with severe bleeding or intractable pain. However, following the publication of several cases of spontaneous resolution of metastatic disease after CN, the routine use of nephrectomy in patients with mRCC began to take hold [10–12]. The rare spontaneous regression of metastatic sites following CN was generally attributed to the immunogenic properties of RCC, which manipulates the function of the immune system to suppress its antitumor defense mechanisms. RCC tumor cells are thought to resist exogenous growth-inhibitory signals, evade apoptosis, and acquire vasculature to proliferate, invade, and metastasize [13]. It has been proposed that CN removes these pro-angiogenic and mitogenic factors as well as relives immunological suppression by the primary tumor resulting in a positive effect on residual disease [14]. Another hypothesis is that the surgical loss of nephrons with CN results in a postoperative azotemia that acts to disrupt the tumor microenvironment and halt metastatic growth [15]. In fact, analysis of a prospective trial evaluating CN demonstrated that those with a postoperative azotemia had an increased overall survival (OS) of 17 months compared to 4 months in those without postoperative azotemia ($P = 0.0007$) [7, 15]. Despite the proposed hypotheses, the exact mechanisms for the observed effect of CN on survival remain unknown.

Cytoreductive Nephrectomy in the Pre-targeted Molecular Therapy Era

Early immunotherapy agents used for the treatment of mRCC included interferon-alpha (IFN-α) and interleukin-2 (IL-2). In retrospective studies of patients with mRCC treated with these agents, it was noted that those undergoing CN prior to immunotherapy administration fared better [16, 17]. Subsequently, the results of two prospective randomized controlled trials demonstrated an OS advantage in patients who underwent CN prior to IFN-α administration [7, 8].

The first of these two trials was SWOG 8949, which randomized 246 patients to upfront CN followed by IFN-α or immediate IFN-α without surgery [7]. The primary endpoint of OS was met demonstrating 11.1 months for CN plus IFN-α versus 8.1 months for IFN-α alone ($P = 0.05$). This survival advantage held true regardless of type of metastases or presence of disease measurability. The second trial was EORTC 30947, which randomized 85 patients in a manner similar to the SWOG trial [8]. This study found an improved OS of 17 months with CN plus IFN-α versus 7 months for the IFN-α only group (HR 0.54, 95% CI 0.31–0.94, $P = 0.03$). A combined analysis of these trials was performed and demonstrated an improved OS of 13.6 months versus 7.8 months in favor of those undergoing CN followed by IFN-α ($P = 0.002$) [18]. When the combined analysis was reviewed in depth, there was no difference seen in survival when stratified based on site of metastasis or disease measurability. There was, however, a survival advantage in those with improved performance status (ECOG 0 vs 1, $P < 0.0001$). In an updated analysis of SWOG 8949, independent predictors of worse survival included performance status, presence of metastatic sites other than the lung, elevated alkaline phosphatase, and anemia [19].

Beyond the survival advantage, these trials also demonstrated that CN is clinically feasible and safe. As compared to the prior retrospective series, mortality and complications associated with CN in both trials were acceptably low [7]. The combined mortality rate in both trials was 1.4%, and only 5.2% experienced a grade IV complication [18]. Moreover, there was no evidence to suggest that CN delays initiation of systemic therapy adversely, as nearly all patients were initiated on INF-α by 1 month postoperatively and only 5.6% of those who underwent CN were unable to receive INF-α. Even more importantly the response rates to INF-α between the two groups were not significantly different, but the observed response rates for both arms in these trials were exceptionally low with both less than 6.9%. Typical response rates for INF-α range from 10% to 15% in most series [6, 20, 21].

The other major immunotherapy agent in the pre-targeted therapy era was IL-2. There is less available evidence for CN prior to IL-2 administration mainly due to the significant toxicity from this agent, thereby limiting the ability to accrue enough participants to power a trial appropriately. Given the significant benefit seen in the trials for INF-α with CN, and owing to the similar immunologic antitumor effects between INF-α and IL-2, it is reasonable to infer a survival benefit with CN prior to IL-2 as well. While the response rates to INF-α range from 10% to 15% [21], the objective response rates to IL-2 have been significantly higher and therefore may demonstrate even better survival with CN [22–24]. Pantuck et al. identified 89 patients treated with IL-2 after undergoing CN and compared the survival of these patients to both arms of the SWOG 8949 trial [25]. The median OS for CN followed by IL-2 was 16.2 months, which was significantly greater than both the surgery plus IFN-α (11.1 months) and IFN-α only (8.1 months) cohorts ($P < 0.05$). Further retrospective studies suggest that CN improves response to IL-2. A comparison of a study of IL-2 with the renal primary in situ compared to those with CN followed by

IL-2 demonstrated a response rate improvement of 6% to 18% by removal of the primary tumor [17, 26]. However, as these are retrospective studies, the potential of selection bias should be kept in mind when interpreting these results.

