Renal cell carcinomas arise within the renal cortex and account for about 80% to 85% of all primary renal neoplasms. Transitional carcinomas arising from the renal pelvis are the next most common, accounting for 7% to 8% of primary renal neoplasms. Other parenchymal epithelial tumors, such as oncocytomas, collecting duct tumors, and renal sarcomas, are uncommon but are becoming more frequently recognized pathologically. Nephroblastoma (Wilms’ tumor) is common in children and accounts for 5% to 6% of all primary renal tumors.

Metastatic lesions to the kidney (secondary neoplasms) occur in 7% to 20% of patients with cancer at autopsy. These secondary lesions are very rare in the absence of progression of the primary neoplasm. This chapter focuses on the epidemiology, pathology, genetics, clinical and radiographic presentation, staging methods, and surgical and systemic management of primary renal neoplasms. A brief description of the biology and management of the less common tumors as well as evaluation of suspected metastatic disease is also presented.

### Renal Cell Carcinoma

#### Epidemiology

In 2009, it was estimated that renal cell and renal pelvic cancer would be newly diagnosed in 58,000 people in the United States and that almost 13,000 people would die of the disease. Renal cell carcinoma represents 3.9% of all U.S. cancers and 2% of all cancer deaths. Worldwide, the mortality from renal cell carcinoma is estimated to exceed 100,000 per year.

The incidence varies widely from country to country, with the highest rates seen in Northern Europe and North America. Although the incidence is reported to be lower in individuals living in African countries, the incidence is equivalent among whites and African Americans living in the United States. Historically, renal cell carcinoma was twice as common in men as in women, but more recent data suggest that this gap is beginning to narrow. The incidence in Asian Americans and Pacific Islanders is half that of their white and African American counterparts. Renal cell carcinoma occurs predominantly in the sixth to eighth decades; it is uncommon in patients younger than 40 years of age and rare in children.

The incidence of renal cell carcinoma has steadily increased over time. Between 1975 and 1995 in the United States the incidence rates per 100,000 person-years increased by 2.3%, 3.1%, 3.9%, and 4.3% annually for white men, white women, African American men, and African American women, respectively. Mortality rates are equivalent for whites (6.2 males and 2.8 females per 100,000 persons) and African Americans (6.1 and 2.7, respectively), whereas Asian American and Pacific Islanders have the lowest mortality rates (2.4 and 1.2, respectively). American Indians and Alaskan Natives have an increased incidence of cancer of the kidney and an alarmingly high mortality rate (9.3 males and 4.3 females per 100,000 persons).

The overall incidence in the United States for all races has risen at a rate that is threefold higher than the mortality rate. Since 1950, there has been a 126% increase in the incidence of renal cell carcinoma.

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accompanied by a 37% increase in annual mortality.\textsuperscript{13,14} The 5-year survival rate of patients with a diagnosis of kidney cancer has improved from 34% for those receiving this diagnosis in 1954 to 67% for those receiving this diagnosis in 2004.\textsuperscript{5} The proportion of renal cell carcinomas discovered incidentally increased from approximately 10% in the 1970s to 60% in 1998.\textsuperscript{14} In addition, at one major institution, the percentage of organ-confined tumors increased from 47% in 1989 to 78% in 1998.\textsuperscript{15} An examination of contemporary data shows that the mortality rate decreased by approximately 5% between 1990 and 2005.\textsuperscript{5} There is a continued stage migration, with stage 1 disease increasing from 43% to 57% between 1993 and 2004, whereas stage 2 and 3 disease showed a statistically significant decline. The incidence of stage 4 disease has remained stable over this time same period.\textsuperscript{16}

Numerous environmental and clinical factors have been implicated in the etiology of renal cell carcinoma.\textsuperscript{17} These include tobacco use; occupational exposure to toxic compounds such as cadmium, asbestos, and petroleum by-products; obesity; acquired polycystic disease of the kidney (typically associated with dialysis); and analgesic abuse nephropathy. Cigarette smoking doubles the likelihood of renal cell carcinoma and contributes to as many as one third of all cases.\textsuperscript{18-20} The risk of developing kidney cancer in patients with acquired polycystic disease of the kidney has been estimated to be 30 times greater than in the general population.\textsuperscript{24} In particular, it is estimated that acquired cystic disease develops in 20% to 90% of patients receiving long-term dialysis, depending on the duration of dialysis,\textsuperscript{22} and that renal cell carcinoma develops in between 3.8% and 4.2% of these patients.\textsuperscript{23} Patients with large cysts appear to be an increased risk for malignant transformation. The carcinomas are multiple and bilateral in approximately one half the cases, a finding that is consistent with the diffuse nature of the underlying disease.\textsuperscript{24} The prolonged ingestion of analgesic combinations, particularly compounds containing phenacetin and aspirin, can lead to chronic renal failure. Such patients are at increased risk of renal pelvic tumors and possibly renal cancer, although the latter association remains controversial.\textsuperscript{25-27} Because of its carcinogenic properties, phenacetin was removed from the U.S. marketplace by the U.S. Food and Drug Administration (FDA) in 1983 and later from European markets.

An enhanced risk of renal cell carcinoma has been observed in patients with certain inherited disorders, which implicates various genetic abnormalities in its etiology. These disorders include von Hippel–Lindau syndrome, hereditary papillary renal cancer, hereditary leiomyoma renal cancer syndrome, and Birt–Hogg–Dube syndrome. In addition patients with tuberous sclerosis and hereditary polycystic kidney disease, although they do not have a dramatically increased incidence of renal cancer, can have cancers with unique features.

Hereditary polycystic kidney disease (autosomal dominant polycystic kidney disease, or ADPKD) has a long-debated association with renal cancer; however, when renal cancer does occur in patients with this disorder, it typically displays a number of distinct clinical characteristics.\textsuperscript{28} The tumors are more often bilateral at presentation, multicentric, and with sarcomatoid features when symptomatic or advanced. A recent analysis of 89 nephrectomy specimens from ADPKD patients who underwent extirpation for nononcologic indications reported an increased risk of renal cancer.\textsuperscript{29} Specifically, overall incidence was increased to 8.3%. The tumors were bilateral in 10% and multifocal in 27.3%, and the histologic subtypes were divided between clear cell renal carcinomas (60%) and papillary renal cell carcinomas (40%). These cancers were all staged as T1 disease, and none of the tumors was seen on preoperative imaging. An increased incidence of sarcomatoid features was not seen in this group, possibly because of the benign indications for extirpation.

Although most renal cell carcinomas are sporadic, factors suggesting a hereditary cause include the occurrence of the disease in first-degree relatives,\textsuperscript{30-33} onset before the age of 40, and bilateral or multifocal disease.\textsuperscript{34} Several kindreds with familial clear cell carcinoma have been identified that have consistent abnormalities on the short arm of chromosome 3.\textsuperscript{35-38} Other kindreds with papillary tumors have been identified with different genetic abnormalities,\textsuperscript{39} which suggests that these tumors represent distinct disease entities. Although the true prevalence of hereditary renal cell carcinoma is unknown, it is estimated that hereditary carcinomas make up 3% to 5% of all renal cell carcinomas.\textsuperscript{40} A more detailed discussion of the molecular biology of renal cell carcinoma is provided in a later section.

Pathology and Cytogenetics

Renal cell carcinoma was first reported by Konig in 1826. In 1883, Grawitz hypothesized on histologic grounds that renal cell carcinomas arose from rests of adrenal tissue within the kidney.\textsuperscript{41} Although immunohistologic and ultrastructural analyses currently point toward the proximal renal tubule as the true cell of origin,\textsuperscript{42} the term hypernephroma continues to be incorrectly applied to these cancers. Renal cell tumors occur with equal frequency in the right and left kidney and are distributed equally throughout the kidney.\textsuperscript{43} The average diameter is about 7 cm, but tumors have ranged from less than 2 cm to more than 25 cm in diameter. Previously, renal lesions smaller than 2 to 3 cm were incorrectly considered to be benign adenomas. Such distinctions between benign and malignant tumors are no longer made on the basis of size but rather according to fundamental histologic criteria. Therefore, from a practical standpoint, all solid renal masses require resection or biopsy for accurate histologic diagnosis. Improved percutaneous biopsy techniques have a role in the management of renal masses, but are definitively less accurate than extirpation in providing pathologic and histologic information.

Renal cell carcinomas have historically been classified according to cell type (clear, granular, spindle, or oncocytic) and growth pattern (acinar, papillary, or sarcomatoid).\textsuperscript{43} This classification has undergone a transformation to more accurately reflect the morphologic, histochemical, and molecular features of different types of adenocarcinomas (Table 40-1).\textsuperscript{44-46} Based on research studies, five distinct subtypes have been identified. These include clear cell (conventional), chromophilic (papillary), chromophobic, oncocytic, and collecting duct (Bellini duct) tumors. Each of these tumors has a unique growth pattern, cell of origin, and cytogenetic characteristics. Table 40-1 summarizes this information, which more accurately reflects the increased knowledge of the molecular and genetic abnormalities of these lesions than did the earlier classification.\textsuperscript{45} Sarcomatoid variants of almost all of the aforementioned histologic subtypes have been described and
represent a dedifferentiation (poor differentiation) of the individual subtype.67

Clear cell or conventional renal cell carcinomas make up 75% to 85% of tumors and are characterized by a deletion or functional inactivation in one or both copies of chromosome arm 3p.48 A higher nuclear grade (Fuhrman classification) or the presence of a sarcomatoid pattern correlates with a poorer prognosis.49,50

Chromophilic or papillary carcinomas (synonymous) make up 10% to 15% of renal cancers. In hereditary disease papillary carcinomas are multifocal and bilateral, and commonly present as small tumors.51 These tumors also appear to arise from the proximal tubule but are both morphologically and genetically distinct from clear cell carcinomas. Although these tumors often have a low stage at presentation and are thus attributed a more favorable prognosis,52 in advanced stages, they can be as aggressive as clear cell lesions.53 In recent years, the class of papillary renal cell carcinoma has been subdivided into papillary type 1 and type 2.54 This differentiation has been based on histologic appearance54 and has been validated through microarray analysis of molecular markers.55 Subtyping permits identification of an independent prognostic factor, because patients with type 2 papillary renal cell carcinoma have a worse outcome even when stratified by TNM stage.54,55

Chromophobe carcinomas make up about 4% of all renal cell carcinomas. Histologically, they are composed of sheets of cells that are uniformly darker cells than those of the usual clear cell carcinoma, with a peripheral eosinophilic granularity. These cells lack the abundant lipid and glycogen characteristic of the clear cell renal cell carcinoma, and are believed to arise from the intercalated cells of the renal collecting ducts.56-58 They have a hypodiploid number of chromosomes, but also no 3p loss.59-61 These tumors are usually well circumscribed and generally have an excellent prognosis. As a group, chromophobe renal cell carcinomas tend to present at lower stages and grades, yet once metastatic, chromophobe carcinomas are highly refractory to therapy and have a prognosis equivalent or worse than that of clear cell carcinomas.62

Collecting duct (Bellini duct) tumors are also very rare but are frequently very aggressive in behavior.63 These tumors are located in the renal medulla and pelvis and thus usually present with gross hematuria. In contrast to clear cell carcinomas, these tumors produce mucin and react with antibodies to both high-molecular-weight and low-molecular-weight keratins.64 Sarcomatoid variants have also been noted. Neither oncocytomas nor collecting duct tumors have been associated with a consistent pattern of genetic abnormalities.

Medullary renal cell carcinoma is a rare aggressive variant usually seen in individuals with sickle cell trait.65 This entity was designated by Davis and colleagues as the "seventh sickle cell nephropathy."65 Histologically, a variety of growth patterns have been described, including reticular, solid, tubular, trabecular, cribriform, sarcomatoid, and micropapillary.66 Little is known about the cytogenetics of this tumor. Gene expression profiling has shown clustering more closely associated with urothelial carcinoma than with renal cell carcinoma.67,68

Classification and further characterization of this rare but lethal entity will require further molecular and pathologic research with a larger collection of specimens.

The Xp11.2 translocation carcinoma was first described in 1991 by Tomlinson and colleagues.69 This translocation results in the fusion of a novel gene, designated RCC17, at chromosome band 17q25 to the gene for transcription factor for immunoglobulin heavy-chain enhancer 3 (TFE3) located on chromosome band Xp11.70 These tumors usually occur in children and young adults, appearing at a median age of 20 years, and account for at least one third of carcinomas seen in childhood and adolescence.67 Tumor cells are described as having voluminous clear cytoplasm and bulging distinct cell borders, reminiscent of soap bubbles. The architecture is predominantly solid, tubular, acinar, or alveolar, with areas with a pseudopapillary appearance.71 Transcription factor 3 is a sensitive and specific marker for translocation carcinomas with a sensitivity ranging from 82% to 97.5%.67 Although relatively indolent, these tumors are refractory to systemic therapy and respond only to aggressive surgical resection.

