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EDITORS

Jay Y. Gillenwater, M.D.
Hovey S. Dabney Professor
Department of Urology
University of Virginia Health Sciences Center
Charlottesville, Virginia

John T. Grayhack, M.D.
Professor
Department of Urology
Northwestern University Medical School
Chicago, Illinois

Stuart S. Howards, M.D.
Professor
Department of Urology
University of Virginia Health Sciences Center
Charlottesville, Virginia

John W. Duckett, M.D.
Professor of Urology
University of Pennsylvania School of Medicine;
Director, Pediatric Urology
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

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CHAPTER 15

Renal, Perirenal, and Ureteral Neoplasms

Scott B. Jennings
W. Marston Linehan

CLASSIFICATION

Upper urinary tract neoplasms (Table 15-1) are of renal parenchymal, urothelial, connective tissue, and metastatic origin. Benign renal tumors include adenomas, oncocytomas, and other tumors derived from vascular and connective tissues. Primary malignant renal tumors include renal cell carcinomas, urothelial carcinomas of the renal pelvis and collecting system, and sarcomas originating in the kidney. Secondary malignant renal tumors may involve the kidney by direct extension or as a result of hematogenous spread. Hematologic malignancies such as leukemia and lymphoma commonly involve the kidney and are usually a manifestation of systemic disease. Primary retroperitoneal tumors are usually malignant and include lipomas as well as the various sarcomas. Primary ureteral tumors may be benign or malignant and include fibroepithelial polyps, inverted papillomas, and the more common urothelial malignancies. The ureters may be involved secondarily by direct extension of adjacent malignancies or, more commonly, from blood-borne metastases.

EVALUATION OF RENAL MASSES

The evaluation of renal masses has changed dramatically with the advent of improved radiologic techniques. Because of the position of the kidney within the retroperitoneum, in the past renal masses sometimes remained undetected until they grew large enough to produce local symptoms, which generally indicated advanced disease. Now, as the routine use of abdominal ultrasonography (US) and computerized tomography (CT) has increased, renal masses are often detected at an earlier stage. A systematic method is necessary to ensure complete evaluation of suspected renal masses, as each radiologic modality has its relative strengths and weaknesses (Fig. 15-1).

Intravenous pyelography (IVP), despite its lack of sensitivity and specificity, remains the initial diagnostic method employed for the evaluation of suspected renal masses because of its familiarity to physicians and its role in the evaluation of hematuria. An IVP can detect many renal masses and provide information regarding the location and function of the kidneys; however, small masses that do not distort the collecting system or periphery of the kidney may not be detected. Also, patients with contrast allergies, renal insufficiency, or other conditions may not be candidates for IVP.

If a renal mass is found on IVP, ultrasonography is often recommended to determine if the mass is solid or cystic. The majority of masses detected by IVP prove to be simple cysts, and US is quite accurate in this diagnosis. Strict sonographic criteria for simple cysts have been defined and include a smooth cyst wall, a round or oval shape without internal echoes, and good through transmission with strong acoustic shadows posteriorly (Fig. 15-2). If these criteria are met, observation is sufficient in asymptomatic patients. A mass that deviates from these findings is studied further. Percutaneous needle puncture of cysts with aspiration of cystic fluid for cytology and biochemical studies and further injection of the cyst cavity with contrast medium for radiographic evaluation were often performed in the past. However, the appearance of cytology of the cyst fluid and biochemical assays were frequently nondiagnostic (Bosniak, 1993) except in the case of simple benign cysts, and thus with modern sonographic techniques these studies are rarely necessary. Indeterminate or complex cystic masses are better evaluated with CT.

Solid renal masses demonstrate varied echogenicity on US, and thus the specificity of this modality is limited. Angiomyolipomas are very brightly echogenic and may be suspected from US, but renal cell carcinomas may mimic this appearance. Other solid renal masses may be isoechoic or hypoechoic and may be

well demarcated or irregular. Because of the lack of specificity, CT is often recommended for solid masses seen on US (Fig. 15-3).

Occasionally, masses seen on IVP are not detected by US. This may be due to the presence of an isoechoic renal mass, patient habitus, or a normal anatomic variant such as fetal lobulation or a hypertrophied column of Bertin. In the past radionuclide renal scanning was recommended, based on the principle that normal functioning renal tissue is necessary to concentrate commonly used radioisotopes (Newhouse, 1993), and thus tumors or cysts appear as areas of decreased activity, and columns of Bertin are evident as areas of increased intensity (Fig. 15-4). However, contrast CT scans can often readily make these diagnoses and in addition provide much more information regarding tumor staging. Thus CT is considered by most to be the modality of choice in this situation, although nuclear renal scans are still commonly performed.

CT scanning is the predominant method used today in the evaluation of renal masses and has largely replaced renal angiography in this regard. The advantages of CT scanning include greater sensitivity in detecting small renal masses, improved detection of small amounts of fat within tumors, the ability to quantitate the density of various components, and more accurate tumor staging because of improved visualization of the retroperitoneal structures, adjacent organs, and associated vasculature. In addition, CT scanning is considered less invasive and less expensive than arteriography. CT scanning is most often performed with and without oral and intravenous contrast administration to fully realize the diagnostic potential of this modality (Bosniak, 1993); thin sections (5 mm or less) may also be important (Fig. 15-5). In a small percentage of patients, CT will not be able to differentiate atypical angiomyolipomas, complex cystic masses, and other inflammatory or infectious masses from more typical solid tumors, and further evaluation with magnetic resonance imaging, renal angiography,

TABLE 15-1
Classification of Renal, Perirenal, and Ureteral Tumors

- Renal tumors
  - Benign
    - Adenoma
    - Oncocytoma
    - Angiomyolipoma
    - Fibroma
    - Leiomyoma
    - Juxtaglomerular tumors
    - Hemangioma
    - Lipoma
  - Primary malignant
    - Renal cell carcinoma
    - Urothelial carcinoma
    - Sarcoma
  - Secondary malignant
    - Retroperitoneal sarcoma, pancreatic carcinoma, colon carcinoma (direct extension)
    - Lung, breast, GI (hematogenous spread)
    - Lymphoma, leukemia
- Primary retroperitoneal tumors
  - Benign
    - Lipoma
    - Leiomyoma
    - Cysts
  - Malignant
    - Liposarcoma
    - Fibrosarcoma
    - Leiomyosarcoma
- Ureteral tumors
  - Benign
    - Papilloma
    - Fibroepithelial polyps
  - Primary malignant
    - Urothelial carcinoma
    - Sarcoma
  - Secondary malignant
    - Retroperitoneal sarcoma, lymphoma, breast, GI, cervix, prostate

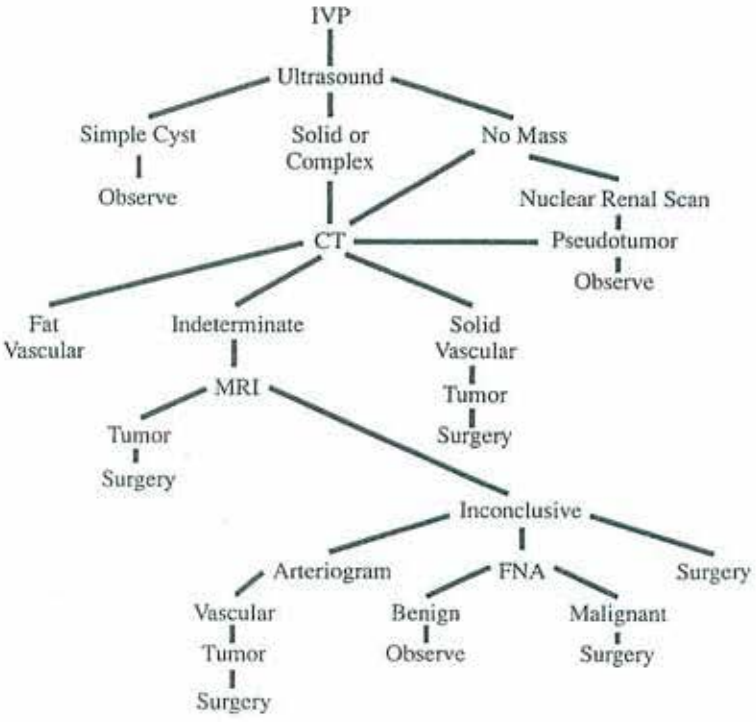


FIG. 15-1
Algorithm for evaluation of a renal mass.

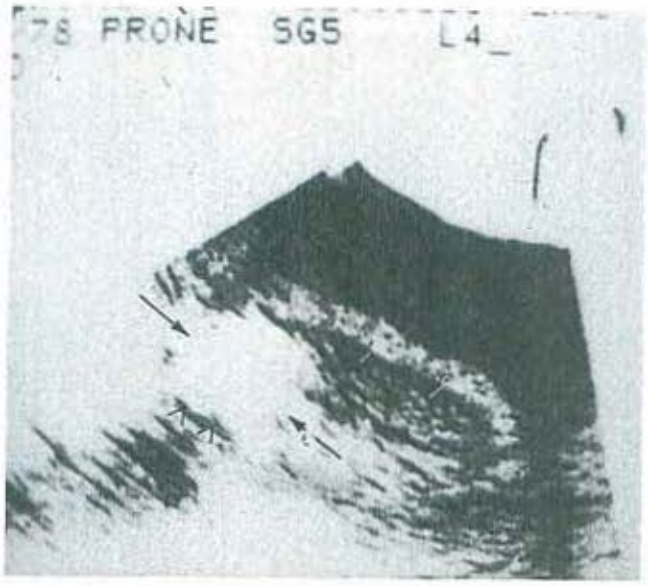


FIG. 15-2
Ultrasound of a simple renal cyst showing renal parenchyma *(short arrows)*, cyst wall *(long arrows)*, and strong posterior wall *(arrowheads)*.

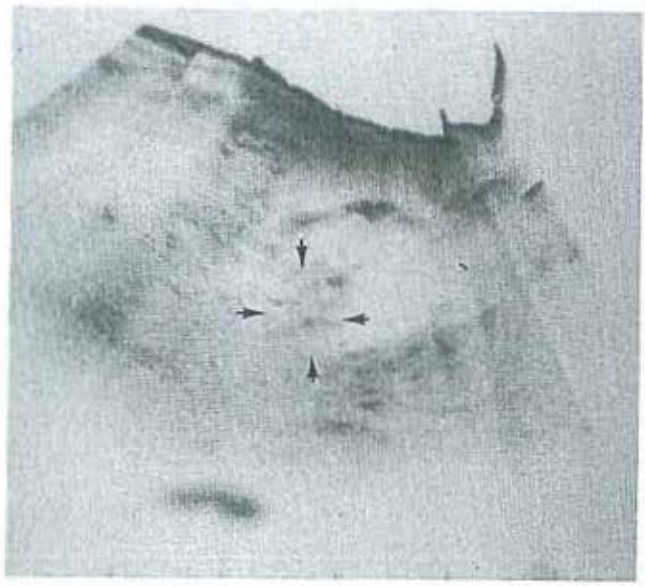


FIG. 15-3
Ultrasound examination of a solid renal mass *(arrows)*.

FIG. 15-4
Dimercaptosuccinic acid (DMSA) scan of a renal pseudotumor (hypertrophied column of Bertin) shown by *arrows*.

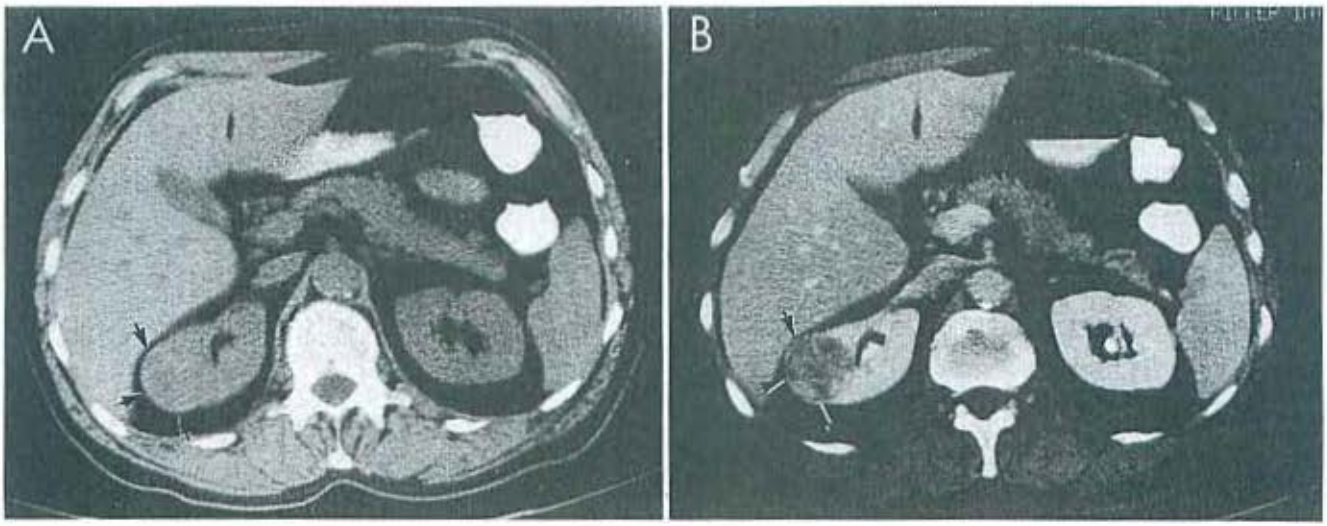


FIG. 15-5
CT of a renal cell carcinoma (RCC) *(arrows)*. **A,** Without contrast enhancement. **B,** With contrast enhancement. (From Williams RD, Tanagho EA: *Current Surgical Diagnosis and Treatment.* Los Altos, Calif, Lange Medical Publications, 1985, p 860. Used by permission.)

fine needle aspiration cytology, or ultimately surgical exploration may be necessary.

In addition to its role in the evaluation of indeterminate renal masses, renal arteriography is also useful in defining the blood supply to large tumors, or for precise delineation of the renal vasculature when nephron-sparing surgery is contemplated. Arteriography is not without risk, and digital subtraction angiography in combination with CT has been proposed as an alternative to decrease morbidity as well as give acceptable anatomic definition (Zabbo et al., 1985).

Magnetic resonance imaging is an increasingly important modality in the diagnosis and staging of renal masses and offers significant advantages over CT in some respects (Fig. 15-6). The technique is particularly useful in the evaluation of vascular invasion and involvement of adjacent organs. The addition of gadolinium contrast administration to MRI has greatly increased its ability to detect renal masses smaller than 3 cm, as well as assisted in the diagnosis of true invasion of the wall of the venal cava (McClennan and Deyoe, 1994). The evaluation of local adenopathy is also improved with MRI (Semelka et al., 1993). In addition, MRI with gadolinium is possible in patients in whom scanning with iodinated contrast agents is contraindicated. At the present time MRI is perhaps most useful as an adjunct to contrast CT scans, partly because of greater cost, but it undoubtedly will play a larger role in the future.

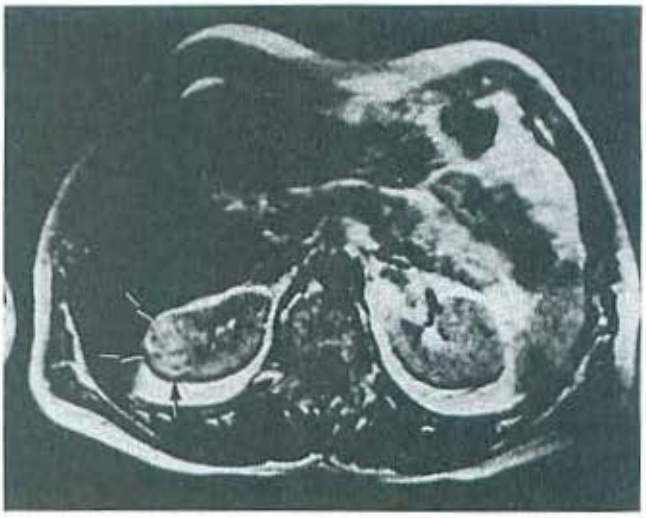


FIG. 15-6
Transaxial T_1-weighted MRI of the same RCC *(arrows)* shown in Fig. 15-5, **A** and **B.** (From Williams RD, Tanagho EA: *Current Surgical Diagnosis and Treatment.* Los Altos, Calif, Lange Medical Publications, 1985, p 860. Used by permission.)

BENIGN RENAL TUMORS

Benign tumors of the kidney are common and in the past were detected primarily at autopsy, as the majority are asymptomatic. However, a growing number of these generally small masses are being detected as the routine use of abdominal sonography and computerized tomography has increased. Often there are no clear-cut clinical or radiologic features to confirm the diagnosis preoperatively, and thus the pathologist determines the true etiology of these tumors following surgery.