Cytoreductive Nephrectomy in the Targeted Molecular Therapy Era

In the past 10 years, TMTs have largely replaced INF-α and IL-2 in the initial treatment of mRCC. TMTs include drugs targeting vascular endothelial growth factor (VEGF) and its receptors, mTOR inhibitors, and most recently immune checkpoint inhibitors. These drugs have demonstrated improved clinical outcomes with more favorable side effect profiles than INF-α and IL-2 [9, 27–32]. This shift in the first-line treatment of mRCC has created an unclear role for CN.

Unlike cytokine therapy, where a durable complete response can be seen in up to 6% of patients, TMTs commonly produce partial responses, with rare durable complete responses [33–36]. Given the numerous options for systemic treatment after initial treatment failure, practitioners have questioned whether CN is still necessary. While no high-level evidence exists in the TMT era, guidelines and experts still rely on the two randomized trials from the cytokine immunotherapy era [9, 37]. In fact, the majority (67–100%) of patients included in trials leading to the approval of the various TMTs underwent CN prior to receiving systemic therapy [27, 28, 31, 32].

At the present time, the evidence of benefit for CN in the TMT era is based entirely on retrospective studies [38–46]. A recent meta-analysis included data from 11 of these studies [47]. A total of 39,983 patients were included in the analysis which demonstrated a 54% reduced risk mortality for those undergoing CN prior to systemic therapy (HR 0.46, 95% CI 0.32–0.64, $P < 0.01$). In an expanded-access trial, Gore et al. reviewed 4543 patients who underwent treatment with sunitinib of whom 89% underwent CN [48]. In a sub-analysis, this trial demonstrated that CN prior to sunitinib compared to sunitinib alone was associated with increased progression-free survival (PFS; 12 vs 6.5 months, $P = 0.021$). Despite the benefit seen in these studies, a recent Cochran review of 13 TMT trials did not show any risk reduction in death with CN [49]. The difficulty in interpreting the results of these retrospective analyses is due to inherent selection bias, as those who have undergone CN are most likely to have favorable characteristics contributing to improved survival.

Two randomized controlled trials have been designed to assess the role of CN in the TMT era: the CARMENA (ClinicalTrials.gov identifier NCT0093033) and SURTIME (ClinicalTrials.gov identifier NCT01099423) trials. CARMENA is a French-led non-inferiority trial randomizing patients to CN followed by sunitinib compared to sunitinib alone. This trial opened in 2009, however, due to slow accrual it is 6 years behind schedule and likely to complete recruitment at the end of 2017 [50]. SURTIME was designed to address the timing of CN by randomizing patients

to sunitinib followed by CN as compared to those who underwent upfront CN followed by sunitinib. Unfortunately this trial also faced significant accrual difficulties and closed prematurely making it underpowered for its primary endpoints of PFS and OS [50]. Data from this trial was recently presented, and since only 99 patients were randomized, a revised statistical design was applied with the primary endpoint of PFS at 28 weeks [51]. The trial ultimately found that the sequence of CN and sunitinib did not affect the PFS at 28 weeks, with 42% of patients in both arms being free of disease progression. It is worth noting, however, that there seemed to be a signal for improved OS with deferred CN in the intention-to-treat population. This finding supports the potential use of TMTs prior to CN to aid with singling out patients with resistance to systemic treatment who might not benefit from CN in the first place.

Despite the evidence supporting continued use of CN in the TMT era, utilization of CN has seen a decrease in the past decade. Prior to the approval of sunitinib in 2005, review of a private insurance database found that the use of CN had peaked at 31.3%, but then declined to 14.8% by 2010 ($P = 0.045$) [52] . An evaluation of the Surveillance, Epidemiology, and End Results registry saw a decrease in CN from 50% in 2005 to 38% in 2008 [53]. With this decline in CN usage contrasting with the perceived benefit based on retrospective studies, there is a continued need for high-level evidence to determine the utility of CN in the TMT era.

