CLINICAL MANAGEMENT OF RENAL TUMORS
Clinical Management of Renal Tumors

Edited by
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and
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To our patients with renal cell carcinoma
Renal cancer accounts for 3% of all malignant tumors. An estimated 39,000 new cases and 13,000 deaths were predicted for 2006. Carcinomas arising from the renal epithelium account for approximately 85% of renal tumors. The major risk factors include smoking (responsible for 24% to 30% of all cases of renal cell carcinoma [RCC]), obesity, and various environmental and occupational factors. Presentation varies, with most patients having a solitary lesion and 33% presenting with locally advanced or metastatic disease. An additional 20% to 40% of surgically resected patients may ultimately develop metastatic disease. Advances in imaging and techniques have increased the percent of patients who have renal masses discovered incidentally, but a significant percent of patients still present with surgically unresectable disease. We now recognize the importance of histology in predicting the biologic characteristics and clinical behavior of renal cancers.

Clear cell renal carcinoma is the most common type of renal cancer, accounting for approximately 70% of renal epithelial malignancies and arising from the proximal convoluted tubule. Papillary renal cancer is the second most common type, comprising 10% to 15% of renal tumors. Understanding histologic subtypes and associated gene alterations has provided the opportunity to develop targeted therapeutic agents.

Patients with the von Hippel–Lindau (VHL) syndrome and RCC have provided a unique opportunity to study the development of clear cell tumors and their genetic characteristics. In sporadic renal cancer, both the maternal and paternal VHL alleles are inactivated by acquired mutations, whereas in the VHL syndrome the first mutation is inherited. Loss of VHL function may be responsible for approximately 60% of cases of sporadic clear cell renal carcinomas.

The VHL protein is the product of the VHL gene, functions as a tumor suppressor gene, and is responsible for ubiquination of hypoxia-inducible factor α (HIF-α) and its subsequent degradation. In conditions of hypoxia or abnormal VHL function, HIF-α accumulates and activates the transcription of a variety of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor β (PDGF-β). Blocking the VEGF pathway and the function of HIF-α, therefore, are currently the major therapeutic strategies for treatment of advanced renal cancer, replacing immunotherapy utilizing cytokines such as interferon and interleukin-2 (IL-2). A series of new agents such as sunitinib, sorafenib, temsirolimus, and bevacizumab are now being utilized in patients with advanced clear cell carcinoma.

Major advances in the surgical management of renal tumors have also occurred over the last 10 to 15 years. The type of surgical intervention is determined by tumor size, location, and involvement of the inferior vena cava (IVC), and includes nephrectomy and partial (nephron-sparing) nephrectomy performed through an open abdominal or laparoscopic procedure. Partial nephrectomy preserves long-term renal function for patients with tumors smaller than 4 cm, and radical nephrectomy remains the treatment of choice for tumors 4 cm or larger or multiple lesions when the opposite kidney is
normal. Partial nephrectomy is also indicated for patients who have a solitary kidney, bilateral renal masses, or severe renal insufficiency. Laparoscopic procedures for complete or partial nephrectomy are emerging minimally invasive procedures with shorter hospitalization, decreased narcotic use, and a more rapid convalescence.

In conclusion, the treatment paradigms for patients with localized and advanced renal cell carcinoma have changed dramatically in the last 5 to 10 years. Surgical advances are now mirrored by the dramatic changes in therapy available for metastatic disease. The chapters in Clinical Management of Renal Tumors provide an update for urologists, medical oncologists, and researchers who are interested in this malignancy.

Ronald M. Bukowski, MD
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The images listed below appear in the color insert following page 334.

**Color Plate 1.**  
Fig. 2, Chapter 4: (A) Papillary renal cell carcinoma (PRCC) has a pseudocapsule and extensive hemorrhage and necrosis. It is composed of papillae covered by a single layer of tumor cells with scant cytoplasm. (B) The fibrovascular cores are expanded with foamy histiocytes.

Fig. 3, Chapter 4: (A) Renal cell carcinoma, chromophobe type (ChRCC) forms a circumscribed, nonencapsulated mass with a homogeneous light brown cut surface. (B) The large and polygonal tumor cells have finely reticulated cytoplasm, prominent cell border, and irregular nuclei with perinuclear clearing.

**Color Plate 2.**  
Fig. 1, Chapter 6: Phenotypic manifestations of von Hippel-Lindau (VHL). Renal masses are common in VHL patients. (A) Computed tomography (CT) scans of a VHL patient demonstrating characteristic bilateral multifocal renal lesions consisting of simple and complex cysts as well as enhancing solid masses. (B) Gross specimen removed from a VHL patient showing classic multiple golden-yellow tumors. (C) Hematoxylin and eosin (H&E) stain of a classic clear cell renal carcinoma found in patients with VHL. (D) In addition to renal manifestations, VHL affects organs systems throughout the body. (From Linehan WM, et al. Genetic Basis of Cancer of the Kidney: Disease-Specific Approaches to Therapy. 2004.)