Adenoma

Renal cortical adenomas are benign tumors that are usually found at autopsy because of their small size

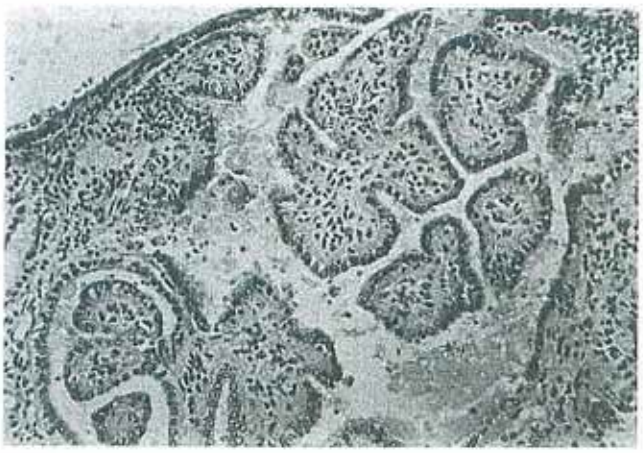


FIG. 15-7
Histologic section of true renal adenoma (original magnification, ×100).

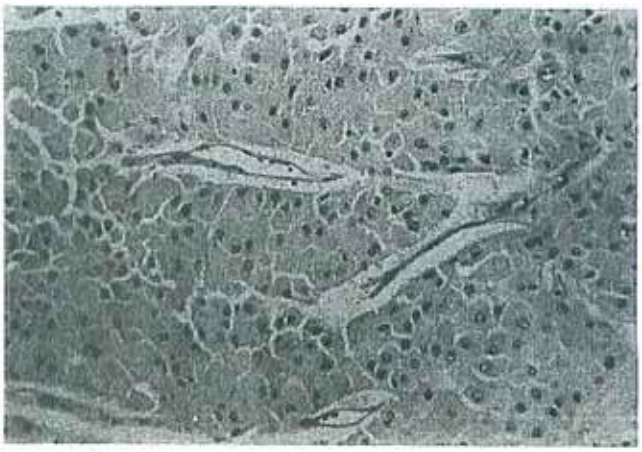


FIG. 15-8
Histologic section of a benign renal oncocytoma (original magnification, ×200).

and generally asymptomatic clinical course. They have been noted in 7% to 22% of autopsy specimens (Bonsib, 1985). Adenomas are usually less than 1 cm in size and located exclusively in the cortex, with a distinctive gray-white or yellow appearance on gross examination, without necrosis or hemorrhage (Fromowitz and Bard, 1990). Histologically they are composed of eosinophilic or basophilic cells in a papillary or tubulopapillary pattern (Fig. 15-7), typically separate from the surrounding parenchyma and usually without a capsule (O'Toole et al., 1993). Any evidence of clear cells, mitoses, nuclear pleomorphism, or necrosis obviates the diagnosis of adenoma.

The etiology of adenomas is unclear, although they have been associated with smoking, arteriolar nephrosclerosis, and dialysis (Mostofi et al., 1988). Histochemical and ultrastructural studies point to a distal tubular origin for adenomas (Fromowitz and Bard, 1990). Other investigators (Kovacs, 1993) have noted the chromosomal changes of trisomy 7, trisomy 17, and loss of the Y chromosome. Meloni and colleagues (1992) found similar changes in adenomas but caution that similar or identical changes are found in tumors that histologically prove to be renal cell carcinomas.

Controversy persists in the literature regarding the true clinical nature of these neoplasms. In an early autopsy series reported by Bell (1950), tumors less than 3 cm in size demonstrated a very low rate of metastasis, and by convention renal masses smaller than 3 cm were referred to as adenomas. However, multiple reports, including Bell's original series, document metastases originating from small tumors, and thus size alone is not an accurate predictor of malignancy (Bonsib, 1985; Curry et al., 1986; Fromowitz and Bard, 1990). Bennington and Beckwith (1975) concluded that adenomas could not reliably be differentiated from small adenocarcinomas. However, other investigators feel that histologic criteria can be used to distinguish these two neoplasms (Bonsib, 1985; Fromowitz and Bard, 1990; Mostofi et al., 1984; O'Toole et al., 1993). Because it is impossible to differentiate adenomas from carcinomas preoperatively on the basis of symptoms, size, or radiographic appearance, small solid renal masses should be considered to be malignant until proven otherwise.

Oncocytoma

Renal oncocytomas are benign renal tumors composed of oncocytes, a cell population with intensely eosinophilic granular cytoplasm. They were first characterized as a clinical entity by Klein and Valensi (1976) and account for 3% to 7% of solid renal tumors (Lieber, 1993). Grossly, oncocytomas have a typical tan or mahogany color and are well circumscribed with a fibrous capsule. Invasion into adjacent parenchyma, collecting system, or renal capsule is rare. On cross-section, the tumor appears to be homogeneous without hemorrhage or necrosis. A central stellate scar is often present, particularly in larger tumors. Oncocytomas are generally unilateral, although approximately 6% of patients have bilateral tumors (Lieber, 1986) and isolated cases of multifocal tumors have been reported (Warfel and Eble, 1982). Oncocytomas may become quite large, with a median diameter of 6 cm in collected series. Oncocytomas are also found in multiple other organs, including the thyroid and parathyroid glands, the adrenal glands, and the salivary glands.

Histologically, oncocytomas are composed of large polygonal cells with an intensely eosinophilic granular cytoplasm (Fig. 15-8). Ultrastructural studies have shown that the granularity is due to abundant mitochondria within the cytoplasm. Mitoses and other cellular organelles are rare, as is nuclear pleomorphism.

The exact cell of origin is unknown, although recent studies suggest an origin from the intercalated cells of the collecting ducts (Storkel et al., 1989; Zerban et al., 1987). Lieber and associates (1981) proposed a grading system for oncocytomas, with grade 1 tumors composed of well-differentiated cells with regular nuclei and abundant cytoplasm, grade 2 tumors demonstrating more variegation of the nuclei and cytoplasm, and grade 3 tumors degrading into significant nuclear pleomorphism with possible mitotic activity. The term *oncocytoma* should be used to refer only to those tumors composed of a pure population of oncocytes, i.e., very well differentiated eosinophilic granular cells. Many renal cell carcinomas also contain granular cells alone or in combination with clear cells or spindle cells, and on occasion pathologic differentiation of oncocytoma from carcinoma may be difficult. However, the granular cells found in these carcinomas are less well differentiated and demonstrate obvious nuclear pleomorphism.

Clinically, most oncocytomas are asymptomatic, despite their occasional large size. Most tumors are discovered incidentally, although occasionally patients present with flank or abdominal pain, microscopic or gross hematuria, or a palpable mass. They are approximately twice as common in males as in females, similar to series of renal cell carcinomas. Oncocytomas most commonly occur in the early seventh decade, somewhat later than renal cell carcinomas (Lieber, 1993).

Radiologically, oncocytomas appear to be typical solid renal mass lesions. There is no pathognomonic finding on intravenous pyelography, renal ultrasonography, or computed tomography, although a central stellate scar can be visualized with sonography or tomography in some cases. However, this finding is nonspecific. Weiner and Bernstein (1977) noted several characteristic findings on renal angiography of oncocytomas and used the term "spoke-wheel" to describe the appearance of the feeding arteries. These findings are not always present, however, and may also be seen in renal cell carcinomas (Morra and Das, 1993).

Flow cytometry studies of renal oncocytomas have yielded conflicting data. Rainwater and colleagues (1986) found aneuploid or tetraploid histograms in 50% of their specimens. Other investigators have reported aneuploidy or tetraploidy in 0% to 4% of patients (Hartwick et al., 1992; Psihramis and Goldberg, 1991; Veloso et al., 1992). The prevalence of aneuploidy or tetraploidy did not correspond with an unfavorable clinical course, and thus flow cytometry does not seem to be useful as a prognostic indicator. Cytogenetic studies also fail to show consistent characteristic abnormalities (Kovacs, 1993).

Since true oncocytomas are almost without exception clinically benign, nephron-sparing surgery has been proposed in selected cases. This treatment presumes an accurate preoperative diagnosis, particularly the exclusion of renal cell carcinoma. As previously noted, there are no completely reliable clinical or radiographic criteria to distinguish oncocytomas from carcinomas. Needle aspiration cytology has been suggested as a diagnostic modality for patients in whom oncocytoma is suspected. Rodriguez and associates (1980) reported the first case of oncocytoma diagnosed preoperatively by aspiration cytology, with final diagnosis confirmed following total nephrectomy. Other small series (Cochand-Priollet et al., 1988; Garcia-Bonafe et al., 1993; Gupta et al., 1990) have confirmed the potential usefulness of preoperative aspiration cytology, but in these series cytologic criteria could not exclude carcinoma in 20% to 33% of patients. If nephron-sparing surgery is contemplated, fine-needle aspiration cytology may be helpful, but thorough tumor sampling must be performed and results should be interpreted with caution, since carcinomas may contain foci of oncocytic cells and apparent pure oncocytomas may harbor small areas of malignant degeneration. Also, the possibility of multifocal tumors must be considered. If the diagnosis of oncocytoma can be unequivocally established prior to surgery, a nephron-sparing approach may be indicated. However, because of the inherent uncertainties in current preoperative diagnostic modalities, most patients with oncocytoma utimately undergo radical nephrectomy.

Angiomyolipoma

Renal angiomyolipomas are benign tumors often associated with tuberous sclerosis, an autosomal dominantly inherited disorder characterized by mental retardation, epilepsy, adenoma sebaceum, and hamartomas of the brain, retina, heart, bone, lung, and kidney (Stillwell et al., 1987). As many as 80% of patients with tuberous sclerosis will ultimately develop renal angiomyolipomas, and in these patients the tumors are generally small, bilateral, and asymptomatic. Renal cysts also commonly occur in patients with tuberous sclerosis. The majority of renal angiomyolipomas are not associated with tuberous sclerosis. In recent series only 17% to 20% of patients with angiomyolipomas also demonstrated evidence of tuberous sclerosis, and thus it does not seem likely that isolated renal angiomyolipoma represents a forme fruste of tuberous sclerosis (Bret et al., 1985; Steiner et al., 1993). In these patients the tumors are unilateral, usually occur in women 40 to 60 years of age, and are often large and symptomatic.

Angiomyolipomas are composed of generally mature fat cells, smooth muscle, and abnormal blood vessels. Sometimes one cell type may predominate. Grossly, the tumors are yellow to gray, depending on the proportion of fat and muscle cells. They are unen-

capsulated and may extend into the collecting system or perirenal fat. Hemorrhage and necrosis are common. Histologically, the adipocytes are usually mature and regular in size (Fig. 15-9). The blood vessels are thick-walled and tortuous. The smooth muscle cells may be sparse or may form sheets of cells that may be confused with leiomyoma (Mostofi and Davis, 1984). Retroperitoneal lymph nodes and adjacent organs such as the liver or spleen may sometimes contain angiomyolipomas identical to the renal tumor, and this is felt to represent multifocality rather than aggressive metastatic behavior, as no distant metastases have been reported from pure angiomyolipomas. However, malignant degeneration of angiomyolipoma into sarcoma with distant metastases has been reported (Ferry et al., 1991; Lowe et al., 1992), and in these instances the outcome was fatal. Angiomyolipomas and renal cell carcinomas may also coexist in the same kidney (Kavaney and Fielding, 1975; Schujman et al., 1981; Takeyama et al., 1982; Silpananta et al., 1984).

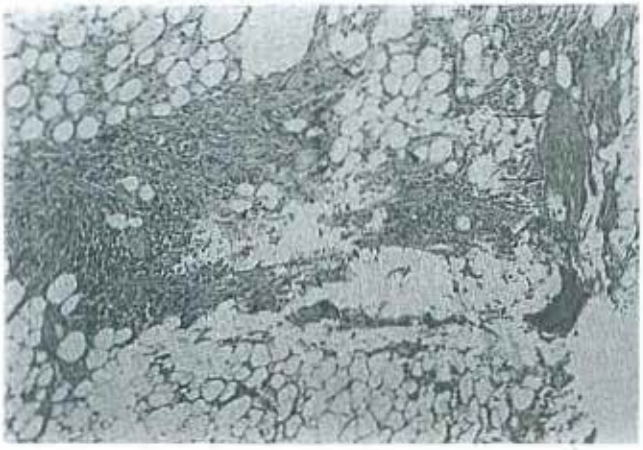


FIG. 15-9
Histologic section of a renal angiomyolipoma showing typical fat *(short arrows)*, muscle *(long arrows)*, and vessels *(arrowheads)* (original magnification, ×63.)

The clinical presentation of angiomyolipomas is variable and appears to be related to the size of the tumor. Steiner and associates (1993) found that no patient with a tumor less than 4 cm in size was symptomatic. Tumors larger than 4 cm in size are symptomatic in 46% to 82% of cases (Oesterling et al., 1986; Steiner et al., 1993). Flank or abdominal pain is the most common presenting symptom, occurring in approximately 50% of patients, followed by palpable mass and hematuria. Hypertension and anemia are also common. Patients may also present in hemorrhagic shock following rupture of the tumor into the kidney or retroperitoneum.

Radiographic studies are usually helpful in the diagnosis of angiomyolipoma. Intravenous pyelography cannot differentiate angiomyolipoma from other solid renal lesions, and the angiographic findings typically seen are also common in renal cell carcinoma. However, ultrasonography and CT scanning can reliably define angiomyolipoma in the majority of cases. Angiomyolipomas are the most echogenic renal masses found on sonography due to the numerous fat-nonfat interfaces seen in most tumors (Pitts et al., 1980). Other renal masses are, however, occasionally highly echogenic, including a small proportion of renal cell carcinomas. The presence of fat densities (−70 to −30 Hounsfield units) on CT scanning is almost pathognomonic for angiomyolipoma (Fig. 15-10). Detection of small amounts of fat within the tumor may therefore be critical for diagnosis, and such detection may be improved by using nonenhanced scans with 1.5 to 5-mm sections (Bosniak et al., 1988; Kurosaki et al., 1993). Magnetic resonance imaging may also be useful

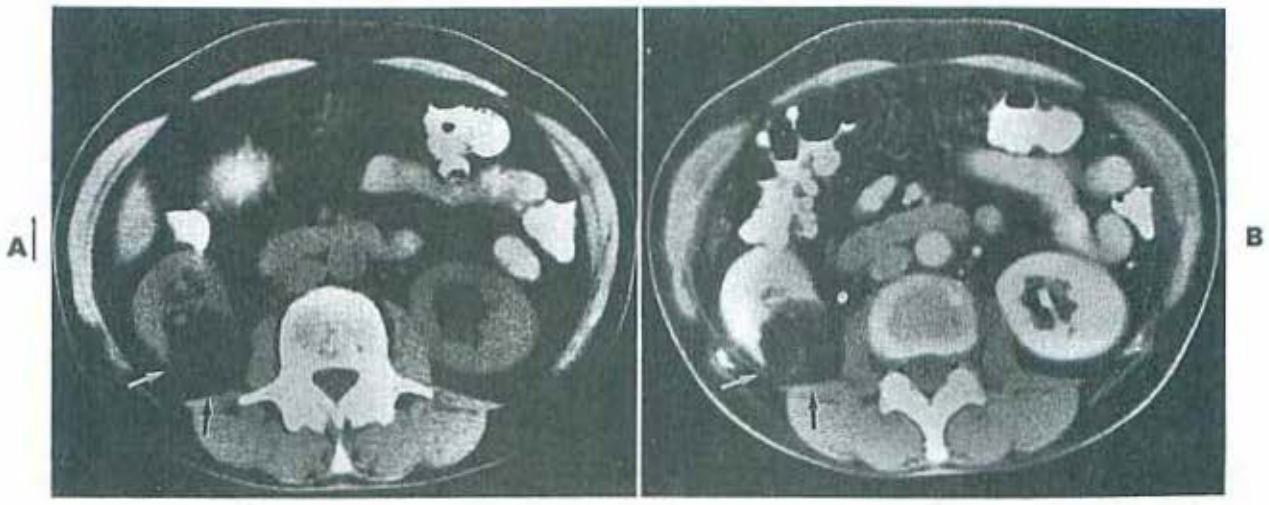


FIG. 15-10
CT of a renal angiomyolipoma. **A**, Typical mass lesion with internal areas of fat *(arrows)*. **B**, Same lesions as in A showing abundant fat *(arrows)*.

because of the characteristic high signal intensity of fat on T_1-weighted images. All these diagnostic modalities are dependent upon the relative proportion of fat within the tumor, and thus a small number of cases will remain of uncertain etiology following complete radiologic evaluation. Fine-needle aspiration biopsy has been recommended in such instances with good results (Sant et al., 1990; Taavitsainen et al., 1989).