Risk Stratification of Patients with Metastatic RCC

Despite the evidence that CN increases OS in patients with mRCC prior to administration of cytokine immunotherapy or TMTs, there remains a subset of patients who will not benefit from CN. Although morbidity and mortality rates have decreased for CN in modern series [7], there are always risks associated with surgery, and it has been shown that CN compared to nephrectomy for localized RCC has an increased mortality rate [54]. Besides the risk of surgery, if the patient has a disease process that does not benefit from CN, then there is an opportunity for disease progression in the postoperative period or potentially eliminating the ability to receive needed systemic therapy [55]. Therefore in order to safely and properly select candidates for CN, it is important to identify the prognostic indicators of survival in these patients.

Using data from the pre-TMT era, multiple models have been developed for the prognostication of patients with mRCC. Perhaps the most widely utilized risk stratification tool is one from Motzer et al. at Memorial Sloan-Kettering Cancer Center (MSKCC, Table 17.1) [6, 56]. After retrospectively evaluating patients with mRCC, five significant prognostic indicators were identified that could be modeled to stratify patients into three risk groups. Heng et al. subsequently developed a similar risk model using data from the TMT era [57]. This risk model, known as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model, uses six

Table 17.1 Prognostic models for patients with mRCC

Model (year)	Prognostic indicators of decreased survival
MSKCC (2002) [6]	Low Karnofsky performance status (<80%)
	High LDH (>1.5× ULN)
	Low serum hemoglobin (<LLN)
	High corrected serum calcium (>10 mg/dL or >ULN)
	Time from initial diagnosis to systemic treatment <1 yr
IMDC (2009) [57]	Low Karnofsky performance status (<80%)
	Time from initial diagnosis to IFN-a <1 yr
	Low serum hemoglobin (<LLN)
	High corrected serum calcium (>10 mg/dL or >ULN)
	High neutrophil count (>ULN)
	High platelet count (>ULN)

Abbreviations: *ULN* upper limit of normal, *LLN* lower limit of normal
Low risk = 0 factors, intermediate risk = 1–2 factors, high risk = >3 factors

prognostic indicators (four of which were included in the prior MSKCC model) to stratify patients into three risk groups. Having been externally validated [58], the IMDC model is now widely utilized for the risk stratification of patients with mRCC undergoing treatment with TMTs [59].

Patient Selection for Cytoreductive Nephrectomy

The MSKCC and IMDC models provided an ability to risk-stratify patients with mRCC but fail to aid in identifying the subset of patients who will not benefit from CN. There have been numerous retrospective analyses of cohorts attempting to identify predictive factors of those not likely to benefit from CN with worse OS [60, 61]. One predictor identified from these reviews was percentage of tumor volume that could be removed by CN. It was found that a reduction in >75% tumor burden was shown in the cytokine immunotherapy era to result in increased survival [60]. This has been shown to still be a predictive factor in the TMT era with some studies reporting that increased survival is seen with >90% tumor debulking [62]. As expected, the patients that benefit most from CN are those without central nervous system, bone, or liver metastasis and those with good performance status [60, 61].

One retrospective study examined 576 patients undergoing CN and identified seven preoperative factors independently associated with decreased survival

associated with the use of CN [63]. These factors included serum albumin less than the lower limit of normal, serum lactate dehydrogenase greater than the upper limit of normal, clinical T3 or T4, symptoms from metastases (e.g., bone pain, neurologic symptoms, etc.), presence of liver metastases, radiographic evidence of >1 cm of retroperitoneal adenopathy, and radiographic evidence of >1 cm of supradiaphragmatic adenopathy [63]. Using these findings, pre- and postoperative nomograms were created for prognostication of cancer-specific survival at 6 and 12 months after CN [64]. The discriminative accuracy of the pre- and postoperative nomograms were 0.76 and 0.74, respectively. A recent attempt at external validation of these nomograms found that only 5 of the 7 criteria are prognostic indicators for OS [65]. This demonstrates a continued need for updated and validated prognostic nomograms, especially as the systemic therapy regimens are rapidly changing.