**Color Plate 3.**  
Fig. 2, Chapter 6: Manifestations and genetics of hereditary papillary renal cancer (HPRC). Patients with HPRC primarily develop bilateral multifocal renal masses. (A) Abdominal CT demonstrates HPRC tumors with characteristic poor enhancement on contrasted study that may frequently be mistaken for simple cysts. The tumors are best seen on late phase images of a contrast CT. Low (B) and high (C) power H&E stain of type I papillary renal cell carcinoma (RCC) seen in patients with HPRC. (D) Fluorescence in situ hybridization (FISH) using a MET probe demonstrating trisomy of chromosome 7 (red signal) in papillary type I RCC compared with chromosome 11 serving as control (green signal).
Color Plate 4.  

Fig. 6, Chapter 6: VHL gene mutation, downstream effects, and molecular targeting of the VHL pathway. (A) With a VHL gene mutation, the VHL complex is disrupted and allows for accumulation of HIF with subsequent activation of downstream pathways for angiogenesis, glucose transport, and growth. (B) Inhibition of over-accumulated HIF and prevention of downstream activation with a small molecule is one of the strategies for molecular targeting of the VHL/HIF pathway. (C) New tyrosine kinase inhibitors as well as direct vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptor blockers are examples of downstream targeting. EGFR, epidermal growth factor receptor; TGF, transforming growth factor. (From Linehan WM et al. Genetic Basis of Cancer of the Kidney: Disease-Specific Approaches to Therapy. 2004.)
Renal Cell Carcinoma: Background

Ronald M. Bukowski and Andrew C. Novick

KEYWORDS
RENAL CELL CARCINOMA

Renal cancer accounts for 2 to 3% of all malignant tumors. An estimated 39,000 new cases and 13,000 deaths were predicted for 2006. Renal cancer is diagnosed in patients ranging from 40 to 70 years of age, with a male predominance of 1.6 to 1.0. A comparison of 43,685 cases of renal cancer diagnosed in the period 1973 to 1985 with those diagnosed from 1986 to 1998 (Surveillance, Epidemiology, and End Results [SEER] database) demonstrated a marginal increase in the proportion of localized cancers and a decrease in advanced cases in the latter group. The differences were not significant, and importantly, overall survival was not improved. While increased imaging and laboratory testing may generally explain the increased incidence, other factors may play a role.

Risk factors include smoking (responsible for 24% to 30% of all cases of renal cell carcinoma [RCC]), obesity, sedentary lifestyle, environmental and occupational factors (asbestos, cadmium, polycyclic hydrocarbons, solvents), and long-term use of diuretics or phenacetin-containing analgesics. Patients with end-stage renal disease undergoing dialysis, particularly those with cystic disease, are also more likely to develop RCC than the general population.

Renal cell carcinomas arising from the renal epithelium account for approximately 85% percent of renal tumors. Presentation varies, with most presenting with a solitary lesion, less than 4% presenting with bilateral renal masses, and 33% presenting with locally advanced or metastatic disease. Additionally, 20% to 40% of surgically resected patients may ultimately develop metastatic disease. Historically, patients presented with the classic triad of symptoms including flank pain, hematuria, and a palpable abdominal mass, but currently, increasing numbers of individuals are being diagnosed when asymptomatic with an incidental renal mass found. Advances in imaging and techniques have increased the percent of patients who are eligible for surgical intervention, but a significant number of patients still present with surgically unresectable disease.

Patients with advanced disease may present with symptoms produced by the tumor or resulting from chemical abnormalities, or paraneoplastic syndromes associated with
the neoplasm. Common sites for metastasis include lung, bone, lymph nodes, adrenal gland, liver, soft tissue, and brain.

HISTOLOGY

The importance of histology in predicting the biologic characteristics and clinical behavior of renal cancers was recognized in the last decade. Renal cell carcinoma represents a group of histologic subtypes with unique morphologic and genetic characteristics. The Heidelberg classification of renal cell tumors was developed to subdivide renal cell tumors into benign and malignant subtypes with associated genetic alterations.5

Clear cell renal carcinoma is the most common type of renal cancer, accounting for approximately 70% of renal epithelial malignancies and arising from the proximal convoluted tubule. Papillary renal cancer is the second most common type, comprising 10% to 15% of renal tumors. Understanding histologic subtypes and associated gene alterations has provided the opportunity to develop targeted therapeutic agents.

VON HIPPEL-LINDAU (VHL) SYNDROME

Patients with the VHL syndrome provided researchers a unique opportunity to study the development of clear cell tumors and their genetic characteristics. In sporadic renal cancer, both the maternal and paternal VHL alleles are inactivated by acquired mutations whereas in the VHL syndrome the first mutation is inherited. Loss of VHL function may be responsible for approximately 60% of cases of sporadic clear-cell renal carcinomas.6

The VHL protein is the product of the VHL gene, functions as a tumor suppressor gene, and is responsible for ubiquitination of hypoxia-inducible factor α (HIF-α), tagging it for degradation.5,6 In conditions of hypoxia or abnormal VHL function, HIF-α accumulates and activates the transcription of a variety of hypoxia-inducible genes. These include vascular endothelial growth factor (VEGF), platelet-derived growth factor β (PDGF-β), transforming growth factor α (TGF-α), and erythropoietin (EPO). The VHL gene may enable this process to be controlled through suppressing angiogenesis, but loss of the VHL gene or its function leads to increased secretion of VEGF and PDGF and appears to produce the vascular phenotype associated with this tumor. Blocking VEGF and thus the function of HIF-α is currently the major therapeutic strategy for treatment of advanced renal cancer, replacing immunotherapy with the cytokines interferon and interleukin-2 (IL-2).