The treatment of angiomyolipoma is dependent upon the size of the tumor, the presence of symptoms, and the accuracy of diagnosis (Andriole, 1992). Small, asymptomatic tumors discovered incidentally may be followed with yearly sonography if the diagnosis is unequivocal. Asymptomatic patients with tumors larger than 4 cm may still be candidates for observation with annual or semiannual ultrasound, but nearly 50% of these tumors will grow (Steiner et al., 1993). Tumor embolization or nephron-sparing surgery should then be considered to prevent further loss of renal parenchyma. Symptomatic patients usually require treatment, regardless of the size of the mass. Embolization or partial nephrectomy are the preferred modes of therapy, although total nephrectomy will be indicated in some cases. Patients who present with life-threatening hemorrhage should undergo immediate surgical exploration. Radical nephrectomy is the treatment of choice, although partial nephrectomy may be considered if the clinical situation allows and if angiomyolipoma is suspected preoperatively and confirmed by intraoperative frozen-section biopsy. Finally, patients in whom the radiologic diagnosis is uncertain should undergo fine-needle aspiration biopsy or surgical exploration, as for any other solid renal mass.

Other Benign Tumors

Tumors have been reported to arise from virtually all of the diverse cell types of which the kidney is composed. Medullary interstitial fibromas are small benign tumors commonly found at autopsy, occurring in 18% to 40% of patients (Reis et al., 1988; Warfel and Eble, 1985). As the name implies, these tumors arise from the interstitial cells of the renal medulla which are believed to cause an antihypertensive effect (Lerman et al., 1972). However, no convincing evidence exists that interstitial fibromas arise as a result of hypertension (Stuart et al., 1976). The tumors are generally small, white or gray in color, and round or oval in shape. The majority are multifocal. They occur in males and females with equal frequency (Eble, 1990) and arise as early as the second decade of life without increasing significantly in frequency with advanced age (Reis et al., 1988). Histologically, the tumors are composed of stellate or spindle-shaped cells loosely arranged in a basophilic or hyalinized matrix, with atrophic renal tubules at the periphery. Most of these tumors are clinically silent, although occasionally they may cause flank or abdominal pain or hematuria. The few symptomatic cases have generally been treated with nephrectomy, although nephron-sparing surgery should be considered if the diagnosis is suspected preoperatively.

Leiomyomas are rare benign tumors found in approximately 5% of patients undergoing autopsy (Xipell, 1971). They are almost always small, subcapsular, and asymptomatic. The occurrence of multiple tumors is common. These tumors arise from the renal capsule, vessels, or, rarely, the renal pelvis. Leiomyomas are gray or white in color, usually smaller than 1 to 2 cm, and usually well encapsulated (Di Palma and Giardini, 1988). Histologically they are composed of fusiform smooth muscle cells arranged in an interlaced fashion. Mitotic figures are rare or absent. A much smaller subset of patients present with large, solitary, symptomatic tumors. A palpable abdominal or flank mass is the most common sign at presentation, followed by abdominal or flank pain and hematuria (Steiner et al., 1990). Clinically apparent leiomyomas are more common in young white women. Total nephrectomy is usually performed because of the uncertainty of diagnosis, but renal-sparing surgery is advocated if technically feasible and if the diagnosis can be confirmed intraoperatively.

Renin-secreting juxtaglomerular cell tumors are rare but important benign renal masses, with fewer than 40 cases reported in the literature. Patients with these tumors present with severe diastolic hypertension, hypokalemia, and elevated plasma renin levels. Typically, patients are young (70% under 25 years of age) and 66% are female (McVicar et al., 1993). Headache is the most common presenting symptom. The diagnosis is usually suspected from the finding of hypertension in a young patient and is confirmed by elevated renin levels and secondary hyperaldosteronism and hypokalemia, although these secondary findings are not always present. Computerized tomography is the most reliable imaging method to demonstrate these tumors. Renal angiography is sometimes useful, primarily to exclude renovascular hypertension. Selective renal vein renin sampling may also be helpful, although this is diagnostic in fewer than 50% of cases (McVicar et al., 1993). Grossly, the tumors are generally smaller than 3 cm, grayish–yellow in color, and well encapsulated. Histologically, they originate from the smooth muscle medial cells of the afferent arterioles of the juxtaglomerular apparatus (Robertson et al., 1967; Corvol et al., 1988). The cells are round, oval, or polygonal, with a faintly eosinophilic cytoplasm. Mitoses are rare or absent. Scattered renal tubules are often seen. Renin granules are usually identified by Bowie's stain or a variety of immunohistochemical methods or Northern blotting (Rossi et al., 1993). Juxtaglomerular cell tumors represent a

surgically curable form of hypertension, and the majority of cases have been treated successfully with total nephrectomy. Because of the benign nature of these tumors, however, partial nephrectomy or enucleation is the treatment of choice, if possible, for technical reasons.

Hemangiomas and lipomas are benign renal tumors that are rare in their pure forms. Hemangiomas are vascular neoplasms consisting of endothelial-lined spaces without contractile elements (Ekelund and Gothlin, 1975). They are generally small but may cause gross hematuria. Selective renal angiography is the diagnostic method of choice, although the tumors can sometimes be visualized by endoscopy. Nephrectomy or partial renal resection is curative. Lipomas are also quite rare and typically are found in middle-aged women. They usually become large enough to cause flank or abdominal pain and sometimes hematuria. They arise from the renal capsule or perinephric tissues and are composed of mature fat cells. The diagnosis can be made by computerized tomography if the tumor is large enough. Again, surgical extirpation is curative.

PRIMARY MALIGNANT RENAL TUMORS

Primary malignant renal tumors are predominantly renal cell carcinomas (85% to 90%) and transitional cell carcinomas of the renal pelvis and collecting system (8%). Various rare carcinomas and sarcomas make up the remainder.

Renal Cell Carcinoma

It is estimated that malignancies of the upper urinary tract will account for 27,600 of all cancers diagnosed in the United States in 1994 (Boring et al., 1994). Of these, approximately 24,000 will be renal cell carcinomas (RCCs), resulting in 10,000 deaths. RCCs occur in roughly a 2:1 male/female ratio and have been reported in children as young as 6 months of age, although the majority of patients are diagnosed in the sixth to seventh decades. Overall, RCCs account for approximately 3% of all adult malignancies, exclusive of skin cancers.

Renal cell carcinomas exist in both sporadic and hereditary forms. Hereditary nonpapillary renal cell carcinomas are associated with constitutional 3p chromosomal translocations, which are inherited in an autosomal dominant fashion. As many as 45% of patients with von Hippel–Lindau (VHL) disease, another autosomal dominant familial disorder, develop RCCs (Glenn et al., 1990). Recently, a third form of familial RCC has been described, hereditary papillary renal cell carcinoma (Zbar et al., 1994). In these familial syndromes, the RCC is often bilateral and multifocal and tends to occur in younger individuals compared with sporadic cases (Table 15-2).

TABLE 15-2
Hereditary Forms of Renal Carcinoma

1. Familial renal carcinoma
2. Renal carcinoma associated with von Hippel–Lindau (VHL) disease
3. Hereditary papillary renal cell carcinoma (HPRCC)

Renal cell carcinoma has also been associated with a number of other disorders, including acquired renal cystic disease (Matson and Cohen, 1990; Levine, 1992), autosomal dominant polycystic kidney disease (Gatalica et al., 1994; Sulser et al., 1993), and tuberous sclerosis (Washecka and Hanna, 1991). In all of these diseases, including von Hippel-Lindau disease, there is a proclivity to develop multiple bilateral renal cysts and renal failure as well as RCC, although the reasons for progression into RCC are unclear. A recent study (Klingel et al., 1992) suggests that hyperproliferation of proximal tubular epithelial cells is a pathogenic pathway common to both RCC and autosomal dominant polycystic kidney disease.

Etiology

The etiology of most renal cell carcinomas is unclear, although a number of factors have been investigated. The majority of studies show a definite link between cigarette smoking and RCC, and in one study as many as 30% of RCCs in men and 24% in women were felt to be due to smoking (McLaughlin et al., 1984). The risk of developing RCC appears to rise with increased duration and number of cigarettes smoked (La Vecchia et al., 1990; McCredie and Stewart, 1992; Yu et al., 1986). Other epidemiologic studies fail to show a relation between smoking and RCC (Benhamou et al., 1993; Talamini et al., 1990).There also seems to be a correlation between obesity and increased risk of RCC, particularly in women (Maclure and Willett, 1990; Mellemgaard et al., 1994). Use of prescription diuretics of all types has also been associated with a nearly threefold increased risk of RCC (Finkle et al., 1993; Lindblad et al., 1993). Also, analgesics containing phenacetin have been linked to an increased risk of RCC as well as urothelial tumors (Lornoy et al., 1986).

Workers in a variety of occupations have been shown to be at increased risk for developing RCC. Lowery and associates (1991) found an increased incidence of RCC among architects. McLaughlin and colleagues (1992) showed no increased risk in architects but did find an elevated incidence in engineers and construction workers, and they postulated that occupational exposure to asbestos may play a role. Maclure (1987) also found an increased risk of RCC in workers exposed to asbestos. Leather workers (Malker et al., 1984) and paperboard printing workers

(Sinks et al., 1992) also seem to be at increased risk for developing RCC, although the reasons for this are unclear. After animal studies showed an increased incidence of kidney tumors in male rats exposed to chronic inhalation of unleaded gasoline fumes, several epidemiologic studies were undertaken to determine if similar findings could be confirmed in humans. Two studies (Enterline and Viren, 1985; McLaughlin et al., 1985) failed to show a definite relationship between RCC and exposure to gasoline or petroleum products, although a slightly increased risk was noted in workers exposed for long periods. Partanen and associates (1991) did note an increased risk and exposure-response relationships among gasoline workers, as well as a slight upward trend in risk in workers exposed to lead and cadmium. Finally, exposure to thorium dioxide (Thorotrast) has been implicated in the development of RCC, presumably because of chronic radiation exposure (Kauzlaric et al., 1987).

Molecular Genetics

Investigators have recently described a new tumor suppressor gene, the VHL gene, which appears to be implicated in clear cell renal carcinomas (Latif et al., 1993; Gnarra et al., 1994). The VHL gene has been localized to the p25-p26 region of chromosome 3, which has long been a site of interest to researchers. In 1979 Cohen and colleagues described a kindred with familial RCC in which a balanced constitutional translocation of the short arm of chromosome 3 to the long arm of chromosome 8 was found. All members of the family who developed RCC demonstrated the translocation; conversely, no family member without the translocation developed kidney cancer. Pathak and associates (1982) described another kindred in which a translocation of chromosome 3 to chromosome 11 was found. Only tumor cells demonstrated this karyotypic abnormality. Kovacs and colleagues (1989) described a family with a constitutional 3;6 translocation and multiple bilateral renal cell carcinomas. In all three kindreds, the chromosomal translocational breakpoint was in the 3p13-3p14 region.

A second form of familial RCC is that associated with VHL, as previously mentioned. In addition to renal cell carcinomas, affected individuals are prone to develop renal cysts, pancreatic cysts and tumors, pheochromocytomas, retinal hemangiomas, and hemangioblastomas of the central nervous system. Renal tumors associated with VHL tend to be multifocal and bilateral and occur earlier in life than sporadic tumors. Because of the consistent abnormalities of chromosome 3 seen in earlier studies as previously cited, Seizinger and associates (1988) used linkage analysis with polymorphic DNA markers to evaluate nine families with RCC and VHL. A potential gene responsible for VHL was linked to cRAF1, a protooncogene mapped to 3p25, but it did not appear to be cRAF1. Tory et al. (1989) evaluated patients with RCC and VHL for loss of alleles on chomosome 3p. They found persistent loss of heterozygosity (LOH) on chromosome 3p in 11 tumors tested, and in each case the wild-type allele from the nonaffected parent was deleted, suggesting loss of a tumor suppressor gene on chromosome 3p. These findings are in accordance with the "two-hit" hypothesis of tumor formation proposed by Knudson (1971) and Knudson and Strong (1972). In other words, a constitutional abnormality of chromosome 3 was inherited from an affected parent (the

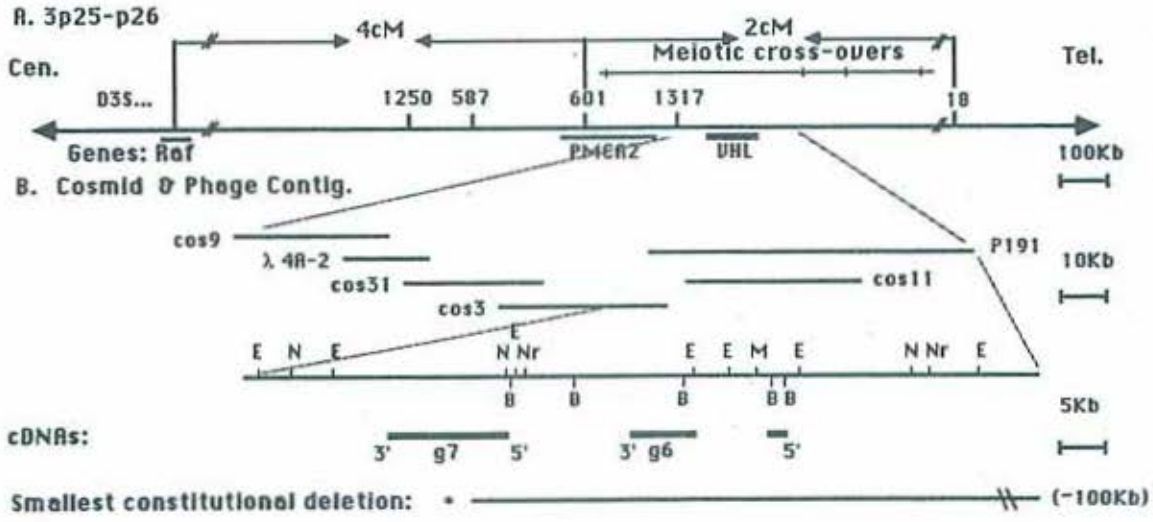


FIG. 15-11
Map of the region of chromosome 3p containing the VHL gene. Yeast artificial chromosome (YAC) and cosmid contigs of the region surrounding the VHL gene were constructed and candidate genes within this region were screened. (From Latif F, Tory K, Gnarra J, et al: Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science* 1993; 260:1317.)

"first hit"), and a second genetic event caused deletion of the remaining wild-type allele. Hosoe and colleagues (1990) subsequently linked the VHL gene to a small region on chromosome 3p between cRAF1 and marker D3S18, located at 3p26. Latif and associates (1993) then used positional cloning techniques to precisely identify the VHL gene (Fig 15-11). Germ line mutations of the VHL gene in patients with VHL disease are seen in all three coding exons, but tend to be clustered in exons 1 and 3 (Fig 15-12). Missense mutations, microdeletions and insertions, nonsense mutations, and large deletions are seen in various affected members.

In addition to the familial renal carcinomas associated with chromosome 3 translocations and VHL disease, hereditary papillary renal cell carcinoma has recently been described (Zbar et al., 1994). In contrast to the clear cell carcinomas seen in other familial RCC syndromes, these tumors exhibit a tubulopapillary growth pattern, with malignant epithelial cells surrounding a fibrovascular core. This growth pattern is found in only 10% of sporadic renal tumors. Hereditary papillary RCC does not link to polymorphic markers in the VHL gene region and is not associated with chromosome 3p translocations. These results suggest that a separate gene or genes, not located on chromosome 3p, are responsible for a distinctive form of RCC.

After earlier reports on kindreds with RCC had focused attention on the short arm of chromosome 3 as a possible tumor suppressor locus, several groups investigated the role of chromosome 3 in sporadic kidney cancer (Carroll et al., 1987; Szucs et al., 1987; Yoshida et al., 1986). Karyotype analysis showed deletions or rearrangements of the short arm of chromosome 3 in the majority of tumors studied. Zbar and associates (1987) then used restriction fragment length polymorphism (RFLP) assays, a more sensitive technique, to detect DNA sequence deletions on the short arm of chromosome 3 in patients with sporadic kidney cancer. All 11 patients with evaluable tumors demonstrated loss of alleles from the short arm of chromosome 3. Anglard and colleagues (1991) extended these studies and found loss of heterozygosity (LOH) at one or more loci in the 3p21-3p26 region in 51 of 58 patients, implicating a tumor suppressor gene in this area. Deletion mapping analysis in RCC cell lines localized the putative tumor suppressor gene to the region of 3p25-3p26, the region previously implicated in VHL-associated RCC (Anglard et al., 1992). Latif and associates (1993) reported mutations of the VHL gene in five RCC cell lines derived from patients with sporadic RCC. Subsequently, Gnarra and colleagues (1994) detected mutations of the VHL gene in 57% of patients with sporadic RCC. Thus, mutation of the VHL gene appears to be a critical step in the tumorigenesis of both sporadic clear cell renal carcinoma and VHL-associated RCC. In contrast to the VHL gene mutations seen in the germ line of patients with VHL disease, VHL gene mutations seen in sporadic RCC are clustered in the second exon, although abnormalities of the first and third exons are also detected (Fig 15-13). A significant proportion of the mutations are frameshifts, which are predicted to result in truncation of the VHL gene protein (Gnarra et al., 1994; Shuin et al., 1994).