Timing of Cytoreductive Nephrectomy

At the present time, there is no clear evidence as to the optimal timing for CN with respect to TMT. In clinical practice, however, CN is typically employed prior to TMT administration. The disadvantage to this approach is that this may result in a delay in the initiation of systemic therapy, potentially resulting in disease progression. The reverse sequence is not without risks as TMT administration may result in increased perioperative complications. There is, however, a case to be made for the performance of CN following initiating systemic therapy, as modern TMT agents have the ability to downsize the primary tumor increasing the feasibility of surgical extirpation. However, the rate of response of the primary tumor to TMT is somewhat limited [66]. For example, in patients with IVC tumor thrombus treated with TMT, 44% had a decrease in thrombus size, but only few patients had a change in thrombus level classification and therefore change of operative approach [67].

A recent phase II trial with upfront pazopanib prior to CN demonstrated the safety and efficacy of this treatment sequence; however, only a 14% mean reduction of primary tumor size was observed [68]. The agent currently demonstrating the highest rates of shrinkage of the primary tumor is axitinib with over 28% tumor diameter reduction [69]. This sequence allows for practitioners to use the TMT as a litmus test for overall treatment response. Indeed, early primary tumor response was identified in one study as an independent predictor of increased OS [70]. Ultimately a randomized clinical trial like SURTIME will better clarify the sequencing and timing of CN and TMT for mRCC and provide more information regarding perioperative complications.

Future of Cytoreductive Nephrectomy

Recently a new era of immunotherapy has emerged in the treatment of mRCC. The first novel immune checkpoint inhibitor, nivolumab, was approved in 2015 as a second-line agent for mRCC [71]. As with prior TMT trials, over 90% of the patients had undergone CN; thus questions remain regarding the benefit of CN in the modern era. This new checkpoint inhibitor is an antibody against programmed cell death protein 1 (PD-1) present on T cells and acts to prevent T-cell tolerance and the ability of tumor cells to escape immune destruction. There is a thought that checkpoint inhibitors may be more effective while the primary tumor is in place due to an increase in circulating tumor antigen that can be recognized by the unbound T cells, which would increase the immune response [72, 73]. There are ongoing trials evaluating presurgical systemic therapy with checkpoint inhibitors while the primary tumor is in place (ClinicalTrials.gov identifiers NCT02210117 & NCT0257522), and the results of these studies will better inform the role of CN when using this new class of therapeutic agents.

In the future we believe that the performance of CN will likely be driven by molecular biomarkers. Although these markers have yet to be identified, a recent study has begun sequencing the primary tumors of patients with mRCC in order to find genomic alterations that are predictors of OS in those undergoing CN [74]. Just as prognostic nomograms currently provide for risk stratification of patients with mRCC, the use of biomarkers may one day allow for the more precise identification of patients who stand to benefit from CN.

Metastasectomy

In the TMT era overall objective response rates to systemic therapy range from 20% to 40% with complete responses observed in less than 3% of patients [32, 35, 36]. Therefore, with the exception of the rare durable response to IL-2, removal of all synchronous or metachronous metastatic lesions provides the only potentially curable treatment alternative. Metastases from RCC are most common in the lung, lymph nodes, bone, liver, adrenal, and brain [3] . The evidence in favor of metastasectomy for oligometastatic mRCC is limited to restrospective studies which are cofounded by selection bias and typically lack of a comparator group [75–85]. Although limited, these studies do support that complete metastasectomy when feasible can improve cancer-specific survival and OS in those with mRCC.

One study in favor of metastasectomy was conducted by Alt et al. and observed that complete surgical resection of multiple RCC metastases was associated with significantly improved cancer-specific survival of 49.9% compared to only 13.9% in those without metastasectomy [76]. Additionally, Eggener et al. found that patients who underwent a complete metastasectomy demonstrated clinical benefit in all three MSKCC risk groups [77]. A thorough systematic review of 18 studies

was recently published and confirmed that a majority of published reports demonstrated a survival benefit with complete metastasectomy as compared to a partial or no resection [75]. Due to the heterogeneity between studies, a meta-analysis could not be conducted, but a review of all studies demonstrates that those with lung-only metastases and those that underwent complete metastasectomy had improved survival outcomes.