SURGICAL MANAGEMENT OF RENAL CELL CARCINOMA

The management of renal cancer is based on the stage at diagnosis, the sites of metastatic disease, and the patient characteristics, including comorbid diseases and functional status. Surgical intervention is determined by tumor size, location, and involvement of the inferior vena cava (IVC), and includes nephrectomy and partial (nephron-sparing) nephrectomy performed through an open abdominal or laparoscopic procedure. Careful case selection allows for surgical resection of renal tumors with vena caval tumor extension and limited metastatic disease using a flank, transperitoneal, transabdominal, or
Partial nephrectomy preserves long-term renal function for patients with tumors <4 cm, and radical nephrectomy remains the treatment of choice for tumors ≥4 cm or multiple lesions when the opposite kidney is normal. Partial nephrectomy is also indicated for patients who have a solitary kidney, bilateral renal masses, or severe renal insufficiency. Laparoscopic procedures for complete or partial nephrectomy are emerging minimally invasive procedures with shorter hospitalization, decreased narcotic use, a more rapid convalescence, with continued efforts to improve operative techniques including reduction of warm renal ischemia time, renal hemorrhage, and urinary leakage.

Cytoreductive nephrectomy may provide survival and palliative advantages, and should be considered for patients presenting with synchronous metastatic renal cancer based on the potential for spontaneous regression of metastatic disease (primarily lung metastasis), but understanding that the primary tumor rarely responds to systemic disease. Studies have demonstrated that cytoreductive nephrectomy followed by interferon-alfa-2b therapy can delay time to progression and improve survival for patients with metastatic renal cancer.

Three approaches for patients with localized renal tumors are currently employed: (1) active surveillance, especially in the older patient; (2) partial nephrectomy; and (3) radical nephrectomy. The latter remains the most commonly performed procedure for patients with localized renal cell carcinoma, and the major story in recent years has been the incorporation or development of laparoscopic nephrectomy as a standard of care for selected patients, namely those who have T1 or T2 renal tumors. The study by Kavoussi et al. demonstrates the long-term efficacy of laparoscopic radical nephrectomy. In this study, open and laparoscopic nephrectomy for T1 to T2 cancers was compared. At a median follow-up in excess of 6 years, 5-year and 10-year cancer-specific survival appears to be similar. For patients with locally advanced disease (T3a and T3b tumors) and those requiring lymphadenectomy, the open technique remains the standard of care.

Currently, increasing numbers of patients are being seen who are candidates for nephron-sparing approaches. Data suggest that the stage I tumors are smaller and are being detected at an earlier stage, increasing the number of patients eligible for nephron-sparing surgery. However, partial nephrectomy is still being performed on a limited number of these cases. A study from the University of Michigan, looking at the percentage of surgically treated patients undergoing partial nephrectomy, shows that only 12.3% had this procedure, suggesting nephron-sparing surgery is still underutilized.

Clinically, preservation of renal function remains an important issue. The patients considered for partial nephrectomy are those with a tumor less than 4 cm in size. In patients with occult multicentric tumors, partial nephrectomy is not optimal, but the incidence of occult multicentric tumors is much less with smaller and with low stage tumors. This observation has led to modification of the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system where patients with T1 tumors are now subdivided into those with T1a versus T1b; the aim here is to delineate those patients, namely those with T1a tumors, who are most suitable for an elective partial nephrectomy with a normal opposite kidney.

The indications for elective partial nephrectomy may be changing, with recent reports suggesting partial nephrectomy in patients with T1b tumors (4 to 7 cm in size) is an option. The experience at the Cleveland Clinic confirms these findings.
The importance of elective partial nephrectomy is related to functional and quality of life advantages associated with preservation of renal tissue, even in the presence of a normal contralateral kidney. Patients with small remnant kidneys and reduced renal function are prone to developing hyperfiltration, renal injury, and remnant kidney nephropathy. The risk of this problem is directly related to the amount of remaining renal tissue and develops over an extended period. Histologically, focal segmental glomerulosclerosis develops, and is characterized by proteinuria.

Open partial nephrectomy is the gold standard, and is associated with the largest experience and longest follow-up. More than 2500 open partial nephrectomies have been performed at the Cleveland Clinic with long-term results in 1231 patients treated prior to 2002. This experience, along with that of many other centers, has shown that preservation of renal function can be achieved in a very high percentage of these cases, with excellent 10-year survival comparable to that obtained with a total nephrectomy. In patients with localized, sporadic renal cell cancer, recurrent malignancy develops in under 10% of treated cases. A new era of minimally invasive nephron-sparing surgery is now being explored.