Other chromosomal abnormalities may also be important in sporadic RCC. Presti and associates (1993) found that deletion of chromosome 17p correlated with tumor stage, grade, and presence of nodal me-

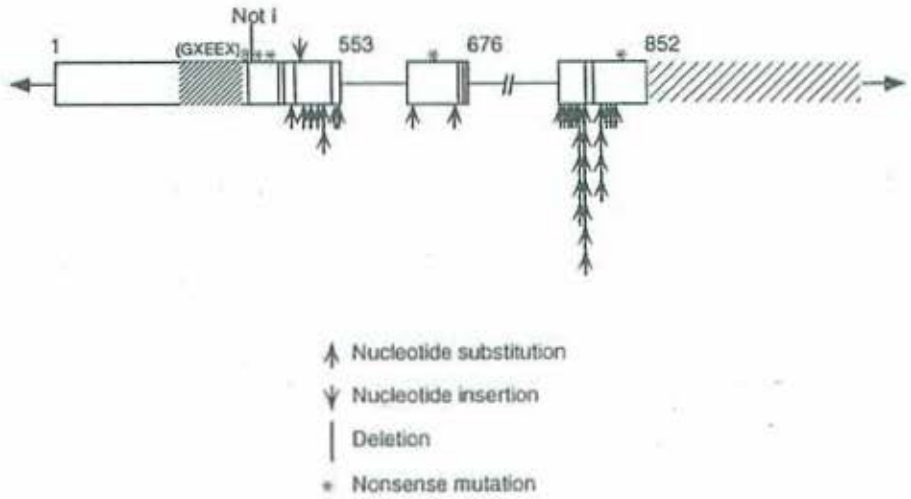


FIG. 15-12
Schematic of the VHL gene showing distribution of germ line mutations seen in patients with VHL disease. The three coding exons of the VHL gene are represented by the rectangular boxes. (From Chen F, Kishida T, Yao M, et al: Germ line mutations in the von Hippel-Lindau disease tumor suppressor gene: correlations with phenotype. *Hum Mutat*, 1995; 5:66.)

FIG. 15-13
Schematic of the VHL gene showing distribution of mutations in tumors from patients with sporadic RCC. Nucleotide deletions or insertions *(vertical lines)*, nonsense mutations *(*)*, nucleotide substitutions *(arrows)*, and splice site mutations *(X)* are commonly seen. (From Gnarra JR, Tory K, Weng Y, et al: Mutations of the VHL tumour suppressor gene in renal carcinoma. *Nature Genet* 1994; 7:85.)

tastases, and postulated that loss of alleles on 17p was related to disease progression. Reiter and associates (1993) analyzed cell lines derived from patients with sporadic RCC and found LOH at the p53 tumor suppressor gene locus in 48%, as well as mutations of the p53 gene itself. In six cell lines, LOH and p53 mutations were both seen, showing loss of both alleles. Abnormalities of the p53 locus were postulated to be associated with progression to metastatic disease.

Clinical Presentation and Diagnosis

Renal cell carcinoma may present itself in a variety of ways. Formerly, the classic triad of flank pain, flank or abdominal mass, and hematuria was considered pathognomonic for RCC; however, few patients present with this combination of symptoms and signs. Also, these clinical manifestations are generally indicative of advanced disease, and more and more tumors are discovered incidentally due to the increased use of CT and ultrasonography. In a recent study of patients with renal tumors less than 3 cm in diameter, 96.7% were discovered incidentally, and 77.4% were initially detected by US or CT (Smith et al., 1989). Historically, only 40% to 45% of patients present with localized disease, 25% to 30% present with locally advanced disease, and 30% present with distant metastases (Golimbu et al., 1986; Silverberg, 1981).

Overall, hematuria is the most common presenting sign, present in 60% of patients (Table 15-3). A sizable proportion of patients also complain of palpable mass, abdominal pain or pain associated with bony metastases, weight loss, cachexia, fever, or varicocele. Physical examination is generally remarkable only for the presence of an upper-quadrant or flank mass and the occasional finding of a varicocele, usually on the left side.

Renal cell carcinoma is also associated with a host of abnormal clinical and laboratory findings. Hypertension is present in 20% to 40% of patients and may be due to a variety of causes (Stenzl and deKernion, 1989). Hyperreninemia is found in approximately 33% of cases, but the hormone is apparently biologically inactive in the majority of instances (Lindop et al., 1986; Lindop and Fleming, 1984; Sufrin et al., 1977). Hypochromic, microcytic anemia is noted in 20% to 40% of patients and may be due to multiple factors, including hematuria, decreased production of red blood cells, or destruction of red blood cells in the circulation or spleen (Cherukuri et al., 1977). In approximately 20% of patients pyrexia is noted, but the cause is unknown. Cachexia and chronic debilitation are noted in another 33% of patients. Other abnormal clinical findings sometimes associated with RCC include vasculitis (Hoag, 1987; Mautner et al., 1993), polymyositis (Wurzer et al., 1993), limbic encephalitis (Newman et al., 1990), liver granulomas (Chagnac et al., 1985), diabetes mellitus (Palgon et al., 1986), motor neuron disease (Evans et al., 1990), and peliosis hepatis (Otani et al., 1992).

TABLE 15-3
Presenting Findings in RCC Patients

Findings	Occurrence (%)
Hematuria	50-60
Elevated erythrocyte sedimentation rate	50-60
Abdominal mass	24-45
Anemia	21-41
Flank pain	35-40
Hypertension	22-38
Weight loss	28-36
Pyrexia	7-17
Hepatic dysfunction	10-15
Classic triad (hematuria, abdominal mass, flank pain)	7-10
Hypercalcemia	3-6
Erythrocytosis	3-4
Varicocele	2-3

Data from Skinner DG, Colvin RB, Vermillion CD, et al: Diagnosis and management of renal cell carcinoma. *Cancer* 1971; 28:1165; Chisholm GD: Nephrogenic ridge tumors and their syndromes. *Ann N Y Acad Sci* 1974; 230:402; Fallon B: Renal parenchymal tumors. B. Clinical and diagnostic features, in Culp DA, Loening SA (eds): *Genitourinary Oncology*. Philadelphia, Lea & Febiger, 1985, p 202.

Myriad laboratory abnormalities are also seen in patients with RCC. An elevated erythrocyte sedimentation rate is commonly seen but is nonspecific. Sufrin and associates (1978) found elevated plasma fibrinogen levels in 31 patients with RCC, correlated to advanced stage and clinical course. Acquired dysfibrinogenemia in a patient with RCC has also been described (Dawson et al., 1985). This abnormality resolved following nephrectomy but recurred with the

development of pulmonary metastases. Nonmetastatic hepatic dysfunction (Stauffer's syndrome) is seen in 10% to 15% of patients with RCC (Stauffer, 1961). This syndrome is characterized by an elevated alkaline phosphatase level, prolonged prothrombin time, increased α_2-globulin levels, and decreased albumin levels. Patients do not have hepatic metastases and the etiology of the hepatic dysfunction is unknown, although recent evidence from animal models implicates tumor production of interleukin-6 and granulocyte colony stimulating factor (Nelson et al., 1994). Failure of liver abnormalities to resolve following nephrectomy is associated with a poor prognosis, with fewer than 25% of patients surviving 2 years (Boxer et al., 1978; Warren et al., 1970). Of patients with RCC, 3% to 6% are found to be hypercalcemic. Suva and colleagues (1987) recently identified a parathyroid hormone–related protein (PTHrP) from a human lung cancer cell line. Like parathyroid hormone (PTH), PTHrP causes elevated cAMP levels in osteoblasts and demonstrates PTH-like activity in monkey kidney cells, and it presumably causes bone resorption and decreased renal excretion of calcium. Gotoh and colleagues (1993) used immunohistochemical staining to demonstrate the presence of PTHrP in 95% of renal cell carcinomas. However, no correlation was seen between intensity of staining and serum calcium levels. Erythrocytosis is noted in 3% to 4% of patients with RCC. Da Silva and associates (1990) demonstrated production of erythropoietin by tumor cells in three patients with RCC and proposed this as a mechanism for erythrocytosis. Amyloidosis is found in 3% to 5% of patients with RCC but is generally discovered at autopsy (Chisholm, 1974). Other abnormal laboratory values associated with RCC include elevated ferritin levels (Mufti et al., 1982), increased levels of insulin and glucagon (Pavelic and Popovic, 1981), and α-fetoprotein, β-human chorionic gonadotropin and PTH elevation (Dexeus et al., 1991).

When the diagnosis of a renal tumor is suspected, based on patient complaints of hematuria, pain, or mass, or from constitutional symptoms or a paraneoplastic syndrome, a careful, thorough evaluation is indicated (Fig. 15-1). Intravenous pyelography (IVP) is still the most commonly used initial diagnostic modality, particularly when hematuria is a presenting sign. The majority of renal masses seen on IVP are benign renal cysts, which are seen in 55% of patients (Lang, 1977). A typical benign cyst is shown in Fig. 15-14. Because of the relative lack of sensitivity and specificity of IVP, all renal masses seen on IVP should be further evaluated, usually initially with ultrasonography. In general, IVP does not provide useful staging information, although it is sometimes helpful in determining the location and function of the contralateral kidney.

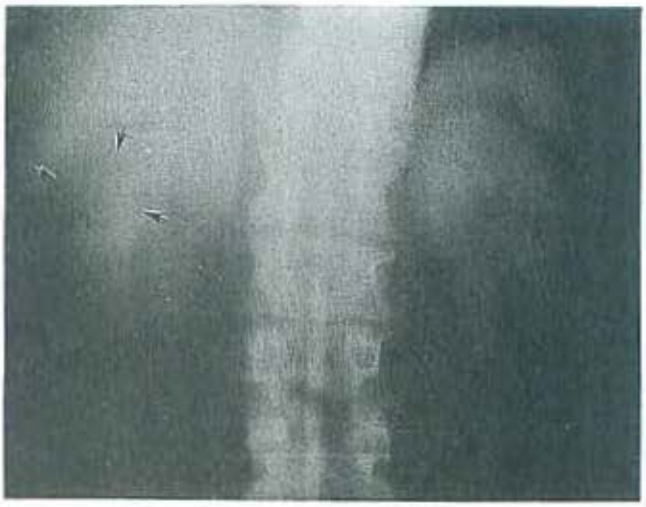


FIG. 15-14
Nephrotomogram of a patient with a simple renal cyst *(arrows)* showing the typical "beak sign" *(arrowheads)*.

Ultrasonography is quite useful in the diagnosis of simple benign cysts. Solid, complex, or indeterminate masses detected by US require further evaluation. Although CT is more accurate in staging, color-flow Doppler ultrasound is a useful modality in imaging of the renal vein and inferior vena cava for the presence and extent of tumor thrombus or compression (Didier et al., 1987; McClennan and Deyoe, 1994). Ultrasonography is also sometimes helpful for guidance during aspiration biopsy of renal masses (Juul et al., 1985).

Prior to the widespread use of CT scanning, renal angiography was commonly employed as a diagnostic modality for renal masses. Typical signs of RCC on arteriography include neovascularity, venous pooling, and arteriovenous fistulae (Fig. 15-15). However, CT has been shown to be more accurate than arteriography in the diagnosis and staging of RCC (Mauro et al., 1982) and is also less invasive. Renal angiography is now primarily used prior to nephron-sparing surgery or in conjunction with renal angioinfarction (McClennan, 1991). Angiography may also play a small role in the evaluation of indeterminate masses. Risks of angiography include contrast-associated renal impairment, hemorrhage, pseudoaneurysm formation, and arterial emboli. In an effort to minimize the morbidity associated with angiographic procedures, Zabbo and colleagues (1985) used digital subtraction angiography (DSA) in combination with CT or US and found that intravenous DSA adequately outlined the main renal arterial anatomy in 83% of cases but failed to demonstrate smaller renal vessels in the majority of instances. Intravenous DSA was also quite accurate in imaging the inferior vena cava, correctly detecting two caval thrombi.

Dynamic contrast-enhanced CT scanning is a very effective modality in the diagnosis and staging of

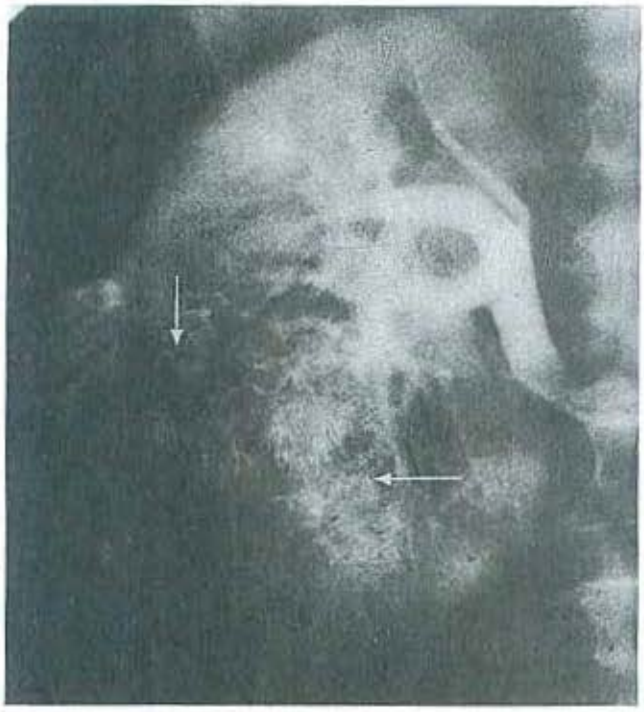


FIG. 15-15
Right renal angiogram showing typical neovascularity in large lower-pole RCC *(arrows)*.

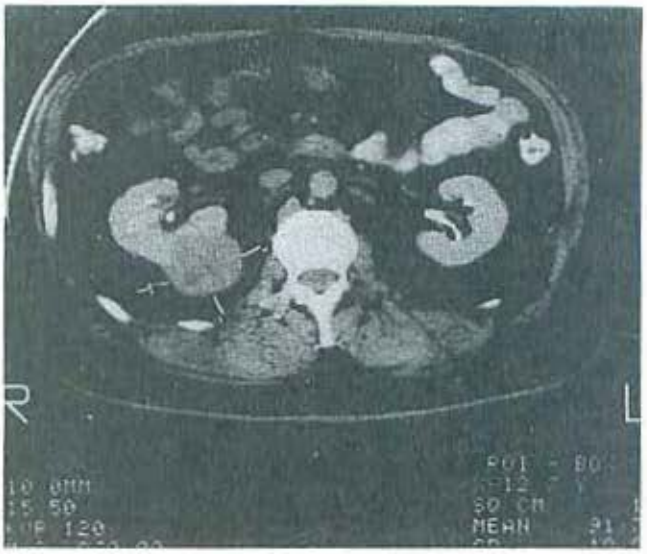


FIG. 15-16
CT of a contrast-enhanced right RCC *(arrows)*. (From Williams RD: Tumors of the kidney, ureter, and bladder, in Wyngaarden JB, Smith LH (eds): *Cecil's Textbook of Medicine*. Philadelphia, WB Saunders, 1985, p 642. Used by permission.)

renal tumors (McClennan and Deyoe, 1994). When typical features of RCC are present, CT is accurate in approximately 95% of cases (Hricak et al., 1985; McClennan, 1985; Didier et al., 1987). In a recent review by Dinney and colleagues (1992), CT was also the most accurate staging modality. Typical findings of RCC on CT include a solid mass that is hypodense or isodense compared with normal renal parenchyma, with densities of 15 to 40 Hounsfield units (McClennan, 1985). Most renal cell carcinomas enhance less than normal parenchyma following contrast injection, but intensely vascular tumors may initially appear hyperdense (Fig. 15-16). Also, rarely RCC may appear hyperdense before contrast administration (McClennan and Rabin, 1989). Other findings on CT associated with RCC include invasion of the mass into normal parenchyma and central calcification with soft tissue extending beyond the calcification. Larger tumors may be quite heterogeneous with areas of hemorrhage or necrosis. Secondary findings indicative of malignancy include grossly enlarged regional lymph nodes, venous invasion, and metastases (McClennan, 1985).

Magnetic resonance imaging (MRI) is an additional modality commonly employed in the diagnosis of renal tumors, particularly in patients in whom contrast CT scanning cannot be used or in whom CT findings are equivocal (McClennan and Deyoe, 1994). Detection rates as high as 95% have been reported (Hricak et al., 1988). MRI was originally less sensitive than CT in the detection of renal masses smaller than 3 cm, unless the mass caused distortion of the renal contour; recent improvements in technique have greatly increased the detection rate of smaller tumors (Semelka et al., 1993). On T_1-weighted images, RCC typically displays a signal intensity intermediate between normal cortex and medulla (Fein et al., 1987). Most renal cell carcinomas appear hyperintense on T_2-weighted images. MRI is also useful in imaging large tumors when the origin of the mass is unclear from CT. Tumor staging is another area in which MRI can play a major role, particularly in assessing vascular involvement and adjacent organ invasion (McClennan and Deyoe, 1994). Currently, although MRI is most commonly used as an adjunct to or in place of contrast CT scanning, improved detection rates as well as certain distinct advantages in tumor staging make MRI an increasingly useful modality.