Conclusions

As the systemic therapies for mRCC are rapidly evolving, the use of CN will need to be continuously refined. Given the high level of evidence from prospective trials in favor of CN prior to cytokine immunotherapy as well as favorable data from retrospective studies performed in the TMT era, CN remains part of the standard treatment paradigm for patients with mRCC. We currently await the results of pending prospective trials that will hopefully yield answers as to the appropriateness and ideal timing of CN relative to the administration of TMTs. Additionally, for patients with a limited number of metastatic sites, metastasectomy should be considered, as the available data supports improved oncologic outcomes with complete surgical resection of metastatic sites. As with CN, questions remain regarding the role of metastasectomy given the availability of new TMTs such as immune checkpoint inhibitors.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7–30.
2. Pantuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. J Urol. 2001;166(5):1611–23.
3. Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urol Clin N Am. 2003;30:843–52.
4. Figlin RA. Renal cell carcinoma: management of advanced disease. J Urol. 1999;161(2):381–7.
5. Dabestani S, Thorstenson A, Lindblad P, Harmenberg U, Ljungberg B, Lundstam S. Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study. World J Urol. 2016;34(8):1081–6.
6. Motzer RJ, Bacik J, Murphy BA, Russo P, Mazumdar M. Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol. 2002;20(1):289–96.
7. Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med. 2001;345(23):1655–9.
8. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. European Organisation for Research and Treatment of Cancer (EORTC) genitourinary group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. Lancet. 2001;358(9286):966–70.

9. Choueiri TK, Motzer RJ. Systemi therapy for metastatic renal-cell carcinoma. N Engl J Med. 2017;376:354–66.
10. Marcus SG, Choyke PL, Reiter R, Jaffe GS, Alexander RB, Linehan WM, et al. Regression of metastatic renal cell carcinoma after cytoreductive nephrectomy. J Urol. 1993;150(2):463–6.
11. Snow R, Schellhammer P. Spontaneous regression of metastatic renal cell carcinoma. Urology. 1982;20(2):177–81.
12. Lokich J. Spontaneous regression of metastatic renal cancer: case report and literature review. Am J Clin Oncol. 1997;20(4):416–8.
13. Hahn WC, Weinberg RA. Rules for making human tumor cells. N Engl J Med. 2002;347(20):1593–603.
14. Rini BI, Campbell SC. The evolving role of surgery for advanced renal cell carcinoma in the era of molecular targeted therapy. J Urol. 2007;177(6):1978–84.
15. Gatenby RA, Gawlinski ET, Tangen CM, Flanigan RC, Crawford ED. The possible role of postoperative azotemia in enhanced survival of patients with metastatic renal cancer after cytoreductive nephrectomy. Cancer Res. 2002;62(18):5218–22.
16. Franklin JR, Figlin R, Rauch J, Gitlitz B, Belldegrun A. Cytoreductive surgery in the management of metastatic renal cell carcinoma: the UCLA experience. Semin Urol Oncol. 1996;14(4):230–6.
17. Walther MM, Yang JC, Pass HI, Linehan WM, Rosenberg SA. Cytoreductive surgery before high dose interleukin-2 based therapy in patients with metastatic renal cell carcinoma. J Urol. 1997;158:1675–8.
18. Flanigan RC, Mickisch G, Sylvester R, Tangen C, van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol. 2004;171(3):1071–6.
19. Lara PN, Tangen CM, Conlon S, Flanigan RC, Crawford ED. Southwest oncology group trial S8949. Predictors of survival in advanced renal cell carcionma: long-term results from southwest oncology group trial S8949. J Urol. 2009;181(2):512–7.
20. Pyrhönen S, Salminen E, Ruutu M, Lehtonen T, Nurmi M, Tammela T, et al. Prospective randomized trial of interferon alfa-2a plus vinblastine versus vinblastine alone in patients with advanced renal cell cancer. J Clin Oncol. 1999;17(9):2859–67.
21. Muss HB. Interferon therapy for renal cell carcinoma. Semin Oncol. 1987;14(2 Suppl 2):36–42.
22. McDermott DF, Regan MM, Clark JI, Flaherty LE, Weiss GR, Logan TF, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. J Clin Oncol. 2005;23(1):133–41.
23. Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. N Engl J Med. 1998;338:1272–8.
24. Yang JC, Sherry RM, Steinberg SM, Topalian SL, Schwartzentruber DJ, Hwu P, et al. Randomized study of high-dose and low-dose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol. 2003;21(16):3127–32.
25. Pantuck AJ, Belldegrun AS, Figlin RA. Nephrectomy and interleukin-2 for metastatic renal-cell carcinoma. N Engl J Med. 2001;345(23):1711–2.
26. Wagner JR, Walther MM, Linehan WM, White DE, Rosenberg SA, Yang JC. Interleukin-2 based immunotherapy for metastatic renal cell carcinoma with the kidney in place. J Urol. 1999;162:43–5.
27. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007;356:125–34.
28. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kappor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007;356:2271–81.
29. Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Archer L, et al. Phase III trial of bevacizumab plus interferon alfa versus interferon alfa monotherapy in patients with metastatic renal cell carcinoma: final results of CALGB 90206. J Clin Oncol. 2010;28(13):2137–43.

30. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010;28(6):1061–8.
31. Escudier B, Bellmunt J, Negrier S, Bajetta E, Melichar B, Bracarda S, et al. Phase III trial of bevacizumab plus interferon alfa-2a in patients with metastatic renal cell carcinoma (AVOREN): final analysis of overall survival. J Clin Oncol. 2010;28(13):2144–50.
32. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115–24.
33. Alva A, Daniels GA, Wong MK, Kaufman HL, Morse MA, McDermott DF, et al. Contemporary experience with high-dose interleukin-2 therapy and impact on survival in patients with metastatic melanoma and metastatic renal cell carcinoma. Cancer Immunol Immunother. 2016;65:1533–44.
34. Robert G, Gabbay G, Bram R, Wallerand H, Deminiere C, Cornelis F, et al. Complete histologic remission after sunitinib neoadjuvant therapy in T3b renal cell carcinoma. Eur Urol. 2009;55:1477–80.
35. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009;27(22):3584–90.
36. Heng DY, Rini BI, Garcia J, Wood L, Bukowski RM. Prolonged complete responses and near-complete responses to sunitinib in metastatic renal cell carcinoma. Clin Genitourin Cancer. 2007;5(7):446–51.
37. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: kidney cancer version 2.2017. National Comprehensive Cancer Network. 2017.
38. Choueiri TK, Xie W, Kollmannsberger C, North S, Knox JJ, Lampard JG, et al. The impact of cytoreductive nephrectomy on survival of patients with metastatic renal cell carcinoma receiving vascular endothelial growth factor targeted therapy. J Urol. 2011;195:60–6.
39. Conti SL, Thomas IC, Jagedorn JC, Chung BI, Chertow GM, Wagner TH, et al. Utilization of cytoreductive nephrectomy and patient survival in the targeted therapy era. Int J Cancer. 2014;134(9):2245–52.
40. Heng DYC, Wells JC, Rini BI, Beuselinck B, Lee JL, Knox JJ, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the international metastatic renal cell carcinoma database consortium. Eur Urol. 2014;66:704–10.
41. Bamias A, Tzannis K, Papatsoris A, Oudard S, Beuselinck B, Escudier B, et al. Prognostic significance of cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma treated with first-line sunitinib: a European multiinstitutional study. Clin Genitourin Cancer. 2014;12(5):373–83.
42. Abern MR, Scosyrev E, Tsivian M, Messing EM, Polascik TJ, Dudek AZ. Survival of patients undergoing cytoreductive surgery for metastatic renal cell carcinoma in the targeted-therapy era. Anticancer Res. 2014;34(5):2405–11.
43. Aizer AA, Urun Y, McKay RR, Kibel AS, Nguyen PL, Choueiri TK. Cytoreductive nephrectomy in patients with metastatic non-clear-cell renal cell carcinoma (RCC). BJU Int. 2014;113(5b):E67–74.
44. Mathieu R, Pignot G, Ingles A, Crepel M, Bigot P, Bernhard JC, et al. Nephrectomy improves overall survival in patients with metastatic renal cell carcinoma in cases of favorable MSKCC or ECOG prognostic features. Urol Oncol. 2015;33(8):e9–15.
45. de Groot S, Redekop WK, Sleijfer S, Oosterwijk E, Bex A, Kiemeney LA, et al. Survival in patients with primary metastatic renal cell carcinoma treated with sunitinib with or without previous cytoreductive nephrectomy: results from a population-based registry. Urology. 2016;95:121–7.
46. Hanna N, Sun M, Meyer CP, Nguyen PL, Pal SK, Chang SL, et al. Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: a National Cancer Data Base study. J Clin Oncol. 2016;32(27):3267–75.