A retrospective review of Cleveland Clinic data in 1049 patients who underwent either a laparoscopic or an open partial nephrectomy for a single, localized, sporadic, suspected renal cancer that was less than 7 cm in size was conducted. There were 595 open and 454 laparoscopic procedures. Patients were not matched, and it is not surprising that there were more high-risk patients in the open group, more with comorbid disease, more with symptomatic tumors, many more with solitary kidneys, more with impaired renal function, more with T1b tumors, and more with central tumors.

Laparoscopic surgery was associated with about 1 hour less of operating time, but longer renal ischemia time. There were a small number of cases in the laparoscopic group that converted to radical nephrectomy, and a small number converted to open surgery, differences that were not significant. The major finding in the study is that while both approaches were successful in the majority of cases, there was an increase in postoperative urologic or renal morbidity with the laparoscopic approach. There were twice as many renal or urologic complications. Most notable among these was postoperative hemorrhage, which occurred in 5.7% of patients in the laparoscopic group, and only 2% in the open group. There was no significant difference in the incidence of urinary fistulas. A few kidneys were lost in the laparoscopic group, but this was not significant. Another major difference was in the need for a subsequent procedure generally to treat a complication. That occurred about twice as commonly in the laparoscopic group as in the open group. A diagnosis of renal cancer was made in 84% of patients in the open group and only 73% in the laparoscopic group, probably based on tumor size. There was no significant difference in positive surgical margin rate or in very early 3-year cancer-specific outcome. Cancer was less likely to be detected with the laparoscopic surgery, and postoperative urological complications, hemorrhage in particular, and the need for a subsequent procedure were respectively two, three, and four times more likely to occur with laparoscopic surgery.

Both of these approaches are successful and effective. For a T1 tumor, the laparoscopic approach can yield functional and short-term oncologic outcomes that appear equivalent to the open technique associated with longer ischemia time and more postoperative complications. The open approach remains the standard for more complex tumors.
Patients with a single small peripheral tumor, particularly older individuals with comorbid disease, may be less than ideal candidates for an open or laparoscopic partial nephrectomy. Patients who have undergone a previous renal operation or have developed a local recurrence after a partial nephrectomy are high-risk surgical candidates, as are individuals with severe azotemia, where any form of major intervention on the kidney may result in a need for dialysis. Ablation may be a safer approach, but the overall utility of these approaches remains to be fully defined.

Control of tumor margins during ablation procedures is at times uncertain. An example is the use of radiofrequency ablation, during which the extent of tumor destruction is difficult to quantitate, in contrast to partial nephrectomy. In this latter case, tissue margins, stage, and grade can be determined. Studies with these forms of ablation currently utilized indirect techniques such as imaging to infer a successful outcome.

A small group of 60 patients with small tumors have been treated with laparoscopic renal cryoablation, and have been followed for 5 years or more at the Cleveland Clinic. Their median follow-up is 6 years. So far the recurrence rate has been relatively low and the cancer specific-survival rate is acceptable. With cryoablation we have a technique for monitoring intraoperative tumor destruction. This has been studied in preclinical models before we applied it to patients, and it involves the use of intraoperative ultrasound, and distinguishes cryoablation from other techniques.

When considering minimally invasive nephron-sparing surgery, two options are available: laparoscopic partial nephrectomy and tumor ablation. The morbidity with laparoscopic partial nephrectomy is somewhat higher. Renal function is equally well preserved with both, but the greater amount of oncologic information that we obtain and the greater oncologic efficacy with laparoscopic partial nephrectomy today is a major advantage over ablative approaches. When nephron-sparing therapy for renal cancer is considered, open partial nephrectomy is the gold standard based on the established long-term efficacy. Laparoscopic partial nephrectomy in the hands of skilled surgeons is applicable for selected patients, but there remain significant technical limitations; tumor ablation approaches still need to be considered investigational pending longer term outcome data.

**SYSTEMIC THERAPY: METASTATIC DISEASE**

Immunotherapy consisting of IL-2 and interferon-α (IFN-α) has been the standard approach for systemic treatment of metastatic renal cell carcinoma, in addition to clinical trials investigating new agents. Responses were best with high-dose intravenous IL-2 (21%) compared to low-dose intravenous IL-2 (11%) and subcutaneous IL-2 (10%), although no survival advantage was observed. Similar response rates were reported comparing high-dose IL-2 (23.2%) versus subcutaneous IL-2 plus IFN-α (9.9%) and no survival advantage. The high-dose IL-2 regimens have been associated with complete durable remissions in 5% to 7% of treated subjects.

Interferon-α has been established as the standard comparative treatment arm for phase 3 clinical trials of new agents for the treatment of metastatic renal cancer. Several randomized trials have demonstrated improvement in medial survival for treated patients, and in a retrospective review a median overall survival (OS) of 13.1 months and a median time to progression (TTP) of 4.7 months for IFN-α patients was noted.
Retrospective analysis of untreated and previously treated patients with metastatic renal cancer has identified clinical characteristics that can be used to categorize patients into groups with differences in prognosis. For previously untreated patients, an initial prognostic model was developed, which has been validated and expanded. Five clinical characteristics were identified and validated at the Cleveland Clinic. These prognostic criteria have been utilized in phase 3 clinical trials of sorafenib, sunitinib, temsirolimus (CCI-779), and bevacizumab.