Multiple diagnostic modalities are used in the evaluation of patients with suspected renal tumors, and no single study can detect, diagnose, and stage all tumors. Occasionally, and increasingly rarely, an accurate diagnosis cannot be made following a complete radiologic evaluation. In these cases fine-needle aspiration biopsy is often recommended, with diagnostic accuracy greater than 80% (Balfe et al., 1982; Juul et al., 1985). In some instances, surgical exploration is necessary to provide the diagnosis.

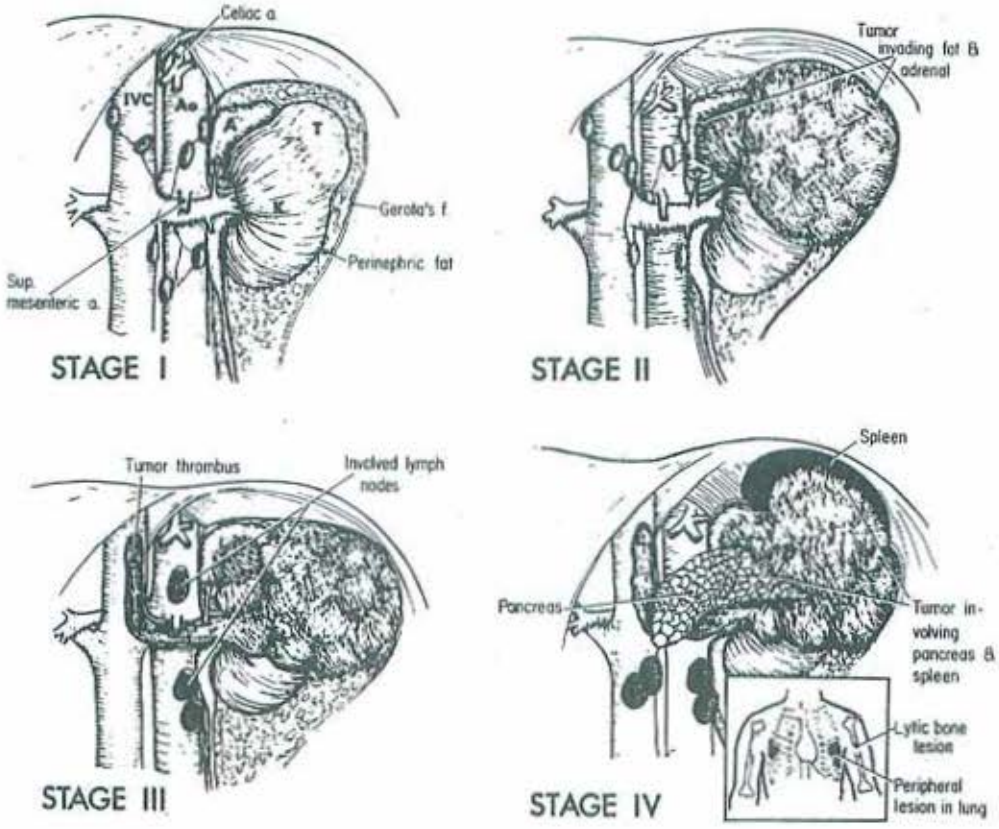


FIG. 15-17
Robson staging system for RCC (see Table 15-4). (Adapted from Robson CJ, Churchill BM, Anderson W: The results of radical nephrectomy for renal cell carcinoma. *J Urol* 1969;101:297.)

Staging and Prognosis

A number of staging systems have been proposed for RCC. The most commonly used system in the United States is that of Robson and colleagues (1969), shown in Fig. 15-17. Briefly, in the Robson system, stage I tumors are contained by the renal capsule, stage II tumors invade the perinephric fat but are contained by Gerota's fascia, Stage IIIa tumors demonstrate involvement of the renal vein or inferior vena cava, stage IIIb tumors involve local lymph nodes, and stage IIIc tumors show a combination of vascular and lymphatic spread. Stage IV tumors invade adjacent organs (other than the ipsilateral adrenal gland) or have metastasized to distant sites. Among the limitations of the Robson system are the definitions of stage III tumors, which combine patients with significantly different prognoses. Patients with nodal involvement (stage IIIb) have a significantly worse prognosis (Bassil et al., 1985; Hermanek and Schrott, 1990; Peters and Brown, 1980; Siminovitch et al., 1983). On the other hand, patients with involvement of the renal vein or vena cava without nodal involvement demonstrate long-term survival nearly comparable to that of patients with more localized disease, provided that all tumor can be surgically removed and that no evidence of metastases exists at time of surgery (Kearney et al., 1981; Sogani et al., 1983; Skinner et al., 1989; Ferrari et al., 1990).

The tumor, nodes, and metastasis (TNM) staging system has been proposed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) to offer greater accuracy in determining the prognosis of patients with RCC. In the TNM staging system, T_1 and T_2 tumors are confined to the kidney but are segregated by size, with tumors larger than 2.5 cm accorded a higher stage. T_3 tumors involve the renal veins, IVC, or perinephric tissues but are confined by Gerota's fascia. T_4 tumors extend beyond Gerota's fascia. Nodal status is stratified by size and number of nodes, and metastatic disease is either present or absent. A comparison of the TNM and Robson staging systems is shown in Table 15-4. Although the TNM staging system allows better prognostic accuracy by subclassification of nodal status and major venous involvement (Bassil et al., 1985; Hermanek and Schrott, 1990), it is considered by many clinicians to be cumbersome to use.

Modalities used for staging of RCC must accurately convey information regarding tumor size, perinephric extent, presence and extent of major vascular involvement, extent of nodal involvement, invasion into adjacent organs, and extent of distant metastases. In the

TABLE 15-4
Comparison of Conventional and TNM Staging Classification of RCC

Robson Stage	T	N	M
I: Tumor confined by capsule	T_1 (tumor 2.5 cm or less) T_2 (tumor >2.5 cm, limited to kidney)		
II: Tumor extension to perirenal fat or ipsilateral adrenal but confined by Gerota's fascia	T_{3a} (tumor invades adrenal gland or perinephric fat but not beyond Gerota's fascia)		
IIIa: Renal vein or inferior vena caval involvement	T_{3b} (renal vein or caval involvement below diaphragm) T_{3c} (caval involvement above diaphragm)	N_0 (nodes negative)	M_0 (no distant metastases)
IIIb: Lymphatic involvement	T_{1-4}	N_1 (single lymph node 2 cm or less) N_2 (single node between 2 and 5 cm, or multiple nodes <5 cm) N_3 (single or multiple nodes >5 cm)	
IIIc: Combination of IIIa and IIIb	$T_{3,4}$		
IVa: Spread to contiguous organs except ipsilateral adrenal	T_4 (tumor extends beyond Gerota's fascia)		
IVb: Distant metastases	T_{1-4}		M_1 (distant metastases)

past, various investigators have evaluated IVP, nephrotomography, arteriography, nuclear renal scans, ultrasonography, cyst puncture and aspiration, and CT for staging renal neoplasms (Dinnie et al., 1992; Karp et al., 1981; Kothari et al., 1981; Lang, 1977; Mauro et al., 1982; Richie et al., 1983; Stephenson et al., 1984). Dynamic contrast-enhanced CT scanning is now accepted as the most effective method available for staging the majority of patients with RCC (McClennan and Deyoe, 1994; Newhouse, 1993). Recently, MRI has been proposed as an equivalent or improved imaging modality for staging of RCC (Hricak et al., 1985; Karstaedt et al., 1986; Fein et al., 1987; Hricak et al., 1988; Amendola, 1989; Semelka et al., 1993). Overall staging accuracies of 74% to 96% have been reported for MRI, compared with 67% to 77% accuracies for CT.

Both CT and MRI are very effective in determining the size of renal masses greater than 1 cm in diameter (Semelka et al., 1993). MRI detected 95% of tumors in 53 patients compared with 89% for CT; all tumors missed by MRI were less than 1 cm in size. Neither CT nor MRI can accurately determine the extent of perinephric invasion (Amendola, 1989; Fein et al., 1987; Hricak et al., 1988). Pathologic examination of the renal capsule, perinephric fat, and Gerota's fascia is often the only accurate staging modality. However, the standard radical nephrectomy encompasses all structures contained within Gerota's fascia, and complete surgical extirpation is more important than perinephric extent.

Both CT and MRI can detect extension of tumor into the renal vein and IVC. Detection rates of 78% to 96% have been reported for CT compared with 95% to 100% for MRI (Fein et al., 1987; Goldfarb et al., 1990; Hricak et al., 1988). MRI does not require intravenous contrast administration to accurately image major vascular structures; in addition, coronal and sagittal planes are readily visible on MRI scans (Amendola, 1989). MRI can also detect true tumor invasion into the vena caval wall (McClennan and Deyoe, 1994). Venacavography is sometimes necessary as a complementary test and can be as accurate as MRI (Fig. 15-18). The combination of venacavography and MRI correctly identified all vena caval thrombi in one series (Horan et al., 1989). Color-flow Doppler ultrasonography is also sometimes useful in delineating vena caval thrombi (McClennan and Deyoe, 1994).

Both CT and MRI are superb in their detection of enlarged retroperitoneal lymph nodes. Unfortunately, neither modality can differentiate hyperplastic nodes from true metastasis (Amendola, 1989; McClennan and Deyoe, 1994). A number of recent studies have shown that MRI is equal to or better than CT in the detection of local adenopathy, particularly in differentiating small lymph nodes from adjacent small vascular structures (Amendola, 1989; Fein et al., 1987; Hricak et al., 1985; Semelka et al., 1993). MRI is clearly superior to CT in the evaluation of adjacent organ invasion, with accuracies of 98% to 100% (Amendola, 1989; Hricak et al., 1988; McClennan and Deyoe, 1994). This is due to the definition of planes between the tumor and adjacent structures, easily seen on MRI.

The most common sites of extraabdominal metastases from RCC are the lungs and bone (see Table 15-5). CT of the chest is the most sensitive method of detecting pulmonary parenchymal masses and is prob-

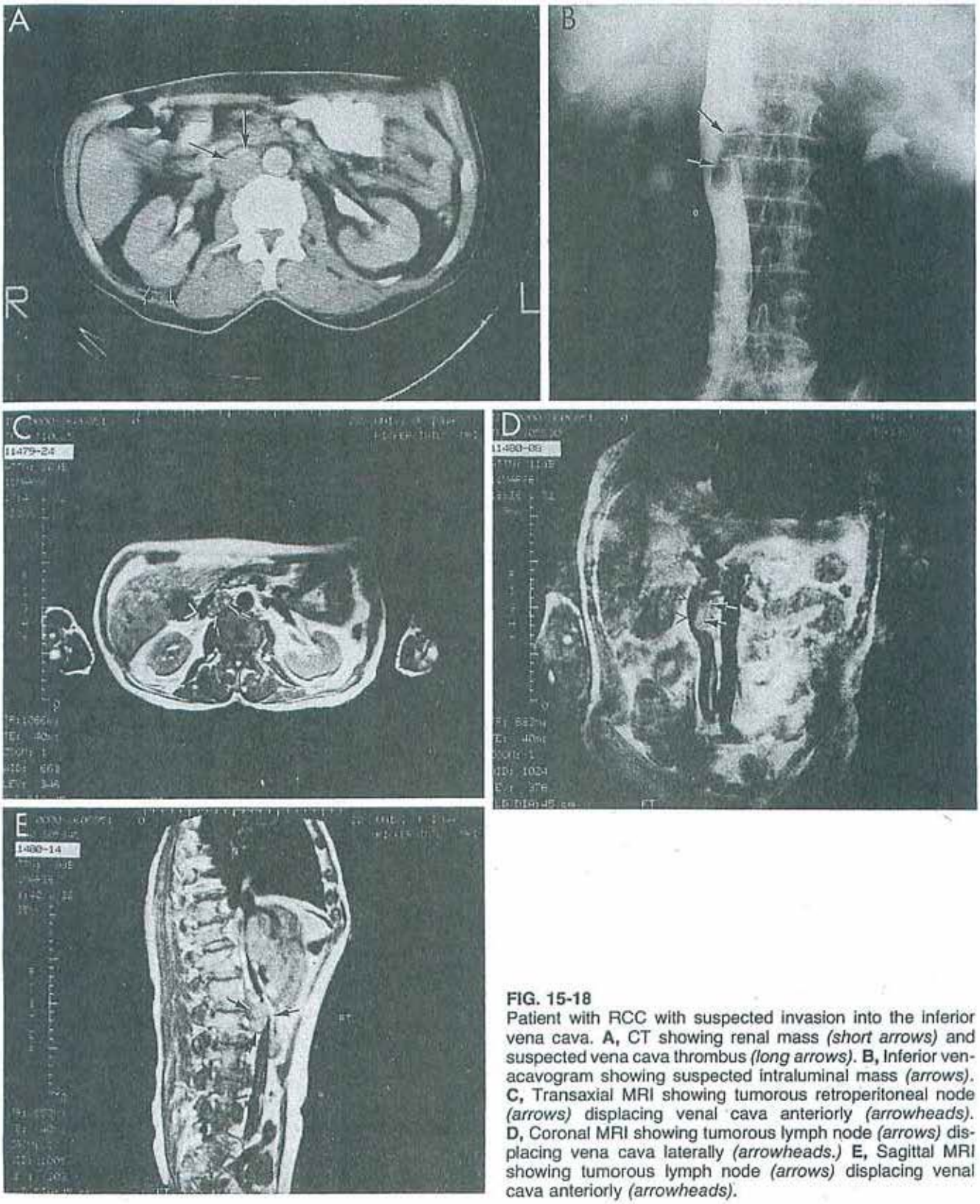


FIG. 15-18
Patient with RCC with suspected invasion into the inferior vena cava. **A,** CT showing renal mass *(short arrows)* and suspected vena cava thrombus *(long arrows)*. **B,** Inferior venacavogram showing suspected intraluminal mass *(arrows)*. **C,** Transaxial MRI showing tumorous retroperitoneal node *(arrows)* displacing venal cava anteriorly *(arrowheads)*. **D,** Coronal MRI showing tumorous lymph node *(arrows)* displacing vena cava laterally *(arrowheads.)* **E,** Sagittal MRI showing tumorous lymph node *(arrows)* displacing venal cava anteriorly *(arrowheads)*.

TABLE 15-5
Common Sites of Metastases in Renal Cancer

Site	%
Lung	50-60
Bone	30-40
Regional nodes	15-30
Main renal vein	15-20
Perirenal fat	10-20
Adrenal (ipsilateral)	10-15
Vena cava	8-15
Brain	10-13
Adjacent organs (colon, pancreas)	10
Kidney (contralateral)	2

Adapted from Fallon B: Renal parenchymal tumors. B. Clinical and diagnostic features, in Culp DA, Loening SA (eds): *Genitourinary Oncology*. Philadelphia, Lea & Febiger, 1985, p 202; Richie JP, Garnick MB: Primary renal and ureteral cancer, in Rieselback RE, Garnick, MB (eds): *Cancer and the Kidney*. Philadelphia, Lea and Febiger, 1982, pp 683-685; Johnson DE, Swanson DA, Von Eschenbach AC: Tumors of the genitourinary tract, in Smith DR (ed): *General Urology*. Los Altos, Calif, Lange Medical Publications, 1984.

TABLE 15-6
Prognosis of Surgically Treated Patients with RCC

TNM Stage	5-Year Survival (%)
I	80-100
II	70-80
III (renal vein or vena cava)	50-60
III (nodal involvement)	15-25
IV	5-10

ably the most cost-effective as well when combined with CT of the abdomen, which is almost universally performed in the staging of renal tumors. Standard posterior-anterior and lateral chest radiography may be sufficient for staging in patients with T_1 tumors and no symptoms of thoracic disease (Lim and Carter, 1993). Bony metastases are best evaluated with radionuclide bone scans, although further evaluation with plain films and sometimes CT or MRI is necessary to confirm the diagnosis, since abnormal bone scans are nonspecific.

In summary, since dynamic contrast-enhanced CT scans are the most commonly employed modality in the diagnosis of renal tumors, and since they offer great accuracy in local staging, often preoperative evaluation for distal metastases with bone scans and CT of the chest is the final necessary step before surgical therapy is undertaken. MRI offers several advantages over CT and is particularly attractive for patients who cannot receive intravenous contrast or in whom CT findings are equivocal. Disadvantages of MRI include higher cost, decreased availability, longer scan times, and claustrophobia (Hricak et al., 1985; McClennan and Deyoe, 1994). Occasionally, studies such as venacavography, color-flow Doppler ultrasonography, and plain bone films are necessary for accurate preoperative staging. Although renal angiography has been replaced by cross-sectional imaging techniques for staging patients with RCC, it is still sometimes useful when nephron-sparing surgery is indicated.