47. Petrelli F, Coinu A, Vavassori I, Cabiddu M, Borgonovo K, Ghilardi M, et al. Cytoreductive nephrectomy in metastatic renal cell carcinoma treated with targeted therapies: a systematic review with a meta-analysis. Clin Genitourin Cancer. 2016;14(6):465–72.
48. Gore ME, Szczylik C, Porta C, Bracarda S, Bjarnason GA, Oudard S, et al. Final results from the large sunitinib global expanded-access trial in metastatic renal cell carcinoma. Br J Cancer. 2015;113(1):12–9.
49. Coppin C, Le L, Wilt TJ, Kollmannsberger C. Targeted therapy for advanced cell carcinoma. Cochrane Database Syst Rev. 2008;2:CD006017.
50. Stewart GD, Aitchison M, Bex A, Larkin J, Lawless C, Mejean A, et al. Cytoreductive nephrectomy in the tyrosine kinase inhibitor era: a question that may never be answered. Eur Urol. 2017;71:845–7.
51. Bex A, Mulders M, Jewett MAS, Wagstaff J, van Velthoven R, Laguna Pes PM, et al. Immediate versus deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma recieving sunitinib. Ann Oncol. 2017;28(suppl_5):v605–49.
52. Psutka SP, Kim SP, Gross CP, van Houten H, Thompson RH, Abouassaly R, et al. The impact of targeted therapy on management of metastatic renal cell carcinoma: trends in systemic therapy and cytoreductive nephrectomy utilization. Urology. 2015;85:442–51.
53. Tsao C, Small AC, Kates M, Moshier EL, Wisnivesky JP, Gartrell BA, et al. Cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy in the United States: a SEER analysis. World J Urol. 2013;31(6):1535–9.
54. Cloutier V, Capitanio U, Zini L, Perotte P, Jeldres C, Shariat SF, et al. Thirty-day mortality after nephrectomy: clinical implications for informed consent. Eur Urol. 2009;56(6):998–1003.
55. Kutikov A, Uzzo RG, Caraway A, Reese CT, Egleston BL, Chet DYT, et al. Utilization of systemic therapy and factors improving survival for patients undergoing cytoreductive nephrectomy. BJU Int. 2010;106(2):218–23.
56. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amserdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol. 1999;17:2530–40.
57. Heng DYC, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009;27(34):5794–9.
58. Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 2013;14(2):141–8.
59. Li H, Samawi H, Heng DY. The use of prognostic factors in metastatic renal cell carcinoma. Urol Oncol. 2015;33(12):509–16.
60. Fallick ML, McDermott DF, LaRock D, Long JP, Atkins MB. Nephrectomy before interleukin-2 therapy for patients with metastatic renal cell carcinoma. J Urol. 1997;158:1691–5.
61. Leibovich BC, Han KR, Bui MH, Pantuck AJ, Dorey FJ, Figlin RA, et al. Scoring algorithm to predict survival after nephrectomy and immunotherapy in patients with metastatic renal cell carcinoma: a stratification tool for prospective clinical trials. Cancer. 2003;98(12):2566–75.
62. Barbastefano J, Garcia JA, Elson P, Wood LS, Lane BR, Dreicer R, et al. Association of percentage of tumour burden removed with debulking nephrectomy and progression-free survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. BJU Int. 2010;106(9):1266–9.
63. Culp SH, Tannir NM, Abel EJ, Margulis V, Tamboli P, Matin SF, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? Cancer. 2010;116(14):3378–88.
64. Margulis V, Shariat SF, Rapoport Y, Rink M, Sjoberg DD, Tannir NM, et al. Development of accurate models for individualized prediction of survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. Eur Urol. 2013;63(5):947–52.
65. Manley BJ, Tennenbaum DM, Vertosick EA, Hsieh HH, Sjoberg DD, Assel M, et al. The difficulty in selecting patients for cytoreductive nephrectomy: an evaluation of previously described predictive models. Urol Oncol. 2017;35:35.e1–5.