Renal oncocytomas are infrequent but increasingly recognized benign tumors.72-74 Oncocytomas are composed of a pure population of oncocytes—large, well-differentiated neoplastic cells with intensely eosinophilic granular cytoplasm. The cytoplasm of these cells is packed with mitochondria, which leads to their histologic appearance. Immunohistochemical studies suggest that oncocytomas probably also arise from the intercalated cells of the distal collecting tubules.73 The pathologic differentiation of a typical renal oncocytoma from an oncocytic renal cell carcinoma can be difficult. Some series suggest that 3% to 7% of solid renocortical tumors previously classified as renal cell carcinomas are in fact oncocytomas.72 Grossly, oncocytomas are generally well encapsulated and are only rarely invasive. Larger oncocytomas frequently

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### TABLE 40-1 Pathologic Classification of Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>CARCINOMA TYPE</th>
<th>GROWTH PATTERN (INCIDENCE)</th>
<th>CELL OF ORIGIN</th>
<th>CYTOGENETIC CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>Acinar or sarcomatoid (75%-85%)</td>
<td>Proximal tubule</td>
<td>-3p, +5, +7, +12, -6p, -8p</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-9, -14q, -Y</td>
</tr>
<tr>
<td>Chromophilic</td>
<td>Papillary or sarcomatoid (12%-14%)</td>
<td>Proximal tubule</td>
<td>+7, +17, -Y, -Y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>+12, +16, +20, -14</td>
</tr>
<tr>
<td>Chromophobic</td>
<td>Solid, tubular, or sarcomatoid (4%-6%)</td>
<td>Intercalated cell of cortical collecting duct</td>
<td>Hypodiploidy</td>
</tr>
<tr>
<td>Oncocytic</td>
<td>Typified by tumor nests (2%-4%)</td>
<td>Intercalated cell of cortical collecting duct</td>
<td>Undetermined</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>Papillary or sarcomatoid (1%)</td>
<td>Medullary collecting duct</td>
<td>Undetermined</td>
</tr>
</tbody>
</table>

*These tumors were previously classified as papillary tumors.
†This classification is based on the work of Storkel and van den Berg.41
The VHL gene in 1993, and the subsequent functional and structural characterization of the gene product, have contributed greatly to our understanding of the genetics of this disease and of renal cell carcinoma in general.

Von Hippel–Lindau syndrome is transmitted in an autosomal dominant fashion and is characterized by a predisposition to various neoplasms, including renal cell carcinoma (with clear cell histology), renal cysts, retinal angiomas, spinal cord hemangioblastomas, pheochromocytomas, and pancreatic carcinomas and cysts. Renal cysts are frequently multiple and bilateral.

Renal cell carcinoma develops in about a third of all patients and is a major cause of death in patients with von Hippel–Lindau syndrome. Tumor development in this setting is linked to somatic inactivation of the remaining wild-type allele. Moreover, biallelic VHL inactivation due to somatic mutations and/or hypermethylation is observed in more than 50% of sporadic clear cell carcinomas. Restoration of VHL function in VHL–/– renal cell carcinoma cell lines suppresses their ability to form tumors in nude mouse xenograft assays, which supports the role of the VHL gene as a renal cancer tumor suppressor gene.

Tumors associated with VHL mutations (including the hereditary tumors in von Hippel–Lindau syndrome and a majority of the sporadic cases of clear cell renal cell carcinoma) are typically hypervascular and occasionally lead to the overproduction of red blood cells (polycythemia). This is due to overproduction of vascular endothelial growth factor (VEGF) and erythropoietin, respectively. Working from the knowledge that the two genes encoding these proteins are hypoxia inducible, several groups went on to show that cells lacking the protein encoded by VHL are unable to suppress the accumulation of hypoxia-inducible factors, including VEGF, under well-oxygenated conditions. The hypoxia-inducible factor (HIF) family of transcription factors is at the center of maintaining oxygen homeostasis and regulates a variety of hypoxia-inducible genes. HIF is a heterodimer composed of HIF-α and HIF-β subunits. Although the HIF-β subunit is constitutively expressed, HIF-α is normally degraded in the presence of oxygen and accumulates only under hypoxic conditions. A 200–amino acid oxygen-dependent degradation domain lies within the central region of HIF1-α. This region is sufficient to target HIF for degradation by the ubiquitin–proteasome pathway in the presence of oxygen (Figure 40-2). At present, several dozen HIF target genes have been identified, including the genes for VEGF, platelet-derived growth factor (PDGF), and transforming growth factor-α. Their protein products play critical roles in cellular and systemic physiologic responses to hypoxia, including glycolysis, erythropoiesis, angiogenesis, and vascular remodeling.

Papillary renal cell carcinoma possesses unique genetic features. In hereditary cases, papillary renal cell carcinoma is characterized by the formation of multiple bilateral tumors with trisomy of chromosomes 7 and 17. The hereditary papillary renal cell carcinoma gene was identified on chromosome bands 7q31.1–34, and germline missense mutations in the tyrosine kinase domain of the c-Met proto-oncogene

### Molecular Biology and Hereditary Disorders

Much of the recent success in developing therapies for renal cell carcinoma has arisen out of an improved understanding of the molecular biology of clear cell renal carcinoma and its highly prevalent mutation in VHL, the von Hippel–Lindau gene. Only 4% of cases of renal cell carcinoma are familial, yet elucidation of the genetic mutations involved in hereditary renal cell carcinoma has led to targeted therapies that benefit the majority of sporadic cases (Figure 40-1).

<table>
<thead>
<tr>
<th>Type</th>
<th>Clear cell</th>
<th>Papillary type 1</th>
<th>Papillary type 2</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>VHL</td>
<td>Met</td>
<td>FH</td>
<td>BHD</td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>75%</td>
<td>5%</td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
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**FIGURE 40-1** Human renal epithelial neoplasms. Histologic classification of renal tumors and incidence. The associated gene for inherited neoplasms is listed, although these genes can also be mutated in sporadic cases (especially the von Hippel–Lindau gene in clear cell carcinomas). (From Linehan WM, Walther MM, Zbar B: The genetic basis of cancer of the kidney, J Urol 170:2163, 2003.)
Disorders exhibit leiomyomas. HLRCC is characterized by cutaneous manifestations, the development of spontaneous cutaneous leiomyomas, uterine fibroids, and renal carcinomas, which are oncogenic and create a constitutively active, ligand-independent autophosphorylation of c-Met. This data may underestimate the significance of alterations in c-Met, because other mutations, chromosomal duplications (e.g., trisomy 7), and epigenetic events likely increase the frequency of c-Met activation.

The disorder that results from autosomal dominant mutations in the fumarate hydratase (FH) gene is known as multiple cutaneous and uterine leiomyomas (MCUL). Overlapping with this syndrome is another autosomal dominant condition, hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC). This syndrome also results from mutations in the FH gene. Autosomal recessive FH gene mutations also underlie the disorder fumarate deficiency. This condition is associated with progressive enccephalopathy, cerebral atrophy, seizures, hypotonia, and renal developmental delay. Heterozygous carriers of FH deficiency occasionally (but only rarely) exhibit leiomyomas. HLRCC is characterized by cutaneous leiomyomas, uterine fibroids, and renal carcinomas, which are predominantly single, although multiple and bilateral tumors have been reported. The renal tumors are aggressive, and they may metastasize and lead to death in patients in their thirties. Although originally classified as hereditary papillary renal cell carcinoma type 2, the unique cytomorphic features of the renal tumors, as well as the finding of mutations in the FH gene in affected families, suggest that this may be a distinct entity.

Birt-Hogg-Dube syndrome is characterized by prominent cutaneous manifestations, the development of spontaneous pneumothorax in association with lung cysts, and a predisposition to kidney neoplasms, which may be chromophobe renal cancers, oncocytomas, or tumors with features of both (termed mixed oncocyte). The characteristic skin lesions, fibrofolliculomas (hamartomas of the hair follicle), consist of multiple painless dome-shaped papules, 2 to 3 mm in diameter, that develop on the skin of the head and neck after age 30. The affected gene, folliculin, was described in 2002. Identification of loss-of-function mutations in the folliculin gene (localized to chromosome arm 17p) suggests that it functions as a tumor suppressor gene. A high frequency of somatic mutations has been detected in renal tumors from patients with germline mutations in the BHD gene, which suggests that malignancy results from the inactivation of both copies of the gene. Mutations in the folliculin gene do not appear to play a role in sporadic renal cell carcinoma.

Foliculin is thought to regulate the activity of mammalian target of rapamycin (mTOR) through complex mechanisms that are yet to be delineated. mTOR has an integral role in pathways relating to the response to hypoxia (HIF), autophagy, and independent gene expression regulation. Tuberous sclerosis is an autosomal dominant condition associated with mutations in the tuberous sclerosis complex genes (TSC1 and TSC2). The TSC1/TSC2 complex mediates multiple inputs (growth factor signals, amino acids, and adenosine triphosphate) that regulate mTOR activity and thus cell growth. Affected individuals typically manifest facial angiofibromas, show cognitive impairment, and develop renal angiomyolipomas. Although the incidence of renal cancer is only slightly increased, such cancers have been associated with biallelic loss of the TSC2 gene, which implicates this pathway in the pathogenesis of renal cancer.
Clinical and Laboratory Features

The propensity of renal cell carcinoma to present with diverse and often obscure signs and symptoms has led to its being labeled the internist’s tumor. The clinical presentation of renal cell carcinoma can be extremely variable. Many tumors are clinically occult, which leads to delayed diagnosis, when a more advanced and symptomatic stage is common. Indeed, 25% of individuals have distant metastases or locally advanced disease at the time of presentation.46 By contrast, other patients harboring renal cell carcinoma experience a wide array of symptoms or have a variety of abnormalities on laboratory tests, even in the absence of metastatic disease. The current clinical paradigm of renal cell carcinoma is the ever-increasing incidental detection of renal cancer through the use of abdominal imaging. Incidentally discovered renal tumors are estimated to represent from 40% to 60% of all pathologically diagnosed renal cell carcinomas. This has led to the recharacterization of the disease as the radiologist’s tumor. Based on an analysis of the Surveillance, Epidemiology, and End Results (SEER) database for the period 1998 through 2002, renal tumor size decreased from 6.7 cm to 5.8 cm with a concordant increase in the age-adjusted incidence in renal cell carcinoma.113

The presence or absence of local or systemic symptoms of renal cell carcinoma has been shown to correlate with TNM stage and grade, and, most importantly, is an independent variable (on multivariate analysis) predicting overall prognosis.114,115 Although the presence of symptoms strongly correlates with prognosis, a significant portion of incidentally discovered (asymptomatic) tumors can lead to cancer-specific mortality. In a recent study of 3912 patients who had been surgically treated for incidentally discovered renal masses, 3650 patients (90%) were diagnosed with a primary renal malignancy, of which 28.3% had locally advanced tumors, 27.6% had high-grade tumors, 5.7% had nodal metastases, and 13% had distant metastases. Cancer-specific mortality in this group of patients with incidentally discovered renal cancers was 14.4% (525 patients). This is the largest series of incidentally discovered renal tumors.114,116

Currently, most patients diagnosed with renal cell carcinoma are asymptomatic. In early reports of patients undergoing nephrectomy for renal cell carcinoma,117,118 the most common presenting symptom was hematuria (which occurred in up to 59% of patients), followed by abdominal mass, pain, and weight loss. In contemporary series these symptoms are less common at presentation and up to 60% of patients are asymptomatic.

The classic triad of flank pain, hematuria, and palpable abdominal renal mass occurs in fewer than 10% of patients and when present it strongly suggests advanced disease.114,115,117 Hematuria, gross or microscopic, is usually observed only if the tumor has invaded the collecting system. Gibbons and associates reported the absence of gross or microscopic hematuria in 63% of their patients with proven renal cell carcinoma.118 Scrotal varicocele was reported in up to 11% of patients.119 Most varicoceles due to an obstructing retroperitoneal mass are left-sided and typically fail to empty in the recumbent position (grade 3 varicocele). Varicoceles typically result from obstruction of the gonadal vein at its entry point into the left renal vein by tumor thrombus. Varicocele development in an adult should always raise the possibility of an associated neoplasm within the kidney. In addition, inferior vena cava involvement by tumor thrombus can produce a variety of clinical manifestations, including ascites; hepatic dysfunction, possibly related to Budd-Chiari syndrome; pulmonary emboli; and bilateral lower extremity edema.