Whether the Robson or TNM staging system is used, tumor stage at the time of surgical exploration is the most valuable prognostic indicator (Thrasher and Paulson, 1993). Reported 5-year survival rates for Robson stage I tumors range from 65% to 93%, and corresponding figures for TNM T_1 and T_2 tumors are 68% to 100% (Bassil et al., 1985; Cherrie et al., 1982; Dinney et al., 1992; Giuliani et al., 1990; Golimbu et al., 1986; Hermanek and Schrott, 1990; Robson et al., 1969; Selli et al., 1983; Siminovitch et al., 1983; Skinner et al., 1971). Survival decreases accordingly with increasing stage (Table 15-6), and only 5% to 10% of patients with distant metastatic disease at the time of diagnosis will survive 5 years (Thrasher and Paulson, 1993). Spread of tumor into regional lymph nodes is also an adverse prognostic indicator, with reported 5-year survival rates of 7% to 52% (Bassil et al., 1985; Dinney et al., 1992; Giuliani et al., 1990; Golimbu et al., 1986; Hermanek and Schrott, 1990; Siminovitch et al., 1983). Extension of tumor thrombus into the vena cava does not have a significant impact upon survival, provided that the tumor is confimed by Gerota's fascia, no evidence of regional nodal or distant metastasis is found, and all tumor and thrombus can be resected completely (Hatcher et al., 1991). Other investigators have found that vena caval extension when coupled with extension of tumor into the perinephric fat, even when confined by Gerota's fascia, portends a poor prognosis (Cherrie et al., 1982; Heney and Nocks, 1982). Since preoperative determination of perinephric tumor extension is often difficult, even with advanced cross-sectional imaging techniques, an aggressive surgical approach, including resection of the vena caval wall if necessary, is sometimes warranted.

Various other prognostic indicators for RCC, including tumor grade, cell type, histologic pattern, tumor size, flow cytometry, and performance status, have been evaluated (Thrasher and Paulson, 1993). With few exceptions, none of these factors seems to add significantly to the prognostic power regarding the extent of tumor at time of diagnosis and staging.

Pathology

In the past, renal cell carcinomas were often called adenocarcinomas, Grawitz' tumors, and hypernephromas. The latter two designations were based on the erroneous conclusion by Grawitz (1883) that renal tumors actually arose from adrenal rests within the kidney. More recent studies using ultrastructural and immunohistochemical techniques have established the

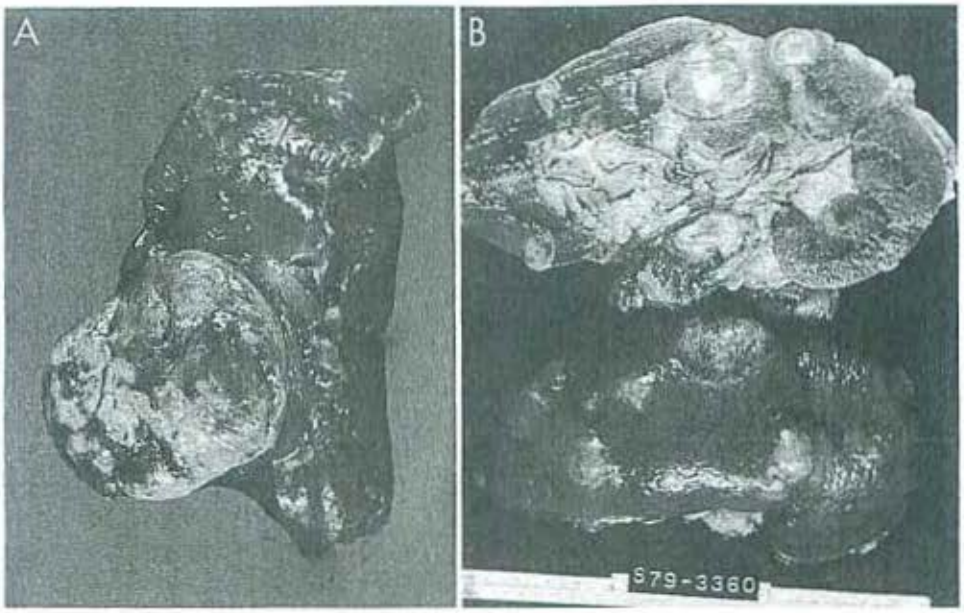


FIG. 15-19
A, Gross pathology of the same right RCC shown in Fig. 15-16. **B,** Photograph of the gross pathology of multiple RCCs in a patient with von Hippel–Lindau disease.

epithelial cells of the proximal tubule as the site of origin of most renal cell carcinomas (Holthofer, 1990; Oberling et al., 1990). Some subtypes of RCC, such as collecting duct carcinomas, chromophobe cell tumors, and at least some papillary renal cell carcinomas, appear to arise from the distal tubule or collecting duct (Fromowitz and Bard, 1990; O'Toole et al., 1993).

Grossly, most renal cell carcinomas originate from the cortex, with an average size of 7 cm (Fromowitz and Bard, 1990). The tumor is generally spherical with a pseudocapsule of compressed renal parenchyma surrounding it (Fig. 15-19). The color of the tumor ranges from gray-white to yellow, depending on the cell type and presence of fibrosis. Tumors composed of predominantly clear cells containing lipids are more often yellow to tan; granular subtypes or tumors containing significant areas of fibrosis are gray to white. Most tumors, especially larger specimens, are quite heterogeneous, with variable areas of viable tumor, necrosis, hemorrhage, fibrosis, calcification, and cyst formation.

Histologically, renal cell carcinomas are composed of a variety of cell types. Clear cells are found in approximately 75% of RCCs (O'Toole et al., 1993) and contain abundant cytoplasmic lipids and glycogen (Fig. 15-20). These substances are removed during fixation, and thus the cytoplasm appears clear on light microscopy (Medeiros and Weiss, 1990). Granular cells are less common than clear cells and have a granular, eosinophilic cytoplasm due to abundant mitochondria (Fromowitz and Bard, 1990). The nuclei are typically larger than in clear cells (Fig. 15-21). Spindle

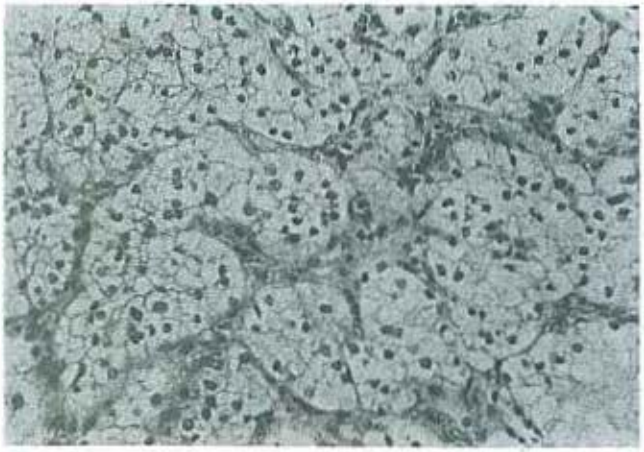


FIG. 15-20
Photomicrograph of clear cell renal adenocarcinoma (original magnification, ×250).

or sarcomatoid cells are the least common cell type found in typical RCC (Fig. 15-22). These cells may resemble fibrosarcoma, rhabdomyosarcoma, or malignant fibrous histiocytoma (Medeiros and Weiss, 1990; Ro et al., 1987). Most renal cell carcinomas are composed of various proportions of clear and granular cells. Pure sarcomatoid RCC is a rare entity, accounting for fewer than 10% of cases (Fromowitz and Bard, 1990). From 5% to 10% of renal cell carcinomas are of papillary histology (Fig. 15-23).

In general, grading systems are not useful in determining prognosis or treatment. As previously discussed, tumor stage is the most important prognostic

FIG. 15-21
Photomicrograph of granular cell adenocarcinoma (original magnification, ×250).

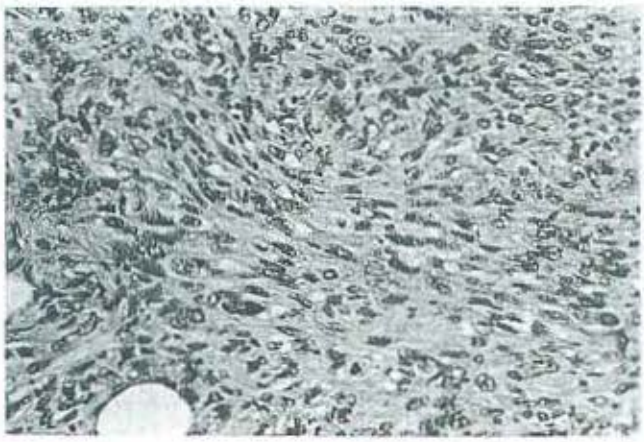


FIG. 15-22
Photomicrograph of sarcomatoid renal adenocarcinoma (original magnification, ×250).

indicator, and high-grade tumors are usually high-stage tumors (Fromowitz and Bard, 1990). Cell type is difficult to evaluate as a prognostic indicator, since most tumors are mixtures of the various cell types. McNichols et al. (1981) found no difference in prognosis between clear cell and granular cell tumors, after correcting for stage and grade. The spindle or sarcomatoid cell type, however, is associated with a grim prognosis. Most patients presented with metastatic disease, and the median survival was only 6.6 months in one series of 44 patients (Sella et al., 1987).

Surgical Treatment

Surgical removal of the kidney is the only known effective treatment modality for localized renal cell carcinoma. Radical nephrectomy is the treatment of choice for stage I, stage II, and some stage III tumors. Nephrectomy in the treatment of metastastic RCC is discussed later. As described by Robson in 1963, radical nephrectomy involves removal of the kidney and ipsilateral adrenal gland en bloc with the perinephric fat, Gerota's fascia, and lymphatics from the crus of the diaphragm to the aortic bifurcation (Fig. 15-24).

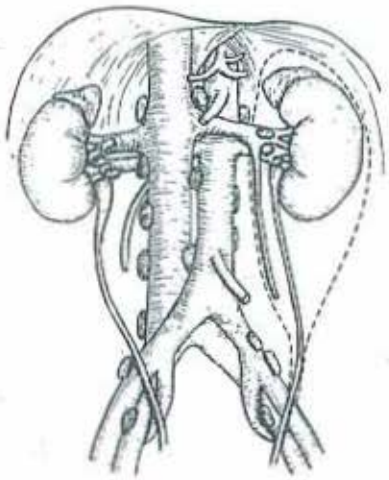


FIG. 15-24
Boundaries of a left radical nephrectomy. Dashed line represents both the surgical margin and Gerota's fascia.

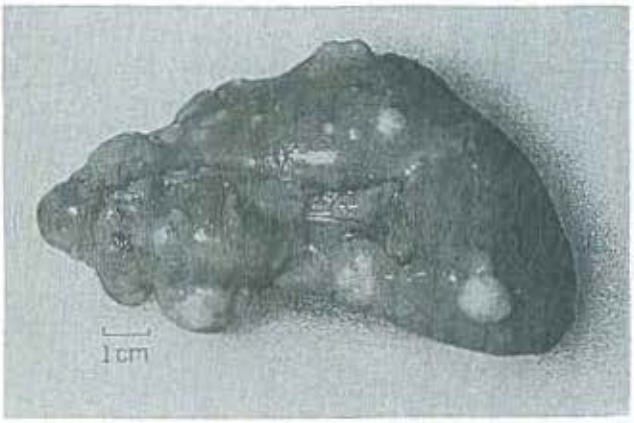


FIG. 15-23
A kidney from a patient with hereditary papillary renal cell carcinoma (HPRCC). In this hereditary form of renal carcinoma, patients develop multiple, bilateral renal tumors. (From Zbar B, Tory K, Merino M, et al: Hereditary papillary renal cell carcinoma. *J Urol* 1994:151:561. Used by permission.)

The surgical approach to renal tumors is dependent upon the size and location of the tumor and the habitus of the patient. The anterior subcostal, thoracoabdominal, and flank approaches are commonly used (Fig. 15-25). In general, the majority of tumors are resectable through a transperitoneal subcostal incision, which offers excellent exposure of the great vessels; very large tumors, particularly in the upper pole, may be best approached through the thoracoabdominal route. After the peritoneal cavity is entered, the intraabdominal contents should be palpated and inspected. The ascending or descending colon is mobilized and reflected medially after incision of the

FIG. 15-25
Patient positioning for a radical nephrectomy through an anterior subcostal incision *(dashed line at costal margin)*. The lower Gibson incision is used for completion of a radical nephroureterectomy.

peritoneal reflection along the line of Toldt. For right-sided masses the duodenum is also mobilized and reflected medially to expose the renal vessels. The renal artery and vein are identified, ligated, and divided. It is helpful to ligate the renal artery early to prevent excessive blood loss. Gerota's fascia surrounding the kidney and adrenal gland is then sharply and bluntly dissected away from surrounding structures. Lymphatics and sympathetic structures along the aorta or vena cava are ligated or clipped and divided. The ureter is ligated and transected, and the specimen may then be removed from the retroperitoneum.

Tumor extension into the renal vein and inferior vena cava may present a formidable surgical challenge. Renal venous extension is usually not problematic, as the tumor thrombus can be milked back toward the kidney as the renal vein is ligated closer to the vena cava. Occasionally, a vascular clamp must be placed at the junction of the renal vein and IVC. The renal vein is divided, the vein and thrombus are resected, and the stump of the renal vein or caval incision is oversewn. Care must be taken not to dislodge the tumor thrombus during these manipulations. Management of tumor thrombus within the IVC is dependent upon the cephalad extent of the thrombus and presence or absence of invasion into the caval wall. Pritchett and associates (1986) described their experience with three groups of patients with extension of renal cell carcinoma into the IVC. Group I thrombi are infrahepatic and accounted for nearly 50% of these patients and those in other series (Burt et al., 1993). Although in some cases the tumor thrombus can be milked back into the renal vein while a vascular clamp is placed at the caval junction, most group I thrombi require isolation and occlusion of the vena cava above and below the thrombus, as well as the opposite renal vein, the lumbar veins, and other tributaries such as the gonadal and adrenal veins. A vertical incision is made in the vena cava and continued circumferentially around the junction of the renal vein, and the thrombus is carefully dissected away from the wall. The nephrectomy is then completed and the vena cava is repaired. Direct invasion of the tumor into the wall of the vena cava requires resection of the involved portion of the side wall or, at times, the entire circumference of the vena cava (Hatcher et al., 1991). Restoration of venous drainage from the contralateral kidney may be difficult. If the left kidney remains, often collateral drainage via the adrenal, gonadal, and lumbar veins is sufficient, particularly if the vena cava had previously been completely occluded by tumor thrombus, although the patient may require short-term dialysis postoperatively (Kearney et al., 1981; Pritchett et al., 1986; Skinner et al., 1989). Because of the lack of collateral venous drainage from the right kidney, vascular reconstruction of the right renal vein must be performed to reestablish drainage if the vena cava is completely resected (Kearney et al., 1981). Group II thrombi as classified by Pritchett and associates (1986) extend into the intrahepatic vena cava, and group III thrombi, which account for approximately 10% of cases, extend into the right atrium. The surgical approach to these thrombi is similar to that for group I, with the addition of occlusion of the superior mesenteric artery and the porta hepatis. For group III thrombi, the assistance of a cardiovascular surgeon may be necessary to open the right atrium and resect the thrombus or push it down into the IVC. These procedures are usually performed in conjunction with cardiopulmonary bypass and sometimes hypothermia and cardiac arrest (Burt et al., 1993; Hatcher et al., 1991; Janosko et al., 1991; Marshall et al., 1984; Stewart et al., 1991).

