TABLE 29-6 TNM STAGING SYSTEM OF RENAL CELL CARCINOMA

PRIMARY TUMOR (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor <7 cm and limited to the kidney		
T1a	Tumor <4 cm and limited to the kidney		
T1b	Tumor >4 cm but <7 cm and limited to the kidney		
T2	Tumor >7 cm and limited to the kidney		
T2a	Tumor >7 cm but <10 cm and limited to the kidney		
T2b	Tumor >10 cm and limited to the kidney		
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia		
T3a	Tumor grossly extends into the renal vein or its segmental branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia		
T3b	Tumor grossly extends into the vena cava below the diaphragm		
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava		
T4	Tumor invades beyond Gerota's fascia, including contiguous extension into the ipsilateral adrenal gland		
REGIONAL LYMPH NODES (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in regional lymph node(s)		
DISTANT METASTASIS (M)			
M0	No distant metastasis		
M1	Distant Metastasis		
ANATOMIC STAGE/PROGNOSIS GROUPS			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0 or N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

From Edge SB, Byrd DR, Compton CC, et al: AJCC cancer staging manual, ed 7, New York, 2010, Springer Verlag, pp 482–487.

ESRD. The prevalence of ACKD varies from 10% to 100%, and it increases with the duration of dialysis, reaching 87% after 10 years of dialysis. Patients with risk factors of male gender, older age, and a history of heart disease, larger kidneys, and kidney calcifications are more likely to develop ACKD.

Neither the cause of the underlying ESRD nor the mode of dialysis influences the progression of ACKD. It has been postulated that damage to the renal parenchyma in chronic kidney disease increases local growth factors levels that promote hypertrophy and cyst generation in the remaining nephrons. In some cases, increased levels of growth factors and mutated genes (e.g. *ERBB2*) may cause the malignant transformation of cysts, the primary clinical concern for 3% to 7% of ACKD patients.

ACKD-related cyst formation is limited to the kidneys and is an incidental finding on radiographic imaging. Patients with ACKD are usually asymptomatic but may develop infectious or bleeding complications. ACKD can be differentiated from hereditary causes of cystic renal disease by presence of chronic kidney disease or ESRD and the absence of any other clinical findings. Routine screening for ACKD among dialysis patients is contentious but is recommended for patients during their pretransplantation evaluation and after kidney transplantation because of the potential for malignancy.

Patients with ACKD do not require specific treatment. Tumors larger than 3 cm may be considered for nephrectomy. Bilateral nephrectomy is suggested in renal transplant candidates due to the higher risk of subsequent malignant transformation with immunosuppression.

TUBEROUS SCLEROSIS

Tuberous sclerosis complex (TSC) (i.e., Bourneville's disease) is an autosomal dominant genetic disorder that affects adults and children. TSC causes benign tumors to form in multiple organ systems, including the skin, brain, and kidneys. TSC is often characterized by related neurologic disorders such as epilepsy and mental retardation.

The prevalence of TSC in the general population is approximately 1 in 10,000, and 50% to 65% of cases are sporadic. Because TSC has an autosomal dominant pattern of inheritance, there is a 50% risk of siblings being affected. Genetic counseling is important for affected families. The overall diagnosis and management of TSC is discussed in Chapter 115.

TSC is caused by inactivating mutations in the *TSC1* or *TSC2* genes. *TSC1* is located on chromosome 9, and *TSC2* is on chromosome 16, adjacent to the *PKD1* gene. They, respectively, encode the hamartin and tuberin proteins, which together form a complex that regulates specific cellular growth, motility, and migration of cells. Inactivating mutations of the *TSC1* or *TSC2* genes result in disruption of these processes and may cause unrestricted growth of cells and tumorigenesis.

TSC conveys a lifetime risk of 2% to 3% for RCC. Renal tumors are usually bilateral and occur at an early age. More commonly, the tumors are benign. Angiomyolipomas, composed of abnormal, thick-walled vessels, smooth muscle cells, and adipose tissue, are seen in about 80% of patients with TSC by the age of 10 years. These benign renal tumors often require no treatment. However, they can grow, become locally invasive, and cause bleeding, pain, and hypertension.

Conclusive guidelines for surveillance are unavailable, but annual MRI of renal and brain lesions is suggested until the age of 21 years and then every 2 to 3 years to monitor their growth. Patients with progressive lesions should have yearly imaging, and those with tumors larger than 4 cm in diameter are at high risk for spontaneous bleeding and life-threatening hemorrhage. If the angiomyolipomas become locally invasive or cause bleeding, surgical intervention is needed.

Mutations in the *TSC1* or *TSC2* gene cause constitutive activation of mTOR. Everolimus, an inhibitor of mTOR, has been approved for the treatment of patients with TSC-associated subependymal giant cell astrocytomas.

VON HIPPEL–LINDAU DISEASE

VHLD is an autosomal dominant disease that affects multiple organ systems. It is caused by germline mutations in *VHL*, a tumor suppressor gene located on chromosome 3. This mutation predisposes to renal cell carcinoma and to tumor formation in other organs, including the eyes, cerebellum, spinal cord, adrenal glands, epididymis, and pancreas. VHLD affects approximately 1 in 40,000 births, and about 7000 patients are affected in the United States. There is an important association with pheochromocytoma in some patients with VHLD that warrants consideration.