The cloning of the VHL tumor suppressor gene and the elucidation of its role in upregulating growth factors associated with angiogenesis are recent discoveries that have provided insights into RCC biology, as well as defining a series of potential targets for novel therapeutic approaches. Renal cell carcinoma is a highly vascularized tumor; therefore, controlling its vascularity by targeting angiogenic factors could theoretically control its growth and survival. Several isoforms of VEGF and its receptors (VEGFR) have been identified; VEGF-A, VEGFR-1, and VEGFR-2 were found to be overexpressed in RCC compared to normal renal tissue, and VEGFR-2 is believed to be the major receptor mediating the angiogenic effects of VEGF. When VEGF binds to the extracellular domain of its receptor, it induces tyrosine autophosphorylation and downstream effects that include tumor-associated angiogenesis, endothelial cell proliferation, migration, and survival. During the past 5 years, a number of agents inhibiting the VEGF pathway have been investigated in advanced RCC patients, and a series of these have clearly demonstrable clinical benefits such as significant increases in progression-free survival (PFS) and overall survival.

Both sorafenib and sunitinib were first studied and shown to have activity in cytokine refractory patients as second-line therapy. The Food and Drug Administration (FDA) label for both describes efficacy for the treatment of “advanced kidney cancer.” Given the lack of efficacy and the toxicity associated with interleukin-2 and interferons, sorafenib and sunitinib will be widely used as initial therapy. Randomized trials with these agents have compared their efficacy to first-line cytokine therapy. A randomized phase 3 trial of sunitinib compared to IFN-α accrued 750 patients, and demonstrated improvement in progression-free survival (primary end point) and preliminarily, in overall survival. Efficacy and safety data for sorafenib in treatment-naïve patients have been assessed in a randomized phase 2 trial, which accrued 190 patients. The data from this study have not been analyzed as yet. A phase 3 trial comparing CCI-779 with or without IFN-α to IFN-α in poor-risk patients demonstrated a survival advantage for patients receiving monotherapy. In the absence of randomized studies directly comparing these agents in similar patient populations, treatment recommendations are problematic. Finally, several phase 2 randomized trials suggest bevacizumab has significant activity in metastatic RCC, and a preliminary report of a phase 3 trial comparing IFN-α with or without bevacizumab suggests a significant increase in PFS associated with administration of this VEGF inhibitor.

Based on the efficacy (overall response rate, PFS, and survival) observed in the randomized phase 3 trial, sunitinib is an accepted standard for therapy and can be offered to patients as initial therapy. An acceptable alternative is sorafenib, but the supporting data are in cytokine refractory patients, with only limited data available in untreated patients. Studies with CCI-779 were performed in poor-risk patients. Data in good- and intermediate-risk patients should be obtained to permit preliminary comparisons with the other targeted agents. It is likely results seen in various subgroups will mirror those
Currently available; however, current recommendations rely on available data. The data with bevacizumab remain very preliminary, but clearly will add another active agent to the list of those available to treat this disease. As with all new treatment options, multiple questions remain to be answered. These include duration of therapy, the importance of stable disease and percent tumor reduction, the issue of sequential therapy, and the use of combination therapy.

Finally, several trials are now in progress to assess the role of targeted therapy in the adjuvant setting. One randomized phase 3 adjuvant trial compared sorafenib to a placebo, and a second National Cancer Institute (NCI)-sponsored phase 3 trial compared sorafenib and sunitinib to a placebo. Data from both trials will not be available for 5 to 10 years. Unless the results of one or both of these trials demonstrates a benefit in relapse-free or overall survival, the standard of care remains observation alone following nephrectomy for localized RCC.

CONCLUSION

The treatment paradigm for patients with localized and advanced renal cell carcinoma has changed dramatically in the last 5 to 10 years. Surgical advances are now mirrored by the dramatic changes in therapy available for metastatic disease. The chapters in this text provide an update for urologists, medical oncologists, and researchers interested in this tumor.

REFERENCES


Imaging of Renal Cell Carcinoma

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KEYWORDS

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ABSTRACT

Imaging of renal neoplasms is performed with computed tomography, magnetic resonance, and ultrasound to detect disease, characterize lesions, stage primary renal neoplasms, and provide surgical planning information. Imaging is also used to distinguish between benign and malignant disease and between surgical and nonsurgical disease. Computed tomography (CT) and magnetic resonance (MR) exams of renal cell carcinoma should be designed to maximize identification of prognostic factors as well as staging features: size, extension outside the renal capsule and fascia, lymphadenopathy, renal vein invasion, and metastatic disease.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 3% of new cancer diagnoses and 3% of deaths from cancer annually. Nearly 36,000 new cases are diagnosed each year. Fortunately, with the common use of cross-sectional imaging, there has been a significant shift in the type of RCCs being identified; more tumors are asymptomatic and these asymptomatic tumors are more frequently lower stage and lower grade tumors with a better prognosis. Goals for the imaging of renal neoplasms are to detect disease, to characterize lesions, to stage primary renal neoplasms, and to provide surgical planning information. Imaging is also performed to distinguish between benign and malignant disease and between surgical and nonsurgical disease. Ideally, imaging would be able to distinguish between primary renal cell carcinoma and benign primary tumors of the kidneys, and between primary and secondary renal tumors, such as metastatic lung cancer and lymphoma.