Regional lymphadenectomy, originally advocated by Robson (1963) and later by others (deKernion, 1980; Herrlinger et al., 1991; Marshall and Powell, 1982; Peters and Brown, 1980), remains controversial. Proponents argue that resection of positive nodes, if they are the only sites of metastatic disease, may benefit a small number of patients, particularly since there are currently no widely effective treatments for metastatic RCC. This seems reasonable if only a few small nodes are involved; however, more extensive nodal involvement portends a poorer prognosis (Hermanek and Schrott, 1990). There are a number of limitations of extended regional lymphadenectomy (deKernion, 1980). Because the lymphatic drainage of the kidney is unpredictable, even an extensive retroperitoneal dissection (see Fig. 15-26) cannot reasonably be expected to remove all possible sites of metastasis, and may increase morbidity and mortality. Patients with lymphatic metastases also commonly demonstrate synchronous or metachronous distant metastases, and regional lymphadenectomy will not benefit these patients. Also, it is possible that in those patients who benefit from lymphadenectomy (i.e., patients with limited nodal involvement), those same nodes would have been removed by a standard radical nephrectomy. A randomized prospective trial would be necessary to determine the role of regional

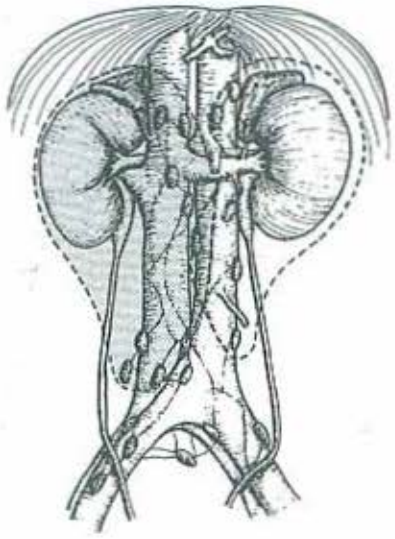


FIG. 15-26
Surgical extent of a radical nephrectomy and lymphadenectomy for RCC on either side *(dashed lines)*.

lymphadenectomy in patients with localized kidney cancer.

Bilateral RCC and Tumors in Solitary Kidneys

Although the radical nephrectomy is the standard form of therapy, there are some situations in which radical nephrectomy would remove all functioning renal tissue. Examples of such situations are bilateral renal cell carcinomas and RCC in an anatomic or functionally solitary kidney. In these instances some surgeons would favor removal of all renal tissue coupled with dialysis and possibly renal transplantation. This is not optimal treatment for some patients because of the morbidity and mortality associated with dialysis and transplantation (Taylor, 1993). Renal-sparing surgery is recommended in selected patients.

Several nephron-sparing techniques have been described, including partial nephrectomy, enucleation, and extracorporeal partial nephrectomy followed by autotransplantation ("bench surgery"). Because of the pseudocapsule that typically forms around renal cell carcinomas, enucleation, which removes tumor in a relatively avascular plane while retaining the maximum amount of functional renal tissue, is considered appropriate in some instances, particularly in the management of patients with hereditary forms of renal carcinoma (Novick, 1992). Survival rates of up to 90% have been reported with this technique (Novick et al., 1986; Steinbach et al., 1991). However, other studies of enucleations of renal tumors following radical nephrectomy report detection of residual tumor in the enucleated bed in 27% to 38% of patients, as well as capsular invasion, venous invasion, occult metastatic disease, and multicentricity (Blackey et al., 1988; Marshall et al., 1986). For these reasons, partial nephrectomy is considered by most to be the preferred method for nephron-sparing surgery.

Preoperative staging is identical to that mentioned previously, with the addition of renal angiography. After the renal vessels are exposed, the kidney is packed in saline slush and the renal artery is clamped following the administration of 20% mannitol. For small peripheral tumors, the procedure may be performed without ischemia or with warm ischemia (Moll et al., 1993). The branches of the renal artery leading to the tumor are identified, ligated, and divided. Partial nephrectomy by wedge resection, guillotine amputation of the upper or lower poles, or circumscription of a margin of normal parenchyma surrounding the tumor is then performed. It is best to leave intact the perirenal fat and Gerota's fascia overlying the tumor. Frozen sections of the margins are taken to ensure complete tumor removal. The collecting system is repaired and hemostasis is achieved. Occasionally in the case of large centrally located tumors, extracorporeal partial nephrectomy with autotransplantation is indicated, but these cases are rare (Novick, 1993).

Results in selected series have been uniformly good, with overall 5-year survival rates of 67% to 80% and cancer-specific 5-year survival rates of 84% to 89% (Morgan and Zincke, 1990; Novick et al., 1989). Local recurrence rates of 6% to 9% have been reported. These data are comparable to most series of Robson stage I and II renal cell carcinomas, and indicate that tumor stage at time of surgical intervention may be more important than choice of surgical procedure (Taylor, 1993). Radical nephrectomy is considered by most physicians to be the treatment of choice in patients with a normal contralateral kidney because of concerns regarding local recurrence and unsuspected multifocality (Novick, 1993; Cheng et al., 1991). Nevertheless, as increased numbers of smaller tumors are discovered incidentally, nephron-sparing surgery may come to play a larger role in the treatment of carefully staged patients. Several authors have reported excellent results for nephron-sparing surgery in cases of unilateral RCC with a normal contralateral kidney. In combined series of 241 patients, the disease-specific survival rate was 95% with a mean follow-up of approximately 3 years (Licht and Novick, 1993). In these series, the tumors were small, with a mean diameter of less than 3.5 cm. Licht and colleagues (1994) reported a 5-year cancer-specific survival rate of 100% with no postoperative recurrences in patients with unilateral stage I tumors smaller than 4 cm which were treated with nephron-sparing surgery, and they proposed that these criteria could be applied to patients with unilateral RCC and a normal contralateral kidney. These authors also found that incidentally detected tumors were smaller (mean diameter 3.6 cm),

more often unilateral, and of lower pathologic stage than symptomatic tumors. Thus, patients with incidentally discovered renal cell carcinomas are more likely to be candidates for proposed nephron-sparing strategies. Ultimately, a randomized trial comparing radical nephrectomy to nephron-sparing surgery in this select group of patients would be necessary to address the issues of long-term survival, local and distant recurrence rates, and attendant morbidities associated with each approach. Until such time as a trial is performed, many clinicians continue to advocate radical nephrectomy as the treatment of choice in these patients.

Bilateral RCC is an infrequent occurrence, noted in 2% to 4% of patients (McDonald, 1982; Vermillion et al., 1972; Viets et al., 1988). For patients with synchronous bilateral RCC, bilateral nephron-sparing surgery is recommended when technically feasible, particularly in patients with familial renal cancer syndromes such as von Hippel-Lindau disease. Alternate strategies include the use of radical nephrectomy on the most severely affected side in conjunction with a contralateral partial nephrectomy. Patients with bilateral asynchronous RCC may also be managed with nephron-sparing surgery, although some series have shown poorer results in this subset of patients (Topley et al., 1984; Zincke and Swanson, 1982).

Locally Invasive RCC

Renal cell carcinomas invade adjacent organs such as the adrenal gland, colon, duodenum, pancreas, or spleen in approximately 10% of cases. Invasion into the ipsilateral adrenal gland (Robson stage II or TNM stage T_{3a}) is not felt to be particularly ominous, since the adrenal gland is typically removed during a radical nephrectomy. Any other direct local organ invasion classifies the tumor as stage IV, with a significantly worsened prognosis; fewer than 5% of patients will survive 5 years (deKernion and Belldegrun, 1992). Occasionally, adjacent organ invasion will cause pain, intestinal bleeding, or intraabdominal bleeding and will necessitate therapeutic intervention. It is often possible to perform en bloc resections of the involved colon, pancreas, spleen, or liver, but patients must be carefully selected, as these procedures can be associated with significant morbidity and mortality. Partial resection or "debulking" procedures are infrequently recommended.

Metastatic Renal Cell Carcinoma

Nephrectomy and Resection of Metastases.—The role of nephrectomy in the patient with metastatic RCC remains to be determined. There are no prospective, randomized trials comparing the course of patients with distant metastases who were observed with those who underwent nephrectomy. In a report from deKernion and associates (1978), 26 patients underwent nephrectomy for palliation. The survival of these patients was no different from that of the series of 86 patients with metastatic disease. Middleton (1967) found in his series of 141 patients with metastatic RCC that nephrectomy did not prolong survival; none of the patients survived 2 years.

There is a subset of patients with metastatic RCC who may derive some benefit from nephrectomy. That is the small number of patients who present with a solitary metastasis, estimated at between 1.6% and 3.2% of patients (Middleton, 1967; Tolia and Whitmore, 1975). Middleton (1967) reported a 34% 5-year survival in patients with a solitary metastasis who underwent nephrectomy and surgical resection of the metastatic site, based on his series and other reports. Tolia and Whitmore (1975) reported a 35.3% 5-year survival in patients with a solitary metastasis. In this series patients were treated with nephrectomy and various modes of treatment of the metastatic site, including surgery and radiation. Patients who present with a solitary metastasis at the time of diagnosis have a poorer prognosis than those in whom a metastasis develops at some point following nephrectomy (deKernion et al., 1978; O'Dea et al., 1978). Among 26 patients who developed a solitary metastasis between 1 month and 7.5 years following nephrectomy, O'Dea and associates (1978) reported a 23% 5-year survival rate following resection of the metastasis, with 3 long-term survivors at 58, 94, and 245 months. Palliative or adjunctive nephrectomy may improve the quality of life in selected patients with intractable pain, severe hemorrhage, or systemic manifestations of RCC such as hypercalcemia, hypertension, and nonmetastatic hepatic dysfunction (deKernion, 1983; Fowler, 1987; Freed, 1977). Nephrectomy in patients with metastatic RCC is recommended primarily for patients with a solitary metastatic site which is amenable to surgical removal. The role of nephrectomy as an adjunct to systemic therapy in patients with metastatic RCC is currently under study.

Angioinfarction.—Angioinfarction of renal tumors has been used both as a preoperative adjunct and as a palliative measure in patients with unresectable or metastatic tumors. Angioinfarction was first described by Lalli and associates (1969), and since then a variety of agents have been used for embolization, including absolute ethanol, autologous blood clot, gelatin sponges (Gelfoam), and Gianturco steel coils (Swanson et al., 1980; McLean and Meranze, 1985). The kidney is an end organ, and thus angioinfarction may be accomplished at minimal risk to adjacent vascular beds. Most patients develop a "postinfarction syndrome" characterized by ileus, fever, flank or abdominal pain, and leukocytosis (McLean and Meranze, 1985). More significant complications include renal failure or im-

pairment from the use of contrast materials, renal abscess, colonic infarction, and pulmonary embolus from ischemic necrosis of tumor thrombus (Cox et al., 1982; Jennings et al., 1993; McLean and Meranze, 1985; Wallace et al., 1981).

In addition to palliation offered to patients with unresectable tumors, theoretical advantages of angioinfarction include decreased operative blood loss, enhancement of perinephric tissue planes, and improvement of preoperative anemia and performance status (Craven et al., 1991; McLean and Meranze, 1985; Singsaas et al., 1979; Wallace et al., 1981). However, there is no good evidence that these advantages are realized in most patients. Renal tumors often develop neovascularization from many different feeding arteries, and thus embolization of the main renal artery cannot be expected to infarct all or even most of the tumor. Angioinfarction appears to have no benefit in improving the prognosis of patients with metastatic disease. Swanson and colleagues (1983) reported a 15% partial and complete response of metastatic sites in patients treated with infarction followed by nephrectomy. However, no difference in survival was noted. Gottesman and associates (1985) treated 30 patients with infarction and nephrectomy. Only 1 partial response was noted, and all patients eventually progressed. The role of angioinfarction seems best suited to those symptomatic patients with metastatic disease who require palliation.

Radiotherapy.—Radiation therapy has been used as an adjuvant therapy and for palliation in patients with metastatic RCC. Although some studies have shown improvement in local recurrence rates following postoperative radiation therapy, others have not confirmed this finding (Kjaer et al., 1987; Stein et al., 1992). Survival does not seem to be enhanced in most series. Radiation therapy can be beneficial in the treatment of symptomatic osseous metastases. Cutuli and colleagues (1990) reported improvement of pain in 50% of patients with metastases to the skull, spine, ribs, pelvis, and long bones. Halperin and Harisiadis (1983) successfully palliated 77% of patients with painful bony metastases. Surgery in combination with radiation therapy has also been used in the treatment of vertebral body metastases with spinal cord compression. Sundaresan and associates (1986) reported neurologic improvement in 7 of 7 patients treated with total tumor resection, spinal stabilization, and postoperative radiation, compared with a 45% success rate in similar patients treated with radiation alone. Radiotherapy also plays a role in the palliation of brain metastases. Maor and colleagues (1988) treated 7 patients with symptomatic cerebral metastases. In 5 of these patients, complete surgical extirpation was successful and was followed by radiation therapy. These 5 patients had a median survival of 63 weeks. In 39 patients from the same study who received only whole-brain irradiation, improvement was seen in only 30%, with a median survival of 17 weeks. Other investigators have also reported an approximate 30% response rate for whole-brain irradiation to cerebral metastases (Halperin and Harisiadis, 1983; Cutuli et al., 1990). Stereotactic radiosurgery may be another useful modality in the treatment of brain metastases. Coffey and associates (1991) found improvement in 2 of 3 patients following cobalt-60 gamma knife radiosurgery, which avoids the risks associated with craniotomy.

Chemotherapy.—To date, the results of chemotherapy for advanced RCC have been disappointing, with an average complete and partial response rate of only 5.6% (Yagoda et al., 1993). The profound resistance of RCC to chemotherapeutic agents is thought to be multifactorial. Fojo and colleagues (1987) found elevated expression of the multidrug resistance gene (mdrl) in 75% of renal cell carcinomas. Kakehi and associates (1988) found similar results in 86% of patients. The mdrl gene encodes for P-glycoprotein, a 170-kilodalton plasma membrane–associated glycoprotein that has been localized to the proximal tubular cells of the kidney (Moscow and Cowan, 1988; Thiebaut et al., 1987). P-glycoprotein functions as a drug efflux pump and appears to be responsible for the decreased intracellular concentrations of various chemotherapeutic agents. Recognition of the role of P-glycoprotein in multidrug resistance has led to the use of several agents (primarily verapamil, quinidine, and their derivatives) that block the action of the pump in vitro (Kanamaru et al., 1989; Lai et al., 1990; Mickisch et al., 1990; Mickisch et al.,1991; Tsuruo et al., 1984). However, early clinical trials have met with only limited success (Chabner and Fojo, 1989). Other mechanisms of drug resistance that appear to be important in some renal cell carcinomas include the glutathione redox cycle, in which glutathione peroxidases bind and inactivate chemotherapeutic agents (Mickisch et al., 1990; Moscow and Cowan, 1988), as well as decreased expression of topoisomerase II (Volm et al., 1992). New chemotherapeutic strategies are being evaluated to take advantage of the information gained from the studies of P-glycoprotein and glutathione function (Table 15-7).

Hormonal Therapy.—The rationale for hormonal therapy in the treatment of RCC is based on the finding of renal tumors in male Syrian golden hamsters exposed to prolonged administration of estrogen (Kirkman and Bacon, 1949). Subsequent studies showed that high doses of progesterone inhibited tumor formation and growth (Bloom et al., 1963; Bloom, 1973). An early clinical series by Bloom (1973) showed a 22% objective response rate in 80 patients with metastatic RCC, as well as a 15% response rate in collected se-

TABLE 15-7
Chemotherapy for Treatment of Metastatic RCC

Agent(s)	No.	% CR/PR*
Single		
Vinblastine	296	16
Hydroxyurea	140	11
Lomustine (CCNU)	79	10
Cyclophosphamide	132	9
Methyl-glyoxal bis(guanylhydrazone)	76	9
Fluorouracil	201	5
Doxorubicin	65	0
Cisplatinum	60	0
Combination		
Vinblastine, cyclophosphamide, hydroxyurea, progesterone, and prednisone	45	16
Vinblastine and CCNU	93	13
Vinblastine and progesterone	38	8

Data from Richie JP, Garnick MB: Primary renal and ureteral cancer, in Rieselback RE, Garnick MB (eds): *Cancer and the Kidney*. Philadelphia, Lea & Febiger, 1982, pp 683-685; Olver IN, Leavitt RD: Chemotherapy and immunotherapy of disseminated renal cancer, in Javadpour N (ed): *Cancer of the Kidney*. New York, Thieme-Stratton Inc, 1984, pp 109-120.
*CR/PR = complete remission/partial remission.

TABLE 15-8
Hormonal Therapy for Metastatic RCC

Agent	No.	% CR/PR*
Progesterone	695	5
Androgen	190	3
Tamoxifen	106	3
Nafoxidine	39	10

Data from Bodey GP: Current status in chemotherapy in metastatic renal carcinoma, in Johnson DE, Samuels ML (eds): *Cancer of the Genitourinary Tract*. New York, Raven Press, 1979, p 67; deKernion JB: Treatment of advanced renal cell cancer—traditional methods and innovative approaches. *J Urol* 1983; 130:2.
*CR/PR = complete remission/partial remission.

ries. However, later studies with various hormonal agents failed to confirm these findings (see Table 15-8). More recent critical reviews (Pizzocaro et al., 1986; Kjaer, 1988) have concluded that RCC is not a hormonally responsive tumor and that realistic response rates (usually only partial) of only 1% to 2% can be expected. Adjuvant hormonal therapy has not been shown to be effective. Although recent studies suggest that agents such as high-dose tamoxifen may offer some benefit (Stahl et al., 1992), hormonal therapy to date remains an ineffective measure against metastatic RCC.