Often, symptoms or signs related to metastases prompt medical evaluation.120 Most patients (75%) presenting with

![FIGURE 40-3 Mammalian target of rapamycin (mTOR) integration with hypoxia-inducible factors. (From Brugarolas J: Renal-cell carcinoma—molecular pathways and therapies, N Engl J Med 356:185, 2007.)](image-url)
metastatic disease have lung involvement (most common site of metastasis). Other common sites, from most to least common, include lymph nodes, bone, liver, adrenal gland, contralateral kidney, and brain. Patients may present with pathologic fractures, cough, hemoptysis, dyspnea related to pleural effusions, or palpable nodal masses. Clear cell pathologic features in the metastatic lesion and/or the finding of a renal mass on staging computed tomographic (CT) scan usually leads to the proper diagnosis.

A number of patients with renal cell carcinoma experience systemic symptoms or paraneoplastic syndromes. Fever is one of the more common manifestations of renal cell carcinoma, occurring in up to 20% of patients. It is usually intermittent and is often accompanied by night sweats, anorexia, weight loss, and fatigue. Secondary amyloidosis has been reported in as many as 3% to 5% of patients. Anemia is also common in patients with renal cell carcinoma and frequently precedes the diagnosis by several months. Hepatic dysfunction in the absence of metastatic disease was noted and labeled Stauffer’s syndrome. This syndrome, manifested by abnormal results on liver function tests (particularly elevated levels of alkaline phosphatase, α₂-globulin, and transaminases) and prolonged prothrombin time, has been reported to occur in up to 7% of patients with renal cell carcinoma. Hepatic dysfunction frequently occurs in association with fever, weight loss, and fatigue. The syndrome likely results from the overproduction of cytokines, such as granulocyte-macrophage colony-stimulating factor or possibly interleukin-6, by the tumor. Even though the laboratory abnormalities and other symptoms often revert to normal after nephrectomy, this syndrome is associated with an elevated risk of recurrence and an overall poor 5-year survival.

Hormones produced by renal cell carcinomas include parathyroid-like hormone, gonadotropins, placental lactogen, adrenocorticotropic hormone–like substance, renin, erythropoietin, glucagon, and insulin. Several of these have been associated with specific paraneoplastic phenomena. Erythrocytosis, defined as a hematocrit value greater than 55 mL/dL, occurs in 1% to 5% of patients with renal cell carcinoma and appears to be due to constitutive erythropoietin production by renal cancer cells.

Hypercalcemia occurs in up to 15% of all patients with renal cell carcinoma. The presence of hypercalcemia has been defined as an independent negative prognostic factor in patients with metastatic renal cell carcinoma and can be associated with lytic bone metastases. Hypercalcemia can occur in the absence of osseous metastases, and the ectopic production of parathyroid hormone–related peptide by the primary tumor has been documented in these cases. In other patients, elevated prostaglandin levels have been implicated in the development of hypercalcemia, which may respond to indomethacin treatment. Long-acting bisphosphonates such as pamidronate or zoledronic acid are the treatment of choice in renal cell carcinoma patients with metastatic disease and hypercalcemia. These agents may be especially beneficial in patients with lytic bone metastases, in whom such therapy might also reduce the incidence of pathologic fractures. The concurrent use of antiangiogenic therapies and bisphosphonates has been found to increase the risk for osteonecrosis of the jaw compared with bisphosphate therapy alone. This finding will prompt further investigation into the risks of concurrent usage.

Radiologic Diagnosis

The prognosis for patients whose tumors were diagnosed incidentally is more favorable than that for patients whose tumors caused symptoms, partly because the former group consists of patients with smaller tumors that tend to be confined to the kidney. For patients with symptoms suggestive of renal cell carcinoma, numerous radiologic approaches are available for the evaluation of the kidney. With the advent of CT, magnetic resonance imaging (MRI), and sophisticated ultrasonography, many of the more invasive procedures of the past are largely of historical interest and are rarely used in clinical practice. Although intravenous pyelography remains useful in the evaluation of hematuria, CT and ultrasonography are the mainstays of evaluation of a suspected renal mass. As seen on CT, the typical renal cell carcinoma has a heterogeneous density and enhances with contrast (Figure 40-4).
Cystic renal masses are graded based on a long-standing classification system first introduced by Bosniak in 1986 and since updated and validated in numerous studies with surgical pathologic assessment. The Bosniak renal cyst classification has been classically applied in evaluation of cystic masses using contrast-enhanced CT. Ultrasonography, although less sensitive than CT in detecting renal masses, can be of use (albeit limited) in characterizing simple or minimally complex renal cysts—those containing one or two hairline thin septa.

Cystic renal masses are characterized based on wall thickness; presence or absence, number, and thickness of septa; enhancement of septa and/or thickened wall; and presence or absence of solid enhancing components (Table 40-2). Presence of malignancy correlates with the Bosniak classification: in category I and II lesions, malignancy is very rare; in category IIF lesions the malignancy rate is approximately 5% to 15%; in category III lesions it is 30% to 60%; and in category IV lesions it is more than 90%. Use of MRI in conjunction with a modified Bosniak system for evaluating cystic masses has been studied and is an acceptable alternative when the patient cannot undergo CT scanning with contrast. In some patients unable to undergo contrast-enhanced CT due to moderate to severe chronic renal insufficiency, the risk of nephrogenic systemic fibrosis may outweigh the potential benefits of imaging. Currently used gadolinium-based MRI contrast agents have an FDA-required black box warning due to the risk of inducing nephrogenic systemic fibrosis.

Renal arteriography is rarely employed in current practice, having been supplanted by magnetic resonance angiography and CT with three-dimensional reconstruction (Figure 40-5) to delineate vascular anatomy and assist in surgical planning. MRI with gadolinium is superior to CT for evaluating the inferior vena cava if tumor extension into this vessel is suspected. MRI is also a useful adjunct to ultrasonography in the evaluation of renal masses if radiographic contrast cannot be administered because of allergy or inadequate renal function.

Although most solid renal masses are renal cell carcinomas, some benign lesions complicate the diagnosis. The most common of these rare tumors are angiomylipomas (renal hamartomas). Unless very small, angiomylipomas are readily distinguishable from renal cell carcinoma by the finding of a distinctive fat density on CT. However, given that several reports have shown that macroscopic fat can be detected within renal cell carcinomas, it may no longer be possible to dismiss all fat-containing lesions identified on CT as benign. Fat-poor angiomylipomas have also been described that are very difficult to distinguish from renal cell carcinomas on preoperative imaging and thus frequently must be resected to rule out a malignant neoplasm. As mentioned previously, renal oncocytomas have been described to present on CT as a central stellate scar within a homogeneous, well-circumscribed

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>I</td>
<td>A benign simple cyst with a hairline thin wall that does not contain septa, calcifications, or solid components. It measures water density and does not enhance.</td>
</tr>
<tr>
<td>II</td>
<td>A benign cyst that may contain a few hairline thin septa in which “perceived” enhancement may be present. Fine calcification or a short segment of slightly thickened calcification may be present in the wall or septa. Uniformly high attenuation lesions &lt;3 cm (so-called high-density cysts) that are well marginated and do not enhance are included in this group. Cysts in this category do not require further evaluation.</td>
</tr>
<tr>
<td>IIF (F for follow-up)</td>
<td>Cysts that may contain multiple hairline thin septa or minimal smooth thickening of their wall or septa. Perceived enhancement of their septa or wall may also be present. Their wall or septa may contain calcification that may be thick and nodular, but no measurable contrast enhancement is present. These lesions are generally well marginated. Totally intrarenal nonenhancing high-attenuation renal lesions &gt;3 cm are also included in this category. These lesions require follow-up studies to prove benignity.</td>
</tr>
<tr>
<td>III</td>
<td>“Indeterminate” cystic masses that have thickened irregular or smooth walls or septa in which measurable enhancement is present. These are surgical lesions, although some will prove to be benign (e.g., hemorrhagic cysts, chronic infected cysts, multiloculated cystic nephroma), and some will be malignant, such as cystic renal cell carcinoma and multiloculated cystic renal cell carcinoma.</td>
</tr>
<tr>
<td>IV</td>
<td>These are clearly malignant cystic masses that can have all the criteria of category III, but also contain enhancing soft tissue components adjacent to, but independent of, the wall of septum. These lesions include cystic carcinomas and require surgical removal.</td>
</tr>
</tbody>
</table>


solid mass. This finding is nonspecific, however, and cannot be used to clinically exclude the diagnosis of clear cell carcinoma.

The role of radionuclide bone scanning in the initial diagnosis and preoperative staging of renal cell carcinoma is unclear. Although bone scanning demonstrates high sensitivity in the detection of osteoblastic metastases, renal cell carcinoma usually produces osteolytic lesions that may be missed by bone scan. Atlas and colleagues suggested that a combination of bone pain on presentation plus an elevated serum alkaline phosphatase level were comparable to bone scan in evaluating patients with renal cell carcinoma. Koga and colleagues demonstrated bone scan to have a sensitivity of 94% and specificity of 86%, with a low yield in patients with earlier-stage primary tumors. They recommended omitting bone scanning in patients with T1 to T3a tumors and no bone pain.

A number of studies have been published evaluating the role of fluorine 18 2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for the detection and management of renal cell carcinoma primary and metastatic lesions. Kang and colleagues studied 66 patients with primary renal carcinoma and reported 60% sensitivity of FDG-PET for the primary renal mass compared with 91.7% for CT, whereas the specificity of both was 100%. Other studies have shown sensitivity rates as low as 31%. FDG-PET is unlikely to be used as a stand-alone study in the evaluation of a patient with a solid renal mass.

In the restaging and follow-up of renal cell carcinoma, FDG-PET scanning provides information that is complementary to that of conventional imaging and can alter management decisions. The sensitivity and specificity of FDG-PET in detecting recurrent or metastatic disease are better than the sensitivity and specificity when it is used for the evaluation of primary lesions. In this disease process, the sensitivity is significantly lower when metastatic lesions smaller than 1 cm are evaluated. False-negative and false-positive readings are significant, and FDG-PET is not a substitute for contrast-enhanced CT in the detection and follow-up of metastatic renal cell carcinoma.

An additional application of PET involves the use of antibodies such as the chimeric monoclonal antibody chimeric G250 to carbonic anhydrase IX. Carbonic anhydrase IX is expressed in more than 90% of clear cell renal carcinomas. Iodine 124–labeled antibody chimeric G250 PET had a sensitivity of 94% in correctly identifying clear cell renal carcinomas. G250 PET also correctly predicted all non–clear cell histologic types. G250 PET is currently being evaluated in a phase III clinical trial. Despite the encouraging result for G250 PET in assessing primary tumors, its performance in evaluating metastatic lesions has been shown to be significantly inferior to that of FDG-PET.

Although morphologic or functional imaging modalities such as CT, MRI, and PET have been used to evaluate renal masses, Doppler ultrasonography with contrast agent injection has been shown to provide both morphologic and functional information regarding renal lesions. The size of tumors can be accurately measured and the percentage of contrast uptake (which provides an approximation of tumor vascularity) can be evaluated using this technique. In the era of new antiangiogenic treatment modalities, assessment of tumor neovascularization is of major importance, and this parameter could be a potential biomarker for treatment evaluation.

**Staging and Prognosis**

After the presumptive diagnosis of renal carcinoma has been made, attention must be turned to the delineation of the extent of involvement of regional and distant metastatic sites. Renal carcinomas can grow locally into very large masses and invade through surrounding fascia into adjacent organs. The most common sites of metastases are the regional lymphatics, lungs, bone, liver, brain, ipsilateral adrenal gland, and contralateral kidney. The frequency of metastases to these sites is listed in Table 40-3. Metastases to unusual sites, such as the thyroid gland, pancreas, mucosal surfaces, skin, and soft tissue, are not uncommon in this disease. CT of the abdomen is the principal radiologic tool for defining the local and regional extent of a renal cell carcinoma. The accuracy of CT in staging renal cell carcinoma is close to 90%. In clinically advanced disease, staging evaluation should also include CT of the chest and bone scanning. Approximately 2% of patients have bilateral tumors and 25% to 30% of patients have overt metastases at initial presentation. If metastatic disease is suspected on the basis of staging studies, pathologic confirmation is required before therapy is contemplated. It is often more useful to perform a biopsy of a metastatic site rather than the primary tumor due to the presence of necrosis in the primary lesion. CT or ultrasound–guided percutaneous needle biopsy of a suspected lung, liver, lymph node, adrenal, or sometimes even skeletal metastasis frequently yields diagnostic material.