The most important prognostic factors for RCC include histologic grade, cell type, patient age, performance status, number and location of metastases, and time to appear-
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ance of metastases. Imaging of RCC, therefore, should be designed to maximize identification of prognostic factors as well as staging features, including tumor size and tumor extension outside the renal capsule and outside Gerota’s and Zuckerkandl’s fascia. Imaging should also be designed to detect pathologically enlarged lymph nodes and renal vein invasion, as well as metastatic disease, either at the time of presentation or on follow-up imaging.

Renal masses have a varied appearance on imaging with a complexity that has resulted in a large body of literature. With the rapid improvements in imaging over the last decade, much of the recent literature has redefined or reversed many of the initial concepts in the imaging of renal masses. This chapter addresses imaging of renal cell carcinoma as it relates to the detection of RCC and the characterization and differential diagnoses of renal masses. It also reviews the detection of factors relevant for treatment and prognosis, such as tumor size and staging, with an assessment of lymphadenopathy, renal vein tumor thrombus, adrenal gland involvement, and metastatic disease. Imaging features of the different cell types of primary RCC are also reviewed. While most RCC is sporadic, solid and cystic renal neoplasms are associated with several syndromes; these are covered elsewhere in this book and thus will not be addressed here.

THE VARIOUS APPEARANCES OF RENAL LESIONS AT IMAGING

Renal lesions can be solid, cystic, infiltrating, or vascular. Renal cell carcinoma can be solid, cystic, or infiltrating; however, many other types of renal pathology can have a similarly varied appearance. Lesion detection and characterization are dependent on the size and cell type of lesion, the blood supply, neovascularity, and the type(s) of tissue in the lesion. The diagnosis and management of renal lesions is highly dependent on the imaging features, due to the high prevalence of RCC in solid and complex cystic renal lesions.

Solid Lesions

The typical appearance of RCC is a heterogeneous, enhancing solid mass following contrast (Figure 2.1). While the majority of RCCs are solid, space-occupying mass lesions, some RCCs are infiltrating or complex cystic mass lesions. Clear cell, papillary, and chromophobe RCC subtypes are all solid on computed tomography (CT), ultrasound (US), and magnetic resonance (MR). Unfortunately, both benign (e.g., oncocyto ma, angiomyolipoma) and malignant (e.g., some transitional cell carcinoma and metastatic disease) lesions are also solid, space-occupying lesions.

Cystic and Complex Cystic Renal Lesions

Renal cell carcinoma can have a cystic histologic growth pattern. Cystic RCC can be unilocular, multilocular, or necrotic, or RCC can develop within the wall of an otherwise benign cyst. Renal epithelial cysts are common, and many individuals have these and other benign renal cysts. Benign cysts typically contain simple serous fluid, but they can also contain fluid with a high protein content, hemorrhage, or infection, making the differentiation between a simple cyst and cystic RCC difficult. Different classification schemes have been proposed to help stratify the likelihood of malignancy of a cystic lesion; one such classification system that is used by both radiologists and urologists was originally described in 1986 by Bosniak and has since been modified. Bosniak originally proposed four categories, with increasing likelihood of malignancy, and this has been modified more recently to include a fifth category.
Figure 2.1. Solid renal mass (arrow) and simple renal cyst (arrowhead) in the same kidney. Most renal cell carcinomas are solid space-occupying lesions that demonstrate intermediate to high soft tissue density enhancing after intravenous (IV) contrast media.

Category I cysts are simple unilocular cysts, either round or oval, with a thin, non-calcified wall. These cysts contain simple serous fluid measuring less than 10 to 20 Hounsfield units (HU) at CT, and have MR signal characteristics of simple fluid (low signal on T1- and high signal on T2-weighted imaging sequences). There is no solid, soft tissue density in the lesion or enhancement after IV contrast.

Category II cysts are minimally complicated cysts either with high-density fluid due to a high protein content or hemorrhage within the cysts (higher than 20 HU density, a “hyperdense” cyst), or are multilocular with a few septations or thin peripheral calcifications. Category II cysts do not demonstrate enhancement after IV contrast and are almost always benign.\(^{19,20}\) Contrast is needed to distinguish between a hyperdense cyst and a homogeneous solid renal neoplasm. Both lesions may look similar on pre- or postcontrast scans, but the hyperdense cyst will not enhance after contrast, whereas the homogeneous solid renal neoplasm will enhance. Category II cysts have a less than 15% change of malignancy in most studies using the Bosniak criteria and, therefore, are often followed to document stability over time.