66. Krabbe LM, Haddad AQ, Westerman ME, Margulis V. Surgical management of metastatic renal cell carcinoma in the era of targeted therapies. World J Urol. 2014;32:615–22.
67. Cost NG, Delacroix SE Jr, Sleeper JP, Smith PJ, Youssef RF, Chapin BF, et al. The impact of targeted molecular therapies on the level of renal cell carcinoma vena caval tumor thrombus. Eur Urol. 2011;59(6):912–8.
68. Powles T, Sarwar N, Stockdale A, Sarker SJ, Boleti E, Protheroe A, et al. Safety and efficacy of pazopanib therapy prior to planned nephrectomy in metastatic clear cell renal cancer. JAMA Oncol. 2016;2(10):1303–9.
69. Karam JA, Devine CE, Urbauer DL, Lozano M, Maity T, Ahrar K, et al. Phase 2 trial of neoadjuvant axitinib in patients with locally advanced nonmetastatic clear cell renal cell carcinoma. Eur Urol. 2014;66(5):874–80.
70. Abel EJ, Culp SH, Tannir NM, Tamboli P, Matin SF, Wood CG. Early primary tumor size reduction is an independent predictor of improved overall survival in metastatic renal cell carcinoma patients treated with sunitinib. Eur Urol. 2011;60(6):1273–9.
71. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med. 2015;373(19):1803–13.
72. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Cancer Res. 2007;13(6):1757–61.
73. Harshman LC, Drake CG, Choueiri TK. PD-1 blockade in renal cell carcinoma: to equilibrium and beyond. Cancer Immunol Res. 2014;2(12):1132–41.
74. Tennenbaum DM, Manley BJ, Zabor E, Becerra MF, Carlo MI, Casuscelli J, et al. Genomic alterations as predictors of survival among patients within a combined cohort with clear cell renal cell carcinoma undergoing cytoreductive nephrectomy. Urol Oncol. 2017;35(8):532.e7–532.e13.
75. Dabestani S, Marconi L, Hofmann F, Stewart F, Lam TB, Canfield SE, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. Lancet Oncol. 2014;15(12):e549–61.
76. Alt AL, Boorjian SA, Lohse CM, Costello BA, Leibovich BC, Blute ML. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. Cancer. 2011;117(13):2873–82.
77. Eggener SE, Yossepowitch O, Kundu S, Motzer RJ, Russo P. Risk score and metastasectomy independently impact prognosis of patients with recurrent renal cell carcinoma. J Urol. 2008;180(3):873–8.
78. Karam JA, Rini BI, Varella L, Garcia JA, Dreicer R, Choueiri TK, et al. Metastasectomy following targeted therapy in patients with advanced renal cell carcinoma. J Urol. 2011;185(2):439–44.
79. van der Poel HG, Roukema JA, Horenblas S, van Geel AN, Debruyne FM. Metastasectomy in renal cell carcinoma: a multicenter retrospective analysis. Eur Urol. 1999;35(3):197–203.
80. Kierney PC, van Heerden JA, Segura JW, Weaver AL. Surgeon's role in the management of solitary renal cell carcinoma metastases occurring subsequent to initial curative nephrectomy: an institutional review. Ann Surg Oncol. 1994;1(4):345–52.
81. Kavolius JP, Mastorakos DP, Pavlovich C, Russo P, Burt ME, Brady MS. Resection of metastatic renal cell carcinoma. J Clin Oncol. 1998;16(6):2261–6.
82. Lee SE, Kwak C, Byun SS, Gill MC, Chang IH, Kim YJ, et al. Metastatectomy prior to immunochemotherapy for metastatic renal cell carcinoma. Urol Int. 2006;76(3):256–63.
83. Russo P, Synder M, Vickers A, Kondagunta V, Motzer R. Cytoreductive nephrectomy and nephrectomy/complete metastasectomy for metastatic renal cancer. Sci World J. 2007;7:768–78.
84. Kwak C, Park YH, Jeong CW, Lee SE, Ku JH. Metastasectomy without systemic therapy in metastatic renal cell carcinoma: comparison with conservative treatment. Urol Int. 2007;79(2):145–51.
85. Tosco L, Van Poppel H, Frea B, Gregoraci G, Joniau S. Survival and impact of clinical prognostic factors in surgically treated metastatic renal cell carcinoma. Eur Urol. 2013;63(4):646–52.

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