The TNM staging system for renal cell carcinoma (Table 40-4) has largely supplanted the previously used system of Robson. This system was modified in 2002 with the division of T1 tumors into T1a for tumors equal to or less than 4 cm in diameter and T1b for tumors larger than 4 cm. It also included renal sinus invasion in the T3a classification and renal vein invasion in the T3b subset. The seventh edition of the American Joint Committee on Cancer (AJCC) staging system was released in 2010 and includes relevant changes to the T3 and T4 definitions; it also defines node–positive disease as N1 regardless of number of positive nodes. This updated system accurately characterizes the disease with respect to prognosis. Pathologic stage remains the most consistent single prognostic variable that influences survival. Survival based on stage is shown in Tables 40-4 and 40-5.

The Fuhrman grading system for renal cell carcinoma is based on nuclear characteristics (size, contour, and nucleoli) and uses a scale from 1 to 4, where 4 represents the highest degree of nucleolar irregularity and indicates a poorer
TABLE 40-4 TNM Staging for Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Stage Grouping</th>
<th>5-Year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Any T Any N M1</td>
<td>&lt;5</td>
</tr>
<tr>
<td>T0</td>
<td>Any T Any N M0</td>
<td>10</td>
</tr>
<tr>
<td>T1a</td>
<td>T1 N0 M0</td>
<td>70-85</td>
</tr>
<tr>
<td>T1b</td>
<td>T1 N0 M1</td>
<td>50-65</td>
</tr>
<tr>
<td>T2a</td>
<td>T2 N0 M0</td>
<td>45-50</td>
</tr>
<tr>
<td>T2b</td>
<td>T2 N1 M0</td>
<td>25-30</td>
</tr>
<tr>
<td>T3a</td>
<td>T3c N0 M0</td>
<td>15-20</td>
</tr>
<tr>
<td>T3b</td>
<td>T4 N0 M0</td>
<td>10</td>
</tr>
<tr>
<td>T4</td>
<td>Any T N2 M0</td>
<td>&lt;5</td>
</tr>
<tr>
<td></td>
<td>Any T N1 M1</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

Regional Lymph Nodes (N)

| N0 | No regional lymph node metastases |
| N1 | Regional lymph node metastases   |

Distant Metastasis (M)

| M0 | No distant metastases            |
| M1 | Distant metastases               |


Significant factors predictive of poor outcome in a multivariate analysis included Karnofsky performance status score of less than 80%, hemoglobin level of less than 10 mg/dL, serum lactate dehydrogenase level of more than 1.5 times the upper limit of normal, corrected serum calcium level of more than 10 mg/dL, and lack of prior nephrectomy. A risk model was created using these five factors to assign patients to one of three groups: those with zero risk factors (favorable risk), those with one or two risk factors (intermediate risk), and those with three or more risk factors (poor risk). Median survival for the group as a whole was 10 months, but ranged from 15 months for patients in the favorable-risk group down to 4 months for patients in the poor-risk group (Figure 40-6). These prognostic factors have been validated in cohorts heavily treated with multiple nonantiangiogenic and noncytokine therapies. The MSKCC criteria have been validated across multiple institutions, and adding the number of metastatic sites to this model even better defines outcomes for patients with favorable, intermediate and poor risk. Currently, this is the most commonly used nomogram for prognostication in clinical and experimental settings.

Investigators at the University of California at Los Angeles (UCLA) have developed the UCLA Integrated Staging System (UISS), a system based on TNM stage, grade, and Eastern Cooperative Oncology Group (ECOG) performance status. Patients are stratified into three risk groups according to the probability of tumor recurrence and survival, and risk group–specific surveillance guidelines are offered. Based on data from a large sample of patients, investigators at the Mayo Clinic devised the stage, size, grade, and necrosis (SSIGN) scoring system, in which patients with clear cell renal carcinoma were assigned a score based on tumor stage, tumor size, nuclear grade, and the presence of necrosis. Using the SSIGN score, cancer-specific survival at 1 to 10 years after treatment can be estimated for an individual patient. Investigators at MSKCC combined tumor stage, tumor size, histologic subtype, and symptoms at presentation into a nomogram that predicted
the probability of freedom from recurrence at 5 years after treatment.\textsuperscript{169} This nomogram has been updated for the clear cell variant of renal cell carcinoma and includes tumor stage, tumor size, nuclear grade, necrosis, vascular invasion, and symptoms at presentation as prognostic factors.\textsuperscript{171} For clear cell carcinomas, clinical factors that influence survival include performance status grade and the presence of paraneoplastic signs or symptoms such as anemia, hypercalcemia, hepatopathy, fever, and weight loss.\textsuperscript{172-174} Various microscopic features, such as Fuhrman nuclear grade, sarcomatoid histologic features, as well as biologic features like interleukin-6 or VEGF production may be useful in predicting survival.\textsuperscript{32,173,175-177}

**Surgical Treatment**

**Nephrectomy**

The mainstay of treatment of primary renal cell carcinoma is surgical excision or nephrectomy. Nephrectomy represents the only proven curative modality. Radical nephrectomy, which involves the early ligation of the renal artery and renal vein and excision en bloc of the kidney with surrounding Gerota's fascia and ipsilateral adrenal gland, became the procedure of choice in the 1960s. Robson reported a 5-year survival rate of 66\% with this procedure, which compared favorably with the previously reported surgical survival rate of 48\% for simple nephrectomy. Various surgical approaches (open and minimally invasive) are available for the effective performance of this procedure. Minimally invasive approaches have been shown to have equivalent oncologic outcomes to open approaches.

With better understanding of tumor biology and changing patterns of presentation, the value of radical nephrectomy is being reassessed. Involvement of the ipsilateral adrenal gland occurs only 4\% of the time, and in most instances, it is associated with direct extension from a large upper-pole lesion or the presence of nodal or distant metastases.\textsuperscript{178-180} As a consequence, adrenalectomy is often reserved for patients with large upper-pole lesions or those with solitary ipsilateral adrenal metastases identified on preoperative staging studies.

**Lymph Node Dissection**

The benefit of performing a regional lymph node dissection in conjunction with the radical nephrectomy is controversial.\textsuperscript{181} With improved preoperative CT staging, the incidence of unsuspected nodal metastases in patients with low-stage tumors is less than 1\%. Multiple preoperative and intraoperative evaluative nomograms exist and can aid the surgeon in determining the benefit of lymph node dissection in conjunction with nephrectomy.\textsuperscript{182,183} The only randomized trial to evaluate lymph node dissection in patients with renal cell carcinoma showed no improvement in survival with such dissection.\textsuperscript{184} The results of this study are tempered by the fact that the majority of patients enrolled had low-stage (T1 and T2) tumors, and thus the higher-risk patients most likely to derive a therapeutic benefit from lymph node dissection were not adequately studied. A therapeutic benefit of lymph node dissection in patients with metastatic disease undergoing cytoreductive nephrectomy has been supported (level 2 data) by the findings of several series.\textsuperscript{185-187} A therapeutic benefit of extended lymphadenectionomy in patients with clinically evident lymphadenopathy but with no evidence of distant metastasis has been suggested.\textsuperscript{188} The overall morbidity of lymph node dissection is very low. The possible therapeutic benefits in selected patients as well as the benefit to staging, especially in patients being enrolled in adjuvant clinical trials, has not been negated by the current literature. In locally advanced disease, regional lymph node dissection should be performed when technically feasible.\textsuperscript{181}

**Nephron-Sparing Surgery**

The American Urological Association recently published guidelines for nephron-sparing surgery or partial nephrectomy.\textsuperscript{189} This has expanded the role of nephron-sparing surgery from elective to standard of care for patients with cT1a tumors (tumors less than 4 cm) amenable to partial nephrectomy, and as an option in patients with tumors from 4 to 7 cm in whom preservation of renal function is a priority. The generally accepted criteria for consideration of nephron-sparing or partial nephrectomy are listed in Table 40-6. These include bilateral tumors, tumor in a solitary kidney, and compromised renal function.\textsuperscript{190,191} Overall survival of patients undergoing partial nephrectomy is equivalent to that of patients with disease of a comparable stage who underwent radical nephrectomy.\textsuperscript{192-194} A recent retrospective review of the data for 648 patients who underwent either radical or partial nephrectomy for cT1a renal masses suggested a survival advantage for partial nephrectomy.\textsuperscript{195} This may be explained by the increased rate of future development of renal insufficiency in patients who undergo radical nephrectomy.\textsuperscript{196,197}

In patients with small, solitary tumors, the rate of local recurrences is 0\% to 7\%,\textsuperscript{198} with a number of series reporting no local recurrences. Several retrospective series,\textsuperscript{15,199-202} and one prospective study\textsuperscript{203} have demonstrated equivalent survival for patients who undergo partial nephrectomy and those who undergo radical nephrectomy. Many urologists recommend complete nephrectomy in patients documented to have

<table>
<thead>
<tr>
<th>TABLE 40-6 Indications for Partial Nephrectomy</th>
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<tbody>
<tr>
<td><strong>Absolute</strong></td>
</tr>
<tr>
<td>All renal masses &lt;4 cm amenable to partial nephrectomy (clinical T1a)</td>
</tr>
<tr>
<td>Bilateral tumors</td>
</tr>
<tr>
<td>Tumor in solitary kidney</td>
</tr>
<tr>
<td>Tumor in functionally solitary kidney</td>
</tr>
<tr>
<td>Compromised renal function</td>
</tr>
<tr>
<td>Multiple recurrent tumors (von Hippel–Lindau syndrome)</td>
</tr>
<tr>
<td><strong>Relative</strong></td>
</tr>
<tr>
<td>Localized tumor with progressive disorder that may impair renal function</td>
</tr>
<tr>
<td>History of familial renal cell carcinoma</td>
</tr>
<tr>
<td>Oncocytoma (preoperative pathologic diagnosis)</td>
</tr>
<tr>
<td><strong>Elective</strong></td>
</tr>
<tr>
<td>Tumors 4-7 cm (clinical T1b) amenable to partial nephrectomy</td>
</tr>
<tr>
<td><strong>Controversial</strong></td>
</tr>
<tr>
<td>Large (&gt;5 cm) tumors in patients with normal contralateral kidney</td>
</tr>
<tr>
<td>Centrally located tumors in patients with normal contralateral kidney</td>
</tr>
</tbody>
</table>
tumors with sarcomatoid histologic features on frozen section or evidence of renal vein invasion.

Minimally Invasive Techniques (Radical and Partial Nephrectomy)

In 1991, Clayman and colleagues published the first case report of a laparoscopic nephrectomy, performed in an 85-year-old woman with renal cell carcinoma.\textsuperscript{204} Since then, a number of groups have reported on increasingly larger series of patients who underwent this procedure.\textsuperscript{205-208} Overall survival and disease-free survival were no different in the groups undergoing laparoscopic surgery and in those undergoing open surgery. With increased experience in the technique, the total intraoperative and postoperative costs became less for patients undergoing minimally invasive procedures due to the shorter postoperative hospital stay.\textsuperscript{209} Laparoscopic radical nephrectomy is a viable alternative to an open procedure, with equivalent surgical efficacy and safety, and substantially reduced postoperative recovery time.\textsuperscript{210}

Minimally invasive techniques (including laparoscopic and robotic partial nephrectomies) are being used in the setting of nephron-sparing surgery.\textsuperscript{211-213} Unfortunately, adoption of partial nephrectomy overall in the United States has been slow. Due to the technical expertise required to perform minimally invasive partial nephrectomy, performance rates are even lower than for open partial nephrectomy, but they are steadily increasing. Laparoscopic techniques have been associated with a higher complication rate (from 1.5 to 2.0 times greater) than their open counterparts and with a warm ischemia time that is approximately 1.5 times longer. Postoperative nadir creatinine levels have not been significantly different in multiple series comparing open partial nephrectomy with laparoscopic partial nephrectomy.\textsuperscript{214} Oncologic outcomes for the laparoscopic procedure have been equivalent to those for open partial nephrectomy at large experienced centers.\textsuperscript{215} Robotic partial nephrectomy is currently being evaluated at multiple sites, and after short follow-up, outcomes seem to duplicate those of laparoscopic partial nephrectomy.\textsuperscript{216} In several retrospective series, robotic partial nephrectomy has been associated with decreased overall blood loss and shorter warm ischemia time compared with laparoscopic partial nephrectomy.\textsuperscript{217,218} The proposed benefit over laparoscopic partial nephrectomy is in reconstruction of the renal unit after extirpation (especially of more complex masses), but this claim awaits validation in larger series with adequate follow-up.