Category IIIF cysts are complex lesions with multiple septations or calcifications that have a more benign appearance. Calcifications, which were once felt to be a potential sign of malignancy, are now considered less important.\(^{17}\)

Category III cysts are complicated cystic lesions that have some features suggesting malignancy—multiple septations, thick or irregular rim—or heterogeneity suggesting necrosis. Category III cysts have an approximately 50% to 60% chance of being a cystic RCC according to published studies.\(^{19,21}\) Typically, these lesions are explored; although controversial, aspiration biopsy can also be performed to diagnose malignancy.

Category IV cysts contain solid, soft tissue enhancing elements seen either within the cyst or as part of a complex cystic mass. These lesions are almost always cystic RCC and should be treated as such (Figures 2.2 and 2.3).
Figure 2.2. Cystic necrotic renal cell carcinoma on computed tomography (CT) (arrow). This renal cell carcinoma has a nonenhancing low attenuation component that was necrosis at pathology. The lack of enhancement in necrosis mimics a cystic lesion.

Management guidelines are based on this stratification, but of course every patient should be treated individually. In general, category I lesions do not need further evaluation; category II lesions, if larger than 3 cm or irregular, and category IIIF lesions should be followed for interval growth or change, which suggest malignancy; category III lesions should be explored or resected; and category IV lesions should be appropriately treated as presumed RCC. Biopsy of indeterminate cystic renal masses can also be performed. It is important to note that the Bosniak criteria are guidelines for describing and managing cystic renal masses. Other factors, including risk factors for RCC, a

Figure 2.3. Complex cystic renal cell carcinoma (arrow) at unenhanced (A) and contrast-enhanced CT (B). This renal cell carcinoma has calcifications seen on the unenhanced image (A), and both a low attenuation cystic nonenhancing component and a higher attenuation enhancing soft tissue component. This lesion meets criteria for a Bosniak IV cyst (cystic renal cell carcinoma).
genetic disorder that predisposes the individual to cystic renal tumors, age, and comorbid conditions should influence any management decision.

**Infiltrating Renal Lesions**

While many renal tumors exhibit radial growth patterns with a space-occupying mass and some cystic growth patterns, RCC can infiltrate within the renal parenchyma along the interstitium (Figure 2.4). In these instances, the renal contour is maintained but the involved portion of the kidney is typically enlarged. Infiltrating tumors encase rather than displace the vasculature and collecting system. On CT, infiltrating lesions are poorly marginated areas of relatively decreased enhancement reflecting the disruption of the normal tubular concentration of contrast. On ultrasound, these are often isoechoic, severely limiting sonographic detection. Only occasionally are infiltrating renal lesions slightly hypoechoic or hyperechoic in relation to the normal renal parenchyma.

Several other tumors demonstrate an infiltrating pattern at imaging. Transitional cell carcinoma (TCC) of the kidney comprises 90% of urothelial tumors; squamous cell carcinoma comprises most of the rest. While typically a slow-growing papillary tumor, TCC of the kidney is occasionally high grade with an infiltrating appearance centrally located in the kidney or in the renal pelvic sinus.

Primary renal non-Hodgkin’s lymphoma (NHL) can arise in the renal parenchyma or renal hilar lymph nodes. Extranodal lymphoma is more common with Hodgkin’s than with non-Hodgkin’s lymphoma. Perinephric confluent tissue is more suggestive of NHL than RCC. In general, however, renal involvement in lymphoma is associated with systemic disease. At CT and MR, renal lymphoma is typically hypovascular with multiple solid or infiltrating masses.

![Figure 2.4](image-url) **Figure 2.4.** Infiltrating renal cell carcinoma (RCC) on CT. This renal cell carcinoma (arrow) enlarges the posterior segment of the kidney and is poorly marginated. Infiltrative RCCs are typically more aggressive than solid lesions. Less than 5% to 10% of renal cell carcinomas demonstrate an infiltrative growth pattern at CT.
Leukemia is always infiltrating, typically enlarging the kidneys.\textsuperscript{24} Metastatic disease to the kidneys presents with multiple, bilateral, poorly marginated solid lesions that can occasionally demonstrate an infiltrative pattern.\textsuperscript{25,26}

Some noncancerous conditions can demonstrate an infiltrating pattern at imaging, and it is vitally important to recognize these entities. Acute pyelonephritis demonstrates a striated nephrogram on CT early after contrast and a dense parenchyma staining on delayed CT due to clearance failure of concentrated contrast. This should be distinguishable from tumor infiltration, and a history of fever, flank pain, and pyuria should certainly suggest pyelonephritis. Chronic infection can result in xanthogranulomatous pyelonephritis (XGP). In XGP, below-water attenuation regions are due to lipid-laden macrophages associated with chronic inflammation and typically are seen in conjunction with a staghorn calculus.

Infiltrating tumors are often associated with a more aggressive behavior than solid or cystic tumors, and can be either an uncommon appearance of common tumors, such as primary renal cell adenocarcinoma, lymphoma, or metastatic disease, or a more common appearance of uncommon tumors, such as collecting duct or medullary RCC.

