and Romania. In addition, upper tract urothelial carcinoma is linked to hereditary nonpolyposis colorectal cancer.

The most common symptom is painless gross hematuria, and the disease is usually detected on imaging during the workup for hematuria. Patterns of spread are like bladder cancer. For low-grade disease localized to the renal pelvis and ureter, nephroureterectomy (including excision of the distal ureter with a portion of the bladder) is associated with 5-year survival of 80–90%. More invasive or poorly differentiated tumors are more likely to recur locally and to metastasize. Metastatic disease is treated with the chemotherapy used in bladder cancer, and the outcome is similar to that of metastatic bladder cancer.

RENAL CELL CARCINOMA

Renal cell carcinomas account for 90–95% of malignant neoplasms arising from the kidney. Notable features include resistance to cytotoxic agents, infrequent responses to biologic response modifiers such as interleukin (IL) 2, robust activity to antiangiogenesis targeted agents, and a variable clinical course for patients with metastatic disease, including anecdotal reports of spontaneous regression.

EPIDEMIOLOGY

The incidence of renal cell carcinoma continues to rise and is now nearly 65,000 cases annually in the United States, resulting in 13,700 deaths. The male-to-female ratio is 2:1. Incidence peaks between the ages of 50 and 70 years, although this malignancy may be diagnosed at any age. Many environmental factors have been investigated as possible contributing causes; the strongest association is with cigarette smoking. Risk is also increased for patients who have acquired cystic disease of the kidney associated with end-stage renal disease and for those with tuberous sclerosis. Most cases are sporadic, although familial forms have been reported. One is associated with von Hippel-Lindau (VHL) syndrome. VHL syndrome is an autosomal dominant disorder. Genetic studies identified the *VHL* gene on the short arm of chromosome 3. Approximately 35% of individuals with VHL disease develop clear cell renal cell carcinoma. Other associated neoplasms include retinal hemangioma, hemangioblastoma of the spinal cord and cerebellum, pheochromocytoma, neuroendocrine tumors and cysts, and cysts in the epididymis of the testis in men and the broad ligament in women.

PATHOLOGY AND GENETICS

Renal cell neoplasia represents a heterogeneous group of tumors with distinct histopathologic, genetic, and clinical features ranging from benign to high-grade malignant (Table 114-3). They are classified on the basis of morphology and histology. Categories include clear cell carcinoma (60% of cases), papillary tumors (5–15%), chromophobe tumors (5–10%), oncocytomas (5–10%), and collecting or Bellini duct tumors (<1%). Papillary tumors tend to be bilateral and multifocal. Chromophobe tumors have a more indolent clinical course, and oncocytomas are considered benign neoplasms. In contrast, Bellini duct carcinomas, which are thought to arise from the collecting ducts within the renal medulla, are rare but often very aggressive. Clear cell tumors, the predominant histology, are found in >80% of patients who develop metastases. Clear cell tumors arise from the epithelial cells of the proximal tubules and usually show chromosome 3p deletions. Deletions of 3p21–26 (where the *VHL* gene maps) are identified in patients with familial as well as sporadic tumors. *VHL* encodes a tumor suppressor protein that is involved in regulating the transcription of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and a number of other hypoxia-inducible proteins. Inactivation of *VHL* leads to overexpression of these agonists of the VEGF and PDGF receptors, which promote tumor angiogenesis and tumor growth. Agents that inhibit proangiogenic growth factor activity show antitumor effects. Enormous genetic variability has been documented in tumors from individual patients. Although the tumors have a clear clonal origin and often contain *VHL* mutations in common, different portions of the primary tumor and different metastatic sites may have wide variation in genetic lesions they contain. This tumor heterogeneity may underlie the emergence of treatment resistance.

TABLE 114-3 CLASSIFICATION OF EPITHELIAL NEOPLASMS ARISING FROM THE KIDNEY

Carcinoma Type	Growth Pattern	Cell of Origin	Cytogenetics
Clear cell	Acinar or sarcomatoid	Proximal tubule	3p-, 5q+, 14q-
Papillary	Papillary or sarcomatoid	Proximal tubule	+7, +17, -Y
Chromophobe	Solid, tubular, or sarcomatoid	Distal tubules/cortical collecting duct	Whole arm losses (1, 2, 6, 10, 13, 17, and 21)
Oncocytic	Tumor nests	Cortical collecting duct	Undetermined
Collecting duct	Papillary or sarcomatoid	Medullary collecting duct	Undetermined

CLINICAL PRESENTATION

The presenting signs and symptoms include hematuria, abdominal pain, and a flank or abdominal mass. Other symptoms are fever, weight loss, anemia, and a varicocele. The tumor is most commonly detected as an incidental finding on a radiograph. Widespread use of radiologic cross-sectional imaging procedures (CT, ultrasound, MRI) contributes to earlier detection, including incidental renal masses detected during evaluation for other medical conditions. The increasing number of incidentally discovered low-stage tumors has contributed to an improved 5-year survival for patients with renal cell carcinoma and increased use of nephron-sparing surgery (partial nephrectomy). A spectrum of paraneoplastic syndromes has been associated with these malignancies, including erythrocytosis, hypercalcemia, nonmetastatic hepatic dysfunction (Stauffer's syndrome), and acquired dysfibrinogenemia. Erythrocytosis is noted at presentation in only about 3% of patients. Anemia, a sign of advanced disease, is more common.

The standard evaluation of patients with suspected renal cell tumors includes a CT scan of the abdomen and pelvis, chest radiograph, urine analysis, and urine cytology. If metastatic disease is suspected from the chest radiograph, a CT of the chest is warranted. MRI is useful in evaluating the inferior vena cava in cases of suspected tumor involvement or invasion by thrombus. In clinical practice, any solid renal masses should be considered malignant until proven otherwise; a definitive diagnosis is required. If no metastases are demonstrated, surgery is indicated, even if the renal vein is invaded. The differential diagnosis of a renal mass includes cysts, benign neoplasms (adenoma, angiomyolipoma, oncocytoma), inflammatory lesions (pyelonephritis or abscesses), and other primary or metastatic cancers. Other malignancies that may involve the kidney include transitional cell carcinoma of the renal pelvis, sarcoma, lymphoma, and Wilms' tumor. All of these are less common causes of renal masses than is renal cell cancer.

STAGING AND PROGNOSIS

Staging is based on the American Joint Committee on Cancer (AJCC) staging system (Fig. 114-2). Stage I tumors are <7 cm in greatest diameter and confined to the kidney, stage II tumors are ≥7 cm and confined to the kidney, stage III tumors extend through the renal capsule but are confined to Gerota's fascia (IIIa) or involve a single hilar lymph node (N1), and stage IV disease includes tumors that have invaded adjacent organs (excluding the adrenal gland) or involve multiple lymph nodes or distant metastases. The 5-year survival rate varies by stage: >90% for stage I, 85% for stage II, 60% for stage III, and 10% for stage IV.

TREATMENT RENAL CELL CARCINOMA

LOCALIZED TUMOR

The standard management for stage I or II tumors and selected cases of stage III disease is radical or partial nephrectomy. A radical nephrectomy involves en bloc removal of Gerota's fascia and