Energy-Based Tissue Ablation

Over the past decade, cryoablution and radiofrequency ablation have emerged as treatment alternatives for a select group of patients with localized renal tumors. Although long-term follow-up has not been achieved, oncologic effectiveness in the intermediate term is comparable to that of the current gold standard treatment modalities.\textsuperscript{219,220} Ablative techniques are hindered by their association with a substantially increased risk of local tumor recurrence compared with extirpative procedures and the need for retreatment. Identification of residual disease also seems to be more problematic with radiofrequency ablation than with cryoablution. There are no randomized trials comparing radiofrequency ablation with cryoablution. A meta-analysis comparing the two modalities favored cryoablution with regard to need for repeat ablation (1.3% for cryoablution vs. 8.5% for radiofrequency ablation) and local tumor progression (5.2% for cryoablation vs. 12.9% for radiofrequency ablation), but a comparison trial needs to be performed because of the many inherent flaws in a comparative analysis of this type.\textsuperscript{218,221}

Surveillance

Surveillance has been considered for patients with multiple and/or bilateral tumors, for example, patients with von Hippel-Lindau syndrome. Some have advocated waiting until the largest lesion is greater than 3 cm before performing a partial nephrectomy.\textsuperscript{222} In the past, others have suggested bilateral nephrectomies with transplantation for this population.\textsuperscript{193} For tumors smaller than 4 cm, progression to metastatic disease has been very low (<2%) in all retrospective series. Active surveillance is a reasonable option for patients with limited life expectancy or for those unfit for intervention.\textsuperscript{189} Patients should be counseled about the risk, albeit small, of progression to metastatic disease. As improvements occur in nephron-sparing surgery and in minimally invasive ablation, surveillance may become less common, and more drastic approaches such as transplantation less necessary.

Vena Caval Involvement

Inferior vena caval involvement with tumor thrombus is found in about 5% of patients undergoing radical nephrectomy.\textsuperscript{223} It occurs more frequently with right-sided tumors and is commonly associated with metastases. Venal caval obstruction may produce various clinical manifestations. These include abdominal distension with ascites; hepatic dysfunction, possibly related to Budd-Chiari syndrome; nephrotic syndrome; caput medusa; varicocele; malabsorption; and pulmonary emboli. The anatomic location of the tumor thrombus is prognostically relevant. Although 5-year survival in patients with subdiaphragmatic lesions approaches 50%, patients with supra-diaphragmatic thrombi do considerably less well.\textsuperscript{224,225} A team of specialists is usually required for the surgical management of these patients, particularly if tumor thrombectomy of an intracardiac tumor is contemplated. Even at experienced centers, the operative morality may be as high as 5% to 10%,\textsuperscript{226,227} Five-year survival in patients with coexisting nodal or systemic metastases is extremely low, yet a distinct subset of patients may benefit from resection and subsequent systemic therapy.\textsuperscript{228}

Cytoreductive Nephrectomy

In 2001, results of two randomized studies were published demonstrating a significant survival advantage in patients with metastatic disease who underwent nephrectomy prior to embarking on a course of cytokine therapy.\textsuperscript{229,230} Important caveats to these reports are the following: nephrectomy did not improve response to immunotherapy per se, and the margin of survival improvement was substantial only in patients with a performance status of grade 0. UCLA investigators reported a median survival of 16.7 months and a 19.6% 5-year survival rate in patients treated with interleukin–2-containing therapy after debulking nephrectomy.\textsuperscript{231} In addition, the Cytokine Working Group reported a 21% to 24% response rate in patients who received cytokine therapy following recent nephrectomy.\textsuperscript{232} These two analyses suggested that interleukin–2-based therapy should be considered after nephrectomy in patients who have metastatic renal cancer.
Several other reports indicated that anywhere from 13% to 77% of patients treated in this way never progressed to immunotherapy because of complications of treatment or rapid, symptomatic disease progression. This further emphasizes the need for proper patient selection if debulking nephrectomy is to be entertained. Recognizing this, Fallick and associates developed strict criteria for determining which patients should undergo debulking nephrectomy before receiving systemic interleukin-2 therapy. The criteria they used are displayed in Table 40-7.

Cytoreductive nephrectomy in the era of molecular targeted agents has not been prospectively evaluated but is generally accepted based on the earlier studies with cytokine-based therapy. A recent abstract reported a lack of survival benefit for nephrectomy in a subset analysis of poor-risk patients treated with temsirolimus for metastatic renal cell carcinoma. This group represented patients with poor prognostic factors, many of whom would not qualify for cytoreductive nephrectomy under current guidelines. However, except in the studies of temsirolimus, more than 90% of the patients included in all randomized clinical trials of the newer target agents had undergone removal of the primary tumor. Newer targeted therapies are better at downsizing the primary tumor than is immunotherapy, but reductions are generally less than 20% by volume. Several centers have reported on small series of patients with neo-adjuvant (presurgical) treatment with molecularly targeted agents. A phase II study evaluating neoadjuvant treatment with bevacizumab or bevacizumab plus erlotinib in patients with metastatic renal cell carcinoma was recently reported. Clinical outcomes were comparable to those when the targeted agents were used in the postsurgical setting, but delayed wound healing resulted in a prolonged time to resumption of systemic therapy in 10% of patients of these patients with metastatic disease. The largest series of metastatic patients undergoing cytoreductive nephrectomy after pretreatment with targeted agents confirmed an increased risk for specific wound related complications, but overall and severe complications (Clavien >3) were not significantly different than in those patients undergoing upfront cytoreductive surgery. These data, combined with those from small case series, have generated hypotheses that should be further evaluated in larger prospective trials.

Palliative Nephrectomy

Although severe local symptoms such as bleeding and pain, systemic symptoms such as fatigue or fever, and abnormal laboratory test results such as hypercalcemia have been frequent justification for nephrectomy in the past, such “palliative nephrectomies” are rarely necessary now. Pain and bleeding can often be controlled with systemic pain medicines or angioinfarction, clot colic can be minimized with ureteral stents and hydration, and hypercalcemia, fatigue, fever, and other systemic symptoms can often be controlled with non-steroidal antiinflammatory drugs, bisphosphonates, hydration, and appetite stimulants such as medroxyprogesterone.

Resection of Metastatic Disease

Surgical resection of metastatic disease has been actively pursued in certain clinical situations. Patients who have a synchronous solitary metastasis at presentation have decreased survival compared with patients who develop metastasis after the primary tumor is removed (metachronous metastasis). Nonetheless, it is common to resect solitary or oligometastatic disease, often in the ipsilateral lung or adrenal gland, in conjunction with nephrectomy, and occasionally patients remain disease free long term. On the other hand, 5-year survival rates as high as 50% have been reported for patients undergoing resection of isolated metachronous metastases. Time to presentation of metastatic disease (after initial nephrectomy) is a significant prognostic indicator for those undergoing metastasectomy.

<table>
<thead>
<tr>
<th>TABLE 40-7 Criteria for Nephrectomy before Interleukin-2–Based Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than 75% debulking of total tumor burden technically feasible</td>
</tr>
<tr>
<td>No central nervous system, bone, or liver metastases</td>
</tr>
<tr>
<td>Adequate pulmonary and cardiac function</td>
</tr>
<tr>
<td>No active infection or significant comorbid condition</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group performance status of 0 or 1</td>
</tr>
<tr>
<td>Predominantly clear cell histologic type*</td>
</tr>
</tbody>
</table>

*Not required prior to surgery, however, patients in whom pretreatment biopsy specimens reveal a predominant non–clear cell histology were not considered for surgery.


Radiation Therapy

Adjuvant Therapy to Nephrectomy

Studies looking at the possible benefit of adjuvant radiation therapy are few, and their results are inconclusive. There has been no well-designed clinical trial of either preoperative or postoperative radiation therapy in patients with renal cell carcinoma. In the absence of such data, adjuvant radiation therapy should be considered unproven and should be used only in an investigational setting.

Radiation Therapy for Metastatic Disease

The major sites of systemic metastases include lung, bone, and brain. Radiation treatment of disease in these areas can provide palliation of bone pain, prevention of cord compression or fracture, regression of central nervous system metastases, and control of hemoptysis or airway obstruction. Objective responses occur in about 50% of patients with symptomatic skeletal metastases. Symptomatic improvement is often achieved even in the absence of radiologically determined tumor regression. Radiation therapy is also highly effective in controlling hemorrhage from bronchial mucosal lesions. Palliation of large renal bed recurrences by external beam irradiation has been unsatisfactory. Some relief of pain has been achieved in about 50% of patients, but it is usually of short duration. In patients with brain metastases, whole-brain radiation therapy alone has not demonstrated significant efficacy. Stereotactic radiation surgery has been reported to be effective therapy in selected patients with small (<3 cm) central nervous system metastases from renal cell carcinomas. Whole-brain radiation treatment may be omitted, even in patients who undergo stereotactic radiosurgery.

Systemic Therapy

Although surgical resection of localized disease can be curative, 25% to 30% of patients have metastatic disease at presentation, and as many as 30% to 40% of patients with a surgical
“cure” later experience a recurrence. The current median survival for patients with metastatic renal cell carcinoma can vary greatly depending on multiple prognostic factors.165 MSKCC-defined risk categories of “favorable,” “intermediate,” and “poor” are associated with median overall survival rates of 26 months, 14.4 months, and 7.3 months, respectively.165,166 Patient selection greatly influences response rate and survival, and this factor must be kept in mind in evaluating the results of any phase II or III study. Treatment options over the years have included hormonal therapy, chemotherapy, and immunotherapy; however, more recently, attention has been given to targeted therapy approaches.

Adjuvant Therapy

Because a substantial number of patients with high-risk features experience recurrence after primary nephrectomy, an adjuvant therapy could be useful in the treatment of these patients. The risk of recurrence after nephrectomy for an individual patient can be calculated using one of the validated models discussed in the staging and prognosis section of this chapter.159 The ECOG completed a trial comparing adjuvant interferon alfa therapy with observation after resection of high-risk renal cell carcinoma. Eligible patients had tumors staged as T3b or T3c, T4, and/or N1 to N3. Patients were randomly assigned to receive either a year of interferon alfa therapy or routine observation. At a minimum follow-up of 36 months and a mean of 68 months overall, no statistically significant difference in disease-free survival was observed between the two study arms.260

A smaller study performed by the European Organization for Research and Treatment of Cancer (EORTC) also showed no benefit for the adjuvant administration of interferon alfa. Although the results were disappointing, the study was useful in providing information on the natural history of stage III renal cell carcinoma. Specifically, it identified a high-risk group, those with T3c, T4, and/or N2 or N3 disease, who had only a 20% to 25% chance of remaining disease free at 2 years.260 This population was believed to be at sufficient risk of relapse to justify exploration of more aggressive therapy, such as high-dose interleukin-2, in an effort to prevent or delay relapse. Consequently, the Cytokine Working Group performed a trial randomly assigning patients who met these high-risk staging criteria to either a single cycle of high-dose interleukin-2 or observation (with interleukin-2–based therapy at the time of recurrence). Unfortunately, this trial showed no survival benefit for the patients receiving high-dose interleukin-2 in the adjuvant setting.261 There is no evidence to support the use of interferon or interleukin-2 in the adjuvant setting in patients with high-risk renal cancer. A small randomized trial using thalidomide for adjuvant treatment also showed no survival benefit.262 Two trials that have investigated vaccine–based treatment in the adjuvant setting are discussed later in this chapter; one has shown promising results.263,264,265

Several adjuvant studies are currently enrolling patients. ECOG trial No. 2805, the Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma (ASSURE) study, is a double-blinded phase III trial randomly assigning 1923 patients to receive no treatment, 1 year of sunitinib treatment, or 1 year of sorafenib treatment. Accrual at the time of submission of this chapter was over 1400 patients.266 The major endpoint being assessed is disease-free survival. Two other phase III trials are currently accruing patients for adjuvant therapy: Sunitinib Treatment of Renal Adjuvant Cancer (S-TRAC) and SORCE, which is evaluating sorafenib therapy in the adjuvant setting.

Neoadjuvant Therapy

The use of targeted agents as neoadjuvant therapy is on the verge of being explored in a large prospective trial. Use could be initiated through a clinical trial in two subsets of patients: (1) patients with metastatic disease, to provide a test of the benefits of cytokine therapy in selected patients. With the influx of so many new targeted agents and a second generation of agents currently being tested, the questions that remain to be answered include the following: (1) What is the appropriate sequencing of the agents? (2) Is combination therapy safe and more effective than single-agent therapy? The development of novel clinical trial designs with multi-institutional and multinational cooperation will be crucial in answering these questions.