**Vascular Lesions**

Vascular lesions of the kidney include renal artery aneurysms (Figure 2.5), renal arteriovenous malformations (AVMs), and renal arteriovenous fistulas. The addition of a corticomedullary phase to renal imaging can help distinguish renal vascular lesions from solid renal masses. On contrast-enhanced CT and MR, renal artery aneurysms demonstrate only arterial blood flow similar to the renal artery. Renal AVMs appear

![Figure 2.5. Renal artery aneurysm on corticomedullary phase (A) and nephrographic phase CT (B). The lesion is soft tissue density mimicking a renal tumor on the nephrographic phase (B, arrow), but markedly hyperdense similar to the aorta on the corticomedullary phase (A, arrow). Vascular renal lesions are typically homogeneous attenuation with density that follows the aorta or renal vein on both the corticomedullary and nephrographic phase scans. This enhancement pattern helps distinguish these lesions from renal cell carcinoma.](image-url)
similar to renal tumors and not cysts because of enhancement after contrast media caused by contrast pooling in the bloodstream. These malformations have a cirrhotic appearance and are typically recognized because at CT they appear as homogeneous lesions with density similar to the vasculature, at ultrasound they demonstrate color flow or pulse Doppler signal, and at MR they exhibit flow enhancement or signal void.

Renal AVMs are significantly less common than primary or secondary renal tumors. Patients with renal AVMs often present with gross or microscopic hematuria, and AVMs have been mistaken for RCC. Renal arteriovenous fistulas are usually post-traumatic, often described after penetrating trauma and after biopsy in renal transplants.

**PRIMARY IMAGING METHODS FOR THE DETECTION OF RENAL CELL CARCINOMA**

Detection of renal lesions on US is dependent on either a contour abnormality or a difference in echogenicity between the lesion and normal parenchyma. Detection of renal lesions on CT and MR is possible because of a difference in density or signal intensity from the normal renal parenchyma. This occurs not only because the kidneys filter contrast, but also because contrast is concentrated within the collecting tubules as water is reabsorbed. Normal renal parenchyma becomes denser at CT and has higher signal on T1-weighted MR as contrast is concentrated. The degree of contrast concentration is dependent on the normal function of nephrons. The degree of contrast excretion and concentration is also dependent on the volume and concentration of contrast given. Neither cysts nor renal tumors concentrate contrast. Therefore, the kidneys should be imaged at peak concentration of contrast with the highest contrast load to maximize detection of renal lesions. Unfortunately, for patients with impaired renal function the risk of contrast-induced nephropathy is increased while detection and characterization of renal masses are decreased.

**ULTRASOUND**

Ultrasound, CT, and MR can all be used to image renal lesions, and each has different advantages and disadvantages. Ultrasound is ideal for distinguishing between cystic and solid renal masses. Ultrasound is not considered the best test for the detection and characterization of renal tumors because small renal tumors are often isoechoic and because detection of fat within a lesion to identify angiomyolipoma (AML) is less sensitive with US than with other cross-sectional imaging. However, renal tumors that are large, contour-deforming, or partially cystic can be detected sonographically (Figures 2.6 and 2.7). On ultrasound, RCC can be hypoechoic, isoechoic, or hyperechoic. Calcifications in renal lesions can obscure tumors because of acoustic shadowing. Advantages of renal ultrasound include the noninvasive nature of the exam without use of contrast agents or radiation. Lack of contrast eliminates the potential nephrotoxicity of iodinated agents.

Ultrasound is performed with a 3- to 6-MHz transducer, and images are obtained through each kidney in both the axial and longitudinal planes. Tissue harmonic imaging can be used to increase the sensitivity of US for renal masses. Cysts appear as round or oval, and anechoic structures appear with a thin or imperceptible wall. Solid and
Figure 2.6. Renal cell carcinoma (RCC) on ultrasound. This large RCC (black arrow) is relatively easy to detect by ultrasound because it deforms the contour of the kidney. It is also mildly hyperechoic to the normal renal parenchyma (white arrow). Renal cell carcinoma can be hypo-, iso-, or hyperechoic at ultrasound.

complex cystic masses either deform the renal contour or are distinguished from the normal renal parenchyma by a difference in echogenicity. The sensitivity of US for the detection of RCC is dependent on the size of the lesion. Ultrasound is insensitive for small tumors. Ultrasound has also been used to screen for RCC in a select patient population, although ultrasound is not a recommended screening exam in the United States.34,35

Kitamura et al.36 compared color flow Doppler (CFD) US to contrast-enhanced CT for the detection of renal tumors. In that study, 91% of clear cell carcinomas seen at CT were identifiable as hypervascular lesions on CFD US. However, there was no additional benefit gained by using CFD US. The sensitivity of US for the detection of renal tumors may improve with IV contrast agents for US, in one study increasing sen-

Figure 2.7. Small renal cell carcinoma on ultrasound. This lesion (arrows) is only 2 cm in diameter but was detected because of the increased echogenicity.