Targeted Agents

Given the frequency of biallelic loss of the VHL gene and associated dysregulation of hypoxia-inducible genes, including those for the proangiogenic growth factors VEGF and PDGF, renal cell carcinoma has been a particularly promising target for antiangiogenic therapy. The use of the term targeted agents is a misnomer, because most of these drugs act on multiple systems within the cell and are multitargeted (Figure 40-7).267,268 The monoclonal antibodies are an exception to this. There are currently six drugs that have shown an improvement in progression-free survival or overall survival in large phase III randomized trials, with several more awaiting data maturity. Response rates and tolerability of these agents are better than those of cytokines, but there are only sporadic cases of durable complete responses. Despite the advances brought by targeted agents, there is still a role for cytokine therapy in selected patients. With the influx of so many new targeted agents and a second generation of agents currently being tested, the questions that remain to be answered include the following: (1) What is the appropriate sequencing of the agents? (2) Is combination therapy safe and more effective than single-agent therapy? The development of novel clinical trial designs with multi-institutional and multinational cooperation will be crucial in answering these questions.

Sunitinib

Sunitinib is a small-molecule multitargeted kinase inhibitor of VEGF receptor (VEGFR), PDGF receptor (PDGFR), c-Kit, and FLT3 (FMS-like tyrosine kinase 3). Two phase II studies were performed in patients with metastatic renal cell carcinoma refractory to cytokine therapy. The first trial enrolled 63 patients, the majority of whom had tumors with clear cell histologic features and had undergone nephrectomy. The response rate was 40% with no patients showing a complete response, and the progression-free survival was 8.1 months.269 A subsequent 106-patient study, in which all individuals had clear cell carcinoma, had undergone nephrectomy, and had shown no response to cytokine therapy, demonstrated a 25% response rate after independent review. Based on these phase II data, sunitinib was approved by the FDA in January 2006.
A phase III trial randomly assigning 750 patients to receive either sunitinib or interferon alfa was completed in July 2005. The primary endpoint, progression-free survival, was 11 months in the sunitinib arm versus 5 months in the interferon arm (P = 0.001), and overall survival was longer in the sunitinib group, 26.4 months versus 21.8 months (P = 0.049). Objective response rate as measured by Response Evaluation Criteria in Solid Tumors (RECIST) was 47% for sunitinib compared with 12% for interferon alfa. The most commonly reported sunitinib–related grade 3 adverse events were hypertension (12%), fatigue (11%), diarrhea (9%), and hand-foot syndrome (9%). Thyroid abnormalities can be found in more than 80% of patients and warrant serial monitoring. The development of grade 3 systemic hypertension during receipt of treatment may be predictive of efficacy.

This oral medication is dosed on a 6-week cycle: 4 weeks at 50 mg/day, followed by 2 weeks off therapy.

**SORAFENIB**

Sorafenib is a bis-aryl urea originally developed as a potent inhibitor of both wild-type and mutant (V599E) B-Raf and c-Raf kinase isofoms. It was also found to possess inhibitory activity against VEGFR, PDGFR, c-KIT, and FLT-3. A phase II randomized discontinuation study accrued 502 patients with renal cell carcinoma. All patients in this study received sorafenib therapy for 12 weeks. Those who had more than 25% shrinkage or 25% growth of disease continued the sorafenib therapy. Median progression-free survival was 5.5 months in the treatment arm and 2.8 months in the placebo arm, and these results were highly statistically significant (P = 0.000001). The survival benefit of sorafenib was FDA approved in December 2005 for use in the treatment of advanced renal cell carcinoma. A later survival analysis, now with substantial patient crossover, showed survival of 17.8 months in the sorafenib arm versus 15.2 months in the placebo arm.
(P = 0.146). When the postcrossover placebo data were censored, the differences in survival became significant: 17.8 months versus 14.3 (P = 0.029). Results of a frontline study comparing sorafenib with interferon were published in 2009.726 Progression-free survival was 5.7 months for sorafenib-treated patients, and 5.6 months for interferon-treated patients. Crossover was permitted in the upfront interferon arm, and patients who subsequently received sorafenib demonstrated a median progression-free survival of 3.6 months. Due to the relatively disappointing progression-free survival data in this study, sorafenib has fallen out of favor as a frontline agent of choice.

This oral medication is dosed at 400 mg/day continuously, with restaging performed every 2 months.

**PAZOPANIB**

Pazopanib is an oral second-generation multitargeted kinase inhibitor of VEGFR types 1, 2, and 3, PDGFR-α, PDGFR-β, and c-Kit.277 In a phase II clinical trial, the tolerability profile was different from that of other multitargeted kinase inhibitors, with hypertension in 8%, grade 4 myelosuppression in 7%, fatigue in 4%, and diarrhea in 3%. Therapy was discontinued in 11% of patients due to toxicity. An international phase III trial in patients with renal cell carcinoma was reported in 2009.278 Patients were randomly assigned in a 2:1 ratio to receive 800 mg pazopanib orally per day or placebo. The primary endpoint was progression-free survival. Crossover was permitted on the placebo arm at the time of progression. Patients were either treatment naïve (n = 233) or had received prior cytokine therapy (n = 202). Median progression-free survival was 9.2 months in the pazopanib-treated group versus 4.2 months in the placebo arm (hazard ratio [HR] = 0.42, 95% confidence interval [CI] = 0.34 to 0.62, P < 0.0000001). In the treatment-naïve subset, the pazopanib-treated group had a progression-free survival of 11.1 months versus 2.8 months in the placebo group (HR = 0.42, 95% CI = 0.27 to 0.60, P < 0.0000001). An ongoing trial is comparing upfront pazopanib to sunitinib therapy, using a noninferiority design.

**AXITINIB**

Axitinib is an oral second-generation multitargeted kinase inhibitor against VEGFR types 1, 2, and 3. A phase II clinical trial involving 52 patients in whom cytokines had been ineffective recorded an overall response rate (complete plus partial responses by RECIST criteria) of 44.2%.279 At a median follow-up of 20 months, median progression-free survival was 15.7 months and median overall survival was 31.1 months. Dosage reduction was required in 29% of patients because of serious adverse events. Unlike with pazopanib, there were no grade 3 or 4 cases of myelosuppression. Another phase II study enrolled 62 patients who showed no response to sorafenib. All patients had received prior sorafenib therapy and 72% had received prior systemic therapy. Axitinib dosages were titrated up and down from 5 mg/day. Overall response rate was 22.6%. Median progression-free and overall survival were 7.4 and 13.6 months, respectively. Serious adverse events (grade 3 or 4) were hand–foot syndrome (16.1%), fatigue (16.1%), hypertension (16.1%), dyspnea (14.5%), diarrhea (14.5%), and hypotension (6.5%).279 A prospective randomized phase III trial of sorafenib versus axitinib is currently under way in patients with metastatic renal cell carcinoma that did not respond to a prior first-line therapy.

**BEVACIZUMAB**

Bevacizumab is an intravenously administered human monoclonal antibody directed against VEGF. All circulating VEGF isoforms are bound and neutralized, which thus prohibits ligand binding to the VEGF receptor and consequently inhibits its signal transduction in the endothelial cell. Bevacizumab in combination with interferon alfa was FDA approved in July 2009 as a first-line therapy for treatment-naïve patients with metastatic renal cell carcinoma. A large (n = 649) phase III randomized trial compared bevacizumab plus interferon alfa to interferon alfa plus placebo. The median progression-free survival was 10.4 months versus 5.5 months (P < 0.0001) in favor of the group receiving the bevacizumab combination.280

Another recently completed phase III trial enrolling 723 treatment-naïve patients showed a median progression-free survival of 8.5 months in patients receiving bevacizumab plus interferon alfa versus 5.2 months in patients receiving interferon alfa monotherapy (P < 0.001). Overall toxicity was greater in the bevacizumab plus interferon group, including significantly more grade 3 hypertension (95% vs. 0%), anorexia (17% vs. 8%), fatigue (35% vs. 28%), and proteinuria (13% vs. 0%). No overall survival difference was reported in either study for the bevacizumab-treated arms.281,282

Studies examining the role of erlotinib (a tyrosine kinase inhibitor of the epidermal growth factor receptor) in combination with bevacizumab have been completed.283 A 63–patient phase II study, which included 43 patients who were previously untreated, demonstrated an 11–month progression-free survival.283 The role of erlotinib was subsequently discounted in a 100-patient study randomly assigning patients to receive either bevacizumab monotherapy or bevacizumab plus erlotinib.284 The progression-free survival for the bevacizumab-only arm was 8.5 months, versus 9.9 months for the combination-therapy arm (P = 0.58). There was no survival difference.

**TEMsiROliMUS**

Temsirolimus is a rapamycin analog that inhibits mTOR downstream of the serine–threonine protein kinase AKT. It is administered intravenously. A randomized phase III three-arm study in which one group received 25 mg of intravenous temsirolimus weekly, one group received 9 million U of interferon αlfa three times weekly, and one group received 15 mg of intravenous temsirolimus weekly plus 6 million U units of interferon αlfa three times weekly showed significant differences between treatment groups.285 Patient inclusion criteria showed significant differences from criteria in contemporary phase III trials: 35% of patients had not undergone cytoreductive nephrectomy; 80% of patients had a Karnofsky performance status score of less than 80; and 20% of patients had tumors with non—clear cell histologic features. The median survival of patients in the temsirolimus-only arm was significantly longer than that in patients receiving interferon monotherapy (10.9 months vs. 7.1 months, P = 0.0069). The objective response rates as measured by RECIST criteria did not differ among the three arms. The median survival of patients receiving the combination therapy was 8.4 months and was not significantly different from that in the temsirolimus-only arm. The most frequent serious adverse events in the temsirolimus-only
The epidermal growth factor receptor (EGFR) antagonists, sunitinib or sorafenib. metastatic renal cell carcinoma after failure of treatment with FDA approved everolimus for the treatment of patients with respectively), and pneumonitis (3% and 0%, respectively). The stomatitis (3% and 0%, respectively), fatigue (3% and 1%, disease progression was documented. Serious adverse events the placebo arm crossed over and received everolimus once compared with those receiving placebo. There were no significant differences in overall survival, likely because most patients in the placebo arm crossed over and received everolimus once disease progression was documented. Serious adverse events (grade 3 or 4) in the everolimus and placebo groups were stomatitis (3% and 0%, respectively), fatigue (3% and 1%, respectively), and pneumonitis (3% and 0%, respectively). The FDA approved everolimus for the treatment of patients with metastatic renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

**Epidermal Growth Factor Receptor–Blocking Agents**

The epidermal growth factor receptor (EGFR) antagonists, despite the presence of compelling preclinical data, have not yet lived up to their promise. A high rate of EGFR expression on renal cell carcinoma tumors, coupled with loss of VHL resulting in increased expression of transforming growth factor alfa, supports the presence of an autocrine loop in renal cell carcinoma. Inhibition of this autocrine loop by blocking either the cell surface receptor (EGFR) or the ligand would be expected to result in growth inhibition and clinical response. However, several phase II studies demonstrated little response to single-agent therapy targeted against EGFR. In another phase II trial, the combination of erlotinib with bevacizumab failed to show any clinical advantage over bevacizumab therapy alone.

**Sequencing of Therapies**

Evidence-based guidelines are lacking with regard to the sequencing of systemic agents. There is evidence from a retrospective study that administration of salvage cytokine therapy after treatment with targeted agents (sunitinib, sorafenib, bevacizumab) is associated with a substantially higher rate of severe cardiac toxicity. In this study, only 1 of 23 patients was able to tolerate a second cycle of interleukin–2, and the incidence of severe cardiac toxicity was extraordinarily high at 40%. Although there are case reports of a small number of complete responses, the durability of which has yet to be determined, all patients receiving targeted therapy can expect to progress through multiple agents. The best optimal sequence of chemotherapy is unknown. One problem with current trial design is lack of flexibility to accept newer drugs into the sequencing. Novel multi-institutional and multinational trial design should be a priority if we are to progress beyond replicating the same data for each new drug. Sequencing may hold promise in extending responses and adequately treating tumors that become resistant. This can only be accomplished through integration of preclinical data (alternative escape pathways) into large clinical trials.

**Vaccines**

Vaccines used for the treatment of metastatic renal cell carcinoma or used in the adjuvant setting fall into four classes:

1. Autologous tumor cell based
2. Genetically modified tumor cell based
3. Dendritic cell based
4. Peptide based

Only two randomized phase III studies have investigated the use of vaccines in the treatment of renal cell carcinoma. Both of these used vaccines in the adjuvant setting. In a phase III multinational open-label clinical trial, over 800 patients with high-risk tumors were randomly assigned to receive a heat shock protein complex (vitespen) derived from autologous tumors or to observation alone. No difference in recurrence-free survival was seen between the groups. Longer follow-up is needed to determine if there is a benefit for patients at lower risk. An autologous tumor vaccine (Reniale) was evaluated in a phase III trial, and improved progression-free survival in patients with high-risk nonmetastatic renal cell carcinoma (P = 0.0476). In the subgroup with T3 tumors (staged according to AJCC edition 4), the 5-year progression-free survival was 67.5% versus 49.7% in the untreated control group. There was also a trend toward increasing overall survival, with the vaccine cohort having an overall survival of 68.9% at 10 years compared with 62.1% in the control group (P = 0.066). A subset analysis of patients with T3 disease also showed a benefit in overall survival (P = 0.024). The vaccine is not commercially available in Europe or the United States at this time. A multinational clinical trial that integrates the current staging system could provide more insight into patient selection and the role of this vaccine in adjuvant treatment of high-risk disease.

Multiple phase I and phase II studies have shown mixed results for vaccine use in patients with metastatic renal cell carcinoma. Ongoing studies are evaluating the effectiveness of combining vaccine therapy with cytokine therapy, but again results have been mixed, as shown by the lack of progression to phase III trials in the population metastatic disease.

**Thalidomide**

Thalidomide has a somewhat unclear mechanism of action but is believed to alter to some degree the expression of angiogenic growth factors, including VEGF and fibroblast growth factor in tissues. Although early anecdotal reports suggested possible objective responses in renal cell carcinoma, most reports of therapy with even high dosages of thalidomide (800+ mg/day) suggest that the agent, atbest, results in disease stabilization. Toxic effects include somnolence, constipation, fatigue, and, with prolonged exposure, peripheral neuropathy. Several small phase II studies of lenalidomide (a thalidomide analog) have shown partial response rates for this agent of 0% to 10% No survival advantage has been detected. At this point, thalidomide therapy is generally not recommended for the treatment of patients with renal cell carcinoma.
**Chemotherapy**

Many studies of single-agent chemotherapy for renal cell carcinoma have been performed, with most agents showing minimal or no activity. In a review of the chemotherapy literature, Yagoda and colleagues reported a 4% overall response rate in 3635 patients with renal cell carcinoma treated with various chemotherapy approaches. More recently, gemcitabine chemotherapy has been studied in renal cell carcinoma. When gemcitabine is used as a single agent, response rates between 6% and 30% are reported. A combination of gemcitabine and 5-fluorouracil demonstrated a response rate of 17% in 41 patients with metastatic renal cell carcinoma. Median progression-free survival in this pretreated group of patients was 28.7 weeks. Follow-up studies using gemcitabine and capcitabine, the oral prodrug form of 5-fluorouracil, demonstrated response rates of 11% and overall survival of 14 months. A more recent study demonstrated a median progression-free survival and overall survival of 4.6 and 17.9 months, respectively. There were six partial responses and one complete response (objective response rate = 8.4%; 95% CI = 3.5 to 16.6). In addition, major responses have been reported with cisplatin- and taxane-based therapy in patients with collecting duct tumors. A case series of patients with sarcomatoid renal cell carcinoma and other aggressive renal cell carcinomas treated with doxorubicin (50 mg/m²) and gemcitabine (1500 or 2000 mg/m²) every 2 to 3 weeks along with granulocyte colony-stimulating factor support was reported in 2004. Two patients had a complete response, five had a partial response, three had a mixed response, and one had stable disease. The median duration of response was 5 months (range = 2 to 21+ months). Prospective studies need to be performed to validate this observation.

**Immunotherapy**

Immunotherapeutic strategies for treatment of renal cell carcinoma have included therapy with nonspecific stimulators of the immune system, specific antitumor immunotherapy, and adoptive immunotherapy. The most consistent results have been reported with interferon alfa and interleukin-2. Although the mechanism of action of these cytokines is incompletely understood, the induction of antitumor responses in mice by interferon alfa and interleukin-2 has been linked to the direct killing of tumor cells by activated T and natural killer cells as well as to the antiangiogenic effects of these agents.

**Interferon**

Interferon alfa has undergone extensive clinical evaluation over the past 2 decades as treatment for metastatic renal cell carcinoma. Results of these investigations are thoroughly described in several reviews. Although no clear dose-response relationship exists, daily doses in the 5 million to 10 million U range appear to have the highest therapeutic index. Toxic effects of interferon include flulike symptoms such as fever, chills, myalgias, and fatigue, as well as weight loss, altered taste, depression, anemia, leukopenia, and elevated values on liver function tests. Most adverse effects, especially the flulike symptoms, tend to diminish with time during long-term therapy.

Two phase III studies using single-agent interferon therapy showed a modest impact on survival in patients with advanced renal cancer. For example, one phase III trial comparing interferon alfa-2a plus vinblastine chemotherapy with vinblastine alone reported a median survival of 67.6 weeks for the interferon-plus-vinblastine arm compared with 37.8 weeks for patients receiving vinblastine alone (P = 0.0049). In another trial that randomly assigned patients with advanced disease to receive either interferon or medroxyprogesterone acetate, there was a 28% reduction in the risk of death in the interferon group (P = 0.017) and an improvement in median survival of 2.5 months.

More recent studies have suggested that the antitumor effects of interferon are quite limited. For example, a French Immunotherapy Group phase III trial comparing interferon with both interleukin-2 and interleukin-2 plus interferon reported a response rate of only 7.5% for the interferon arm with a 1-year event-free survival rate of only 12%. In the Programme Etude Rein Cytokines (PERCY) Quattro trial, untreated patients with more than one metastatic site and a Karnofsky performance score of 80 or higher were randomly assigned to receive either medroxyprogesterone, interferon alfa, subcutaneous interleukin-2, or interferon plus subcutaneous interleukin-2 in a 2 × 2 factorial design. The primary endpoint was overall survival, which did not differ among the groups (median overall survival = 15 months, all P values >0.5). This study casts doubt on the utility of outpatient cytokine therapy in the treatment of patients with metastatic renal cell carcinoma of intermediate prognosis.

Efforts to improve upon the clinical activity of interferon alfa have included combining it with 5-fluorouracil, 13-cis-retinoic acid, interferon gamma, thalidomide, and interleukin-2. For the most part these efforts have met with limited success, with occasionally promising phase II findings failing to be confirmed in phase III trials.

**Interleukin-2**

Clinical investigation of interleukin-2 as treatment for renal cell carcinoma began in the mid-1980s. Initial studies were performed with high-dose bolus interleukin-2 and lymphokine-activated killer cells, because animal studies had shown a steep dose–response curve for interleukin-2 and benefit for the addition of lymphokine-activated killer cells. Dramatic and durable responses were reported in a small subset of patients. Subsequent clinical studies have shown that high-dose bolus interleukin-2 alone possesses antitumor activity that is essentially equivalent to that of the combination of interleukin-2 and lymphokine-activated killer cells.

In 1992, high-dose bolus interleukin-2 received FDA approval for treatment of metastatic renal cell carcinoma based on data from 255 patients treated in seven clinical trials at 21 institutions. In these studies, recombinant interleukin-2 (Proleukin, Chiron Corporation, Emeryville, Calif) at a dose of 600,000 to 720,000 IU/kg was administered by 15-minute intravenous infusion every 8 hours on days 1 to 5 and 15 to 19 (maximum, 28 doses). Treatment was repeated at approximately 12-week intervals for a maximum of three cycles in patients showing a tumor response. There were 12 complete responses (5% of patients) and 24 partial responses (9% of patients). Follow-up data on the study patients were accumulated through late 1998 (median follow-up = 8 years).
The clinical results appear to have steadily improved over time. At last report 17 patients (7%) were classified as complete responders and 20 (8%) as partial responders. The median survival for the group as a whole was 16.3 months, with 10% to 15% of patients estimated to remain alive 5 to 10 years after treatment with high-dose interleukin-2. A large percentage of patients showed a response, particularly those remaining free from progression for longer than 2 years and those resected to disease-free status after responding to high-dose interleukin-2, appear unlikely to experience progression and may actually be “cured.”

Several investigators have evaluated regimens involving interleukin-2 administered by alternative routes or in lower dosages in an attempt to reduce toxicity. Continuous intravenous infusion regimens of interleukin-2 and lymphokine-activated killer cells appeared to produce tumor response rates similar to those seen with high-dose bolus intravenous interleukin-2. Although more convenient to administer, continuous-infusion regimens, on a milligram per milligram basis, were actually more toxic than high-dose bolus interleukin-2. Furthermore, omitting the lymphokine-activated killer cells and/or reducing the dose of interleukin-2 further to allow prolonged administration, although it produced enhanced immune activation, appeared to limit antitumor activity.

Attempts to improve efficacy have included the addition of interferon alfa and 5-fluorouracil to interleukin-2. Studies can be differentiated according to route of interleukin-2 administration—high-dose intravenous bolus injection, continuous intravenous infusion, or subcutaneous injection—and whether or not the drug was given in combination with 5-fluorouracil. Despite publication of promising data by several groups, follow-up trials conducted by the Cytokine Working Group failed to confirm the promise of cyto-kin-2. Interleukin-2 and interferon alfa administered subcutaneously with or without weekly 5-fluorouracil produced response rates and median survival similar to those observed with high-dose interleukin-2 alone or high-dose interleukin-2 and interferon; however, the quality and durability of the responses appeared to be considerably less than those observed with high-dose interleukin-2 alone.

Investigators in France reported the results of a large-scale phase III randomized trial comparing intermediate-dose interleukin-2 administered by continuous intravenous infusion plus subcutaneous interferon alfa with either interleukin-2 or interferon alfa administered alone. The response rate and 1-year event-free survival were significantly greater for the combined interleukin-2 and interferon alfa arm than for either of the single-agent arms, although there was no significant difference in overall survival among the three groups.

The Cytokine Working Group conducted a randomized phase III trial to determine the value of outpatient interleukin-2 plus interferon alfa-2b therapy compared with high-dose intravenous interleukin-2 therapy in patients with metastatic renal cell carcinoma. One hundred ninety-two patients were enrolled. One death was reported in each arm. The response rate was 23.2% (22 of 95 patients) in the high-dose interleukin-2 group versus 9.9% (9 of 91 patients) in the interleukin-2 plus interferon group (P = 0.018). Median survivals were 17.5 and 13 months (P = 0.24), respectively, in the two groups. Survival was superior with high-dose interleukin-2 in patients with bone or liver metastases (P = 0.001) or a primary tumor in place (P = 0.040), a surprising finding since liver and bone lesions were generally considered to be relatively refractory to immunotherapy.

The National Cancer Institute published results of a study comparing high-dose interleukin-2, low-dose inpatient bolus interleukin-2, and outpatient subcutaneous interleukin-2. Patients with measurable metastatic renal cell carcinoma and a good performance status were randomly assigned to receive either 720,000 U/kg (high-dose) or 72,000 U/kg (low-dose) interleukin-2, both given by intravenous bolus every 8 hours. After 117 patients were randomly assigned to these treatments, a third arm of low-dose daily subcutaneous interleukin-2 was added. A total of 156 patients were randomly assigned to receive high-dose intravenous interleukin-2, and 150 patients received low-dose intravenous interleukin-2. There were no interleukin-2–related deaths in any arm. There was a higher proportion of responses with high-dose intravenous interleukin-2 (21%) than with low-dose intravenous interleukin-2 (13%; P = 0.048), but no overall survival difference was seen. The response rate for subcutaneous interleukin-2 was 10%. In patients showing a complete response, response durability and survival were better with high-dose intravenous therapy than with low-dose intravenous therapy (P = 0.04).

### Nonmyeloablative Allogeneic Transplantation

Since its inception as a therapy, allogeneic bone marrow transplantation has evolved from a means to achieve chemotherapy dose escalation to a form of adoptive immunotherapy. There is extensive evidence supporting the presence of a graft-versus-malignancy effect in hematologic malignancies, and preclinical data demonstrate the presence of a graft-versus-tumor effect in solid tumors as well. In patients with breast cancer, several reports have demonstrated the presence of a graft-versus-tumor effect in the setting of conventional ablative allogeneic transplantation for metastatic disease. Due to the high level of morbidity and mortality experienced in standard high-dose allogeneic transplantation, and the evidence supporting the therapeutic importance of the immune-mediated effect of the donor graft, different groups began developing nonmyeloablative allogeneic bone marrow and peripheral blood stem cell transplantation regimens for use in the treatment of both hematologic and solid tumors. The goal of these regimens is to create a conditioning regimen sufficient for proper donor engraftment with the least recipient graft ablation possible.

Preliminary experiences with nonmyeloablative allogeneic transplantation in patients with renal cell carcinoma have been reported by a number of centers. In all studies, the provision existed for posttransplantation donor lymphocyte infusion if complete donor chimerism was not achieved. The largest series, reported by Childs and colleagues, demonstrated response in 10 of 19 patients after a conditioning regimen of cyclophosphamide and fludarabine. Complete donor chimerism appeared to be a prerequisite for response, as was some degree of graft-versus-host disease. More recently, Bregni and colleagues reported partial or complete responses in 5 out of 24 patients with metastatic renal cell carcinoma after allogeneic nonmyeloablative transplantation with thiotepa, cyclophosphamide, and fludarabine conditioning.
Pedrazzoli and colleagues reported on 17 patients with treatment-refractory solid tumors, of whom 7 had renal cell carcinoma, who underwent conditioning with fludarabine and cyclophosphamide. Four of the patients had a performance status of 2 or poorer, and the remaining three had a performance status of 1. In the study reported by Pedrazzoli and colleagues, all renal cell carcinoma patients died of progressive disease before day 100. All studies reported substantial hematologic toxicities as well as graft-versus-host disease. Bad outcome was also consistently associated with poorer pretransplantation performance status.

Nonmyeloablative transplantation requires substantial further development before it can be considered for a larger number of patients. The conditioning regimens need to be rendered less toxic. Posttransplantation immunosuppression needs to be refined to decrease graft failure and graft-versus-host disease, and to permit bone marrow from unrelated donors to be used. Ideally, as our understanding of the antigens that elicit a graft-versus-renal cell carcinoma response is improved, modification of the donor graft or the donor lymphocyte infusion to enrich for renal cell carcinoma–specific T cell clones may enhance response. With appropriate tumor antigens in hand, it will also be possible to combine transplantation with vaccination.

Renal Pelvic Tumors

The cellular lining of the urinary collecting system, originating in the proximal renal pelvis, traversing the ureter and urinary bladder, and ending in the distal urethra, is composed of transitional epithelium or urothelium. This entire surface may be affected by carcinogenic influences, and this may help explain the multiplicity in time and place of “urothelial” tumors, which some have termed polychronotropism. Renal pelvic tumors account for approximately 10% of all primary renal cancers.

Tumors of the upper tract are twice as common in men, generally occur in patients older than 65 years of age, and are usually unilateral. The disease is more common in the Balkan region (Bulgaria, Greece, Romania, Yugoslavia), where it is often bilateral. As with urothelial tumors of the urinary bladder, exposure to cigarette smoke, certain chemicals, plastics, coal, tar, and asphalt may increase the incidence of the disease. Long-term exposure to the analgesic phenacetin, usually ingested over years by women for headache relief, has been associated with the development of renal pelvic tumors.

Although most tumors of the upper tract are transitional cell carcinomas, which account for over 90% of lesions, squamous carcinomas also occur, usually in the setting of chronic infections with kidney stones.

Adenocarcinomas and other miscellaneous subtypes are rare.

Clinical Features and Diagnostic Evaluation

The most common presenting feature is gross hematuria, which occurs in 75% of patients, followed by flank pain, which is seen in 30%. Evaluation may reveal either a nonfunctioning kidney and nonvisualization of the collecting system, or, more commonly, a filling defect of the calyceal system, renal pelvis, or ureter on CT urogram. Exfoliative cytologic analysis commonly yields positive findings, as in bladder cancers. A positive cytologic result in the presence of a filling defect of the renal pelvis or ureter confirms the diagnosis. Results of retrograde pyelography with brush biopsy of suspicious lesions may also yield the diagnosis of cancer. If there is still uncertainty in the diagnosis after pyelography, including a retrograde evaluation, ureteroscopy may be performed to further evaluate the filling defect or obstruction.

Staging and Grading of Renal Pelvic Tumors

Upper tract urothelial carcinomas (UTUCs) are graded on a scale from grade I, representing a well-differentiated lesion, to grade IV, representing an anaplastic and undifferentiated lesion. Because of the difficult access to some tumors of the upper tract, clinical staging is difficult. Histologic grade of biopsy specimens can be used to predict pathologic stage of disease. In a staging system similar to that used for urinary bladder cancer, stage O is disease limited to the mucosa; stage A is invasion into the lamina propria without muscularis invasion; stage B is invasion into the muscularis; stage C is invasion into the serosa; and stage D is metastatic disease. Lymphatic metastases usually indicate that more widespread metastatic disease is or will be present. The AJCC TNM classification is also similar to the staging for bladder carcinoma.

Treatment

For low-grade, low-stage transitional cancers, the general approach to treatment is conservative, consisting of local excision and preservation of the kidney parenchyma. For high-stage and high-grade lesions that have infiltrated into the renal parenchyma, the surgical treatment of choice is nephroureterectomy and removal of a cuff of bladder that encompasses the ipsilateral ureteral orifice. This approach is generally required because of the high likelihood of local recurrence in the bladder at the ureterovesical junction or in the distal ureter. Five-year recurrence-free and cancer-specific survival rates for patients with UTUC who undergo radical nephroureterectomy are 69% and 73%, respectively. In patients with regionally advanced or metastatic renal pelvic tumors, systemic chemotherapy; identical to that administered for bladder cancer, is often employed.

Adjuvant therapy has not been adequately assessed, but one study identified 415 patients with T3N0 and T4N0 UTUCs of whom 16% and 25%, respectively, received adjuvant chemotherapy. Chemotherapy status was not associated with any significant cancer-specific or overall survival differences.

Another problem when reviewing the literature on adjuvant chemotherapy for high-risk disease is the paucity of descriptions of lymph node dissection in the initial surgery. Despite this, definitions of regional templates for lymphadenectomy in this disease have been developed. For patients with pathologically determined T3 disease the extent of lymph node dissection is a significant prognostic indicator and correlates with cancer-specific survival. Standard first-line regimens for patients with locally advanced or metastatic transitional cell carcinoma mirror those used in bladder cancer and include methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (MVAC) as well as gemcitabine and cisplatin (GC).
Initial response rates may vary depending on prognostic factors, but long-term survival is poor.

Another consideration is neoadjuvant chemotherapy in high-risk/locally advanced disease because of the risk to the patient of renal insufficiency after nephroureterectomy and the resultant inability to receive optimal adjuvant chemotherapy.\(^\text{355,356}\) This is a difficult argument to make considering the clear lack of data regarding the overall effectiveness of adjuvant treatment in UTUC, but management practice has been extrapolated from the literature on bladder transitional cell carcinoma. Data reported for a large cohort of patients who underwent nephroureterectomy for UTUC provided some insight into operative decisions.\(^\text{356}\) Based on the criterion of a glomerular filtration rate of 60 mL/min or above, only 48% of patients were eligible for chemotherapy preoperatively, and that number decreased to 22% postoperatively. After nephroureterectomy the opportunity for treatment with optimal chemotherapy was lost in 61% of patients able to receive it preoperatively. In a patient at risk for postoperative renal insufficiency and a significant risk for advanced UTUC, strong consideration should be given to the neoadjuvant administration of chemotherapy.

### Other Kidney Tumors

#### Renal Sarcomas

Renal sarcomas account for approximately 1% to 2% of primary renal cancers. Fibrosarcomas are the most common and have a poor prognosis as a result of their typically late presentation and the presence of locally advanced involvement into the renal vein or metastatic disease at presentation. Five-year survival rates are less than 20%. Other, rarer sarcoma variants may occur and include leiomyosarcoma, rhabdomyosarcoma, osteogenic sarcoma, and liposarcoma.

#### Wilms’ Tumor

In children, Wilms’ tumor (nephroblastoma) is the most common cancer of the kidney, accounting for approximately 400 new cases per year in the United States. The development of a successful treatment regimen for the disease in the 1990s was due to the coordinated efforts of a multidisciplinary team of oncologists, radiation therapists, and surgeons. The disease tends to occur more frequently in African American children. A variety of etiologic factors have been suggested to increase the risk of Wilms’ tumor, but for none has a definitive link been established.

#### Genetics

Several well-described genetic abnormalities are associated with Wilms’ tumor. Patients with Wilms’ tumor may also manifest other abnormalities, which include aniridia, WAGR syndrome (Wilms’ tumor, aniridia, other genitourinary abnormalities, mental retardation), Denys-Drash syndrome (Wilms’ tumor, glomerulitis, pseudohermaphroditism), hemihypertrophy, trisomy, other rare physical abnormalities such as macroglossia, and developmental sexual disorders.

Abnormalities of the genes WT1 (chromosome arm 11p13) and WT2 (11p15), and mutations at 16q have all been implicated in the molecular genetics of Wilms’ tumor. Loss of heterozygosity in WT1 and at 16q occur in 20% of patients; inactivation of WT2 has also been described. Other genetic abnormalities have suggested the presence of other abnormal chromosomal locations. Patients with trisomy\(^\text{357}\) and XX/XY mosaicism have been reported to have an increased incidence of Wilms’ tumor.

### Pathology and Staging

Microscopically, Wilms’ tumors consist of blastemic, epithelial, and stromal cells, often arranged in patterns that resemble tubular or glomeruloid features. The multipotential aspects of Wilms’ tumors may be characterized by the presence of teratomatous or teratoid features, including components of mesenchymal structures such as muscle, cartilage, and lipid tissues. In contrast to these differentiated structures, undifferentiated or sarcomatoid lesions can also occur and are associated with a worse prognosis. The presence of nephrogenic rests in the setting of Wilms’ tumors is common; they are thought to be precursor lesions. According to Wilimas and associates,\(^\text{358}\) these rests are “defined as a focus of persistent nephrogenic cells, some of which can be induced to form a Wilms tumor.” The most common staging system divides Wilms’ tumors into five categories (Table 40-8).

### Clinical Features

The most common presentation of Wilms’ tumor is as an asymptomatic abdominal mass in a young patient (median age of 3.5 years). Other physical abnormalities, including aniridia, genitourinary abnormalities, and hemihypertrophy, may occasionally be detected. Hematuria, anemia, hypertension, and/or acute severe abdominal pain may also be present. Abdominal ultrasonography is an important diagnostic test to further evaluate the mass and its anatomic extension, which may include inferior or superior extension into the vena cava. Intravenous pyelography and CT are also warranted. Assessment for metastases to liver, chest, and bone complement the evaluation. The lungs are the most common site of metastasis. The diagnosis is usually established by surgery. If the diagnostic tests and clinical features suggest the presence of a Wilms’ tumor, preoperative needle biopsy should be avoided because of the attendant risks of tumor spillage and subsequent upstaging.

### Multimodality Treatment

High cure rates have been achieved with the concerted effort of multimodality teams performing surgery, radiation therapy, and chemotherapy. Surgical removal of the affected kidney,
along with examination of the regional lymph nodes, and detailed abdominal exploration are the goal. Removal of all gross tumor should be attempted and justifies the radical resection that is often required. Tumors are classified as favorable and unfavorable in histologic features. All patients receive at least two-drug chemotherapy with daunorubicin and vinristine; those with more advanced disease receive additional daunorubicin, cyclophosphamide, and etoposide with abdominal radiation (1080 Gy) and possibly radiation to the chest (1200 Gy). Specific recommendations regarding the exact protocols to be used are determined by the operative findings, the histologic subtype of the tumor, and whether there was evidence of tumor spillage during the resection.

Chemotherapy is an important component of treatment for Wilms’ tumors. Not only is chemotherapy administered after surgery, but neoadjuvant chemotherapy can diminish the size of the primary tumor and cause regression of metastatic lesions as well as downsize tumors in patients with stage 5 disease (bilateral disease). Before the extensive use of chemotherapy, the survival rate for patients with stage 2 or 3 tumors was less than 45%. Now, cure rates approaching 80% to 90% are routinely achieved; survival rates of 92% to 97% are obtainable in earlier stages of disease. Chemotherapy administration in the adjuvant and neoadjuvant settings varies greatly between Europe (studies of the International Society of Paediatric Oncology [SIOP]) and the United States (Wilms’ Tumor Study Group [WTSG]).

As these excellent results continue to accumulate, treatment programs aimed at lessening treatment duration and minimizing long-term consequences, such as induction of second tumors, continue to be evaluated. Such programs include the more selective use of radiation therapy and a decrease in the duration of chemotherapy.

References


86. Bruck RK, McKnight SL. A conserved family of prolyl-4-hydroxylases that modify HIF. Science. 2001;294:1337.


Disorders