Immunotherapy.—The role of immunotherapy in the treatment of patients with advanced RCC is being evaluated by a number of investigators. Rare but documented cases of spontaneous tumor regression, as well as cases of metastatic disease appearing many years following nephrectomy, led investigators to postulate that immunologic factors may play an important role in the host's response to this malignancy. Separate studies published in 1983 evaluated the effectiveness of α-interferon in metastatic RCC (deKernion et al., 1983; Quesada et al., 1983) and showed combined complete and partial response rates of 16.5% and 26.5%. Subsequent phase II trials have consistently shown objective response rates (complete and partial) of 10% to 27% (Abratt et al., 1993; Chaitchik, 1992; Kirkwood et al., 1985; Levens et al., 1989; Merimsky and Chaitchik, 1992; Muss et al., 1987; Quesada et al., 1985). Despite ten years of clinical experience with this agent, the exact mechanism of action, as well as the optimum treatment regimen, are unclear, although intermediate to high doses appear to be more effective (Krown, 1987; Quesada et al., 1985). Side effects of interferon therapy include fever, fatigue, nausea, vomiting, and diarrhea, especially at higher doses (Muss, 1991). The survival benefit of interferon remains unproven (Quesada, 1989) since all studies to date have been single arm phase II trials. The median duration of response is approximately 6 to 10 months in most series, and complete remissions are rare (Figlin et al., 1991). Patients who do respond tend to be males who have undergone prior nephrectomy, with pulmonary or mediastinal metastases and an excellent performance status. In these patients a higher response rate (up to 40%) can be expected (Quesada, 1989).

Other studies have evaluated β-interferon and γ-interferon in the treatment of metastatic RCC. The effects of β-interferon appear to be similar to those of α-interferon (Kinney et al., 1990; Rinehart et al., 1986). Responses to γ-interferon are seen in approximately 15% of patients (Aulitzky et al., 1989; Foon et al., 1988; Garnick et al., 1988; RHIGRG, 1987). Other investigators have used various combinations of α-interferon and γ-interferon; no clear advantage is seen with combination therapy (Ernstoff et al., 1990; Foon et al., 1988; Geboers et al., 1988; Quesada et al., 1988). Similarly, combinations of α-interferon and various chemotherapeutic agents show no decided advantage over α-interferon alone and are associated with added toxicity (Figlin et al., 1985; Neidhart et al., 1991, Murphy et al., 1992; Muss, 1991). The use of α-interferon with interleukin-2 is discussed below.

Interleukin-2 (IL-2) was first described by Morgan and colleagues in 1976. IL-2 is produced by lymphocytes and activates several immune mechanisms, including stimulation of tumoricidal activity in lymphokine-activated killer (LAK) cells and promotion of growth in T-lymphocytes (Cantrell and Smith, 1984; Mule et al., 1985). Clinical trials involving patients with advanced RCC and other malignancies were begun in 1983 by Rosenberg at the National Cancer Institute, and since then IL-2 has been extensively

studied using various doses, routes of administration, and combinations with other agents.

A number of investigators have evaluated the use of intravenous high-dose IL-2 in the treatment of metastatic RCC. In the largest series to date, Rosenberg et al. (1994) treated 149 patients with 720,000 IU/kg IL-2 intravenously every 8 hours for a maximum of 15 doses per cycle. This experience resulted in a 7% complete response rate and a 13% partial response rate. Of the 10 patients who manifested a complete response, 7 continued to be in remission for 7 to 76 months following therapy. Other groups, using slightly lower doses of IL-2 (600,000 IU/kg every 8 hours) have shown response rates of 8% to 17%, with good duration of response (Atkins et al., 1993; Bukowski et al., 1990; McCabe et al., 1991). Clinical trials are in progress to prospectively evaluate responses to high-dose or low-dose bolus IL-2. In an attempt to decrease the toxicity associated with high-dose bolus IL-2, other investigators have utilized lower doses of IL-2 via continuous intravenous infusion, with response rates of 12% to 23% (Geertsen et al., 1992; Maase et al., 1991; Marumo et al., 1989; Negrier et al., 1992; Sosman et al., 1988). Despite the lower cumulative doses of IL-2 given through continuous intravenous infusion, toxicity profiles are similar to those of high-dose IL-2 regimens (Geertsen et al., 1992; Maase et al., 1991), although fewer patients required intensive resuscitation. High-dose IL-2 has been approved by the FDA for use in the treatment of patients with advanced renal carcinoma and is the only agent approved by the FDA specifically for this purpose.

The investigational nature of IL-2, until its recent approval by the FDA and its associated cardiopulmonary, renal, and hepatic toxicities, meant that most patients entered in early trials had excellent performance status and were carefully screened for major coexisting illnesses. In an attempt to widen the applicability of IL-2 therapy, several investigators have used subcutaneous injections of IL-2 as a means of minimizing toxicity while treating patients who otherwise would not be candidates for intravenous IL-2. Response rates of 17% to 23%, mostly partial, have been reported (Atzpodien et al., 1990; Sleijfer et al., 1992; Stein et al., 1991). Toxicities were minor for the most part. The relative benefits of high and low dose IL-2 regimens are currently the subject of randomized trials.

Interleukin-2 has also been administered in combination with other agents. Based on animal data that showed improvement of antitumor activity in mice treated with IL-2 plus LAK cells (Lafreniere and Rosenberg, 1985; Papa et al., 1986), clinical trials were begun using LAK cells and IL-2 by intravenous bolus and continuous intravenous infusion. Most studies have reported responses in 15% to 30% of patients treated with IL-2 plus LAK cells (Dillman et al., 1991; Fisher et al., 1988; Gaynor et al., 1990; Parkinson et al., 1990; Rosenberg et al., 1989; Thompson et al., 1992; Weiss et al., 1992; West et al., 1987). Prospective randomized trials comparing IL-2 alone with IL-2 plus LAK cells have failed to show any significant differences in response rates or survival (Bajorin et al., 1990; Rosenberg et al.,1993).

Animal models also showed synergistic antitumor effects when IL-2 was combined with α-interferon (Cameron et al., 1988). A number of clinical trials have been performed, using a wide variety of dosages and routes of administration. Response rates (complete and partial) in most series range from 11% to 33% (Atkins et al., 1993; Ilson et al., 1992; Figlin et al., 1992; Lipton et al., 1993; Ratain et al., 1993; Rosenberg et al., 1989; Sznol et al., 1990; Vogelzang et al., 1993). One randomized trial (Atkins et al., 1993) compared therapy with high-dose bolus IL-2 alone with a lower dose of IL-2 plus α-interferon. No major difference in response rates was noted in the relatively small number of patients treated.

Recently, investigators have also utilized tumor-infiltrating lymphocytes (TIL) in combination with IL-2 and α-interferon in the treatment of metastatic RCC (Belldegrun et al., 1993). In a series of 10 patients, there were 3 complete responders, with durations of response greater than 23 and 24 months. In addition, 1 partial responder was able to be surgically rendered free of disease. Further clinical trials are ongoing. Autolymphocyte therapy (ALT) has also been utilized, with response rates of approximately 20% (Osband et al., 1990; Krane et al., 1992). Most responses appear to be partial, although the investigators suggested that survival may be prolonged. It is difficult to draw conclusions from small studies, and a confirmatory randomized trial of ALT is being performed by ECOG.

Although it is clear that IL-2–based immunotherapy can produce durable complete and partial responses in a minority of patients with metastatic RCC, a number of questions remain to be answered. The optimum dose and route of administration have yet to be determined. Neither the combination of IL-2 with LAK cells nor the addition of α-interferon to IL-2 demonstrated a significant advantage over IL-2 alone; further randomized trials addressing this question are clearly needed. Although immunotherapy clearly appears to be more effective than other systemic modalities for metastastic RCC (Table 15-9), further studies will be needed to develop more effective and less toxic forms of therapy for patients with this malignancy. Identification of patient and tumor characteristics that mediate the response to immunotherapy is essential to further advances using this modality.

TABLE 15-9
Immunotherapy for the Treatment of Metastatic RCC

Agent	% CR/PR
Interleukin-2	15-25
Interleukin-2 plus LAK	15-25
Interleukin-2 plus α-interferon	10-25
Interleukin-2, α-interferon, and TIL	20
α-Interferon	10-20
β-Interferon	10-20
γ-Interferon	10-15

CR/PR = complete response/partial response; LAK = lymphokine-activated killer cells; TIL = tumor-infiltrating lymphocytes.

Cancer of the Renal Pelvis

After RCC, malignant tumors of the renal pelvis are the most common primary cancers of the kidney, but they account for only approximately 5% to 10% of cases (Fraley, 1978). Men are affected two to three times more frequently then women, and the peak age of incidence is 60 to 70 years (Clayman et al., 1983). Approximately 2% to 4% of patients develop bilateral disease, either synchronous or metachronous. In 30% to 50% of patients with urothelial tumors of the renal pelvis or ureter, bladder cancer is found before, at, or after the time of diagnosis of the upper tract tumor (Abercrombie et al., 1988; Huben et al., 1988; Kakizoe et al., 1980). Only 2% of patients treated for bladder cancer subsequently develop carcinoma of the upper urinary tract (Oldbring et al., 1989). This is thought to be due to seeding of tumor cells by antegrade urine flow as well as to greater exposure of the bladder mucosa to potential carcinogens (Catalona, 1992).

Etiology

Cigarette smoking is the major risk factor for development of cancer of the renal pelvis. One case-control study showed that cigarette smoking was associated with a three- to seven-fold increased risk of cancer development and concluded that approximately 70% and 40% of renal pelvic malignancies were due to smoking by men and women, respectively (McLaughlin et al., 1992). This and other studies have also shown that cessation of smoking is associated with decreased risk of development of renal pelvic cancer (McCredie and Stewart, 1992; McLaughlin et al., 1992).

Numerous investigators have also found an increased risk of developing cancer of the renal pelvis in patients who abuse analgesics, particularly phenacetin-containing compounds (Adam et al., 1970; Bengtsson et al., 1968; Gaakeer and De Ruiter, 1979; Hoybye and Nielsen, 1971; Jensen et al., 1989; Mahony et al., 1977). The prolonged use of high doses of phenacetin or related compounds may lead to thickening of the basement membranes surrounding suburothelial capillaries, which in turn may cause papillary necrosis (McCredie et al., 1986; Palvio et al., 1987). The presence of papillary necrosis is not necessary for development of cancer of the renal pelvis; however, the combination of phenacetin use and renal papillary necrosis was found to confer a twenty-fold increased risk, suggesting that papillary necrosis and phenacetin abuse are both powerful independent risk factors (McCredie et al., 1986; McCredie et al., 1993).

Cancer of the renal pelvis is also associated with Balkan endemic nephropathy, a chronic tubulointerstitial disorder that ultimately results in renal failure. This disease appears to be confined to areas of the Balkan states that lie along tributaries of the Danube River (Cukuranovic et al., 1991). In these countries cancer of the renal pelvis accounts for as many as 42% of renal tumors (Markovic, 1972). Cancer of the renal pelvis is 60 to 100 times more common in these regions than in control regions, and in one study 57% of patients with renal pelvic tumors were from endemic areas (Markovic, 1972; Petronic et al., 1991). The causative factor or factors responsible for both Balkan nephropathy and renal pelvic malignancies in these patients are unknown. The renal pelvic tumors are generally low grade, multifocal, and slow growing, and are bilateral in 10% of cases (Petkovic, 1975). For these reasons, conservative surgery is advocated when possible.

A number of occupational risk factors have been associated with the development of renal pelvic malignancies, including employment in the chemical, petrochemical, plastics, dry cleaning, and iron and steel industries (Jensen et al., 1988; McCredie and Stewart, 1993). Numerous potential carcinogens are found in these industries, and the exact causative mechanisms of development of cancer of the renal pelvis have yet to be determined.

Molecular Genetics

Little is known about the molecular genetics of renal pelvic malignancies. However, urothelial malignancies are felt to be the result of "field change" phenomena; that is, events common to all urothelial-lined tissues may result in neoplastic changes at any anatomic location from the renal collecting system to the proximal urethra. Thus, studies of the molecular genetics of bladder cancer will probably be informative regarding urothelial tumors of the renal pelvis and ureter, but this premise awaits further investigation. Numerous chromosomal abnormalities associated with bladder cancer have been identified. Partial or complete deletions of chromosomes 9p, 9q, 17p, 11p, and 3p have been described (Dalbagni et al., 1993; Knowles et al., 1994; Miyao et al., 1993; Presti et al., 1991; Sidransky et al., 1991; Tsai et al., 1990). Mutations, inactivation, or altered expression of the Rb

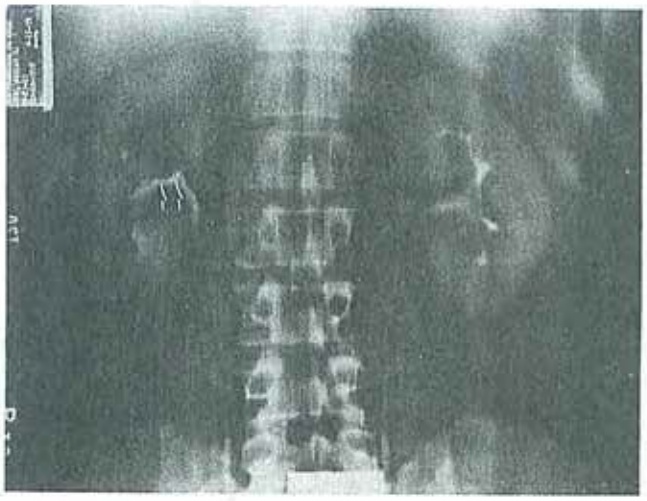


FIG. 15-27
Nephrotomogram from an IVP of a patient with a right renal pelvic urothelial cancer. The renal pelvic filling defect is marked by arrows.

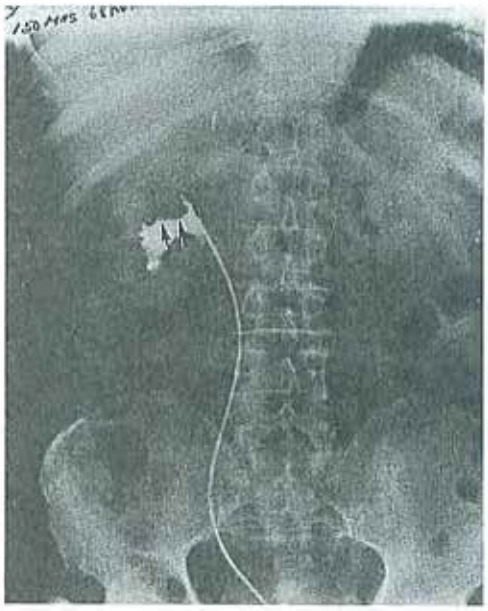


FIG. 15-28
Retrograde pyelogram of the same patient as in Fig. 15-27. (From Williams RD, Tanagho EA: *Current Surgical Diagnosis and Treatment.* Los Altos, Calif, Lange Medical Publications, 1985, p 863. Used by permission.)

and p53 tumor suppressor genes have also been demonstrated (Ishikawa et al., 1991; Miyao et al., 1993; Oka et al., 1991; Presti et al., 1991; Sidransky et al., 1991). The weight of current evidence suggests that at least two tumor suppressor genes on chromosome 9 are implicated in the tumorigenesis of urothelial malignancies, and abnormalities of other chromosomal loci are involved in the progression of disease (Dalbagni et al., 1993; Ruppert et al., 1993).

Further evidence for a genetic basis of urothelial malignancies comes from studies of familial transitional cell carcinomas of the renal pelvis, ureter, and bladder. Orphali and associates (1986) reported three siblings with renal pelvic or ureteral carcinomas and reviewed eight additional families. The majority of patients (53%) had bladder cancer only, but 30% of patients had tumors confined to the upper urinary tract. Lynch and colleagues (1990) described four kindreds with ureteral carcinomas as well as other primary malignancies of the colon, endometrium, breast, stomach, and pancreas. Further studies of the molecular genetics of urothelial malignancies should provide greater insights into the mechanisms of tumorigenesis.

Clinical Presentation and Diagnosis

Gross hematuria is the most common presenting symptom, occurring in 75% to 95% of patients (Murphy et al., 1981; Wagle et al., 1974). Microscopic hematuria is found in 3% to 11% of patients. Total gross hematuria is indicative of a bleeding source in the upper urinary tracts, as are vermiform clots. From 14% to 37% of patients complain of pain (Grabstald et al., 1971; Murphy et al., 1981; Wagle et al., 1974). In general, the pain is a dull ache caused by gradual obstruction of the collecting system. Renal colic from the passage of blood clots can also occur. A palpable mass is noted in fewer than 20% of patients. Likewise, the clinical triad of hematuria, pain, and mass is quite rare (approximately 15% of patients) and is usually associated with advanced disease. In large series of patients, only 1% to 2% are asymptomatic (Grabstald et al., 1971; Wagle et al., 1974).

IVP is the most commonly used initial diagnostic modality in the evaluation of patients with hematuria (Fig. 15-27). Approximately 50% to 75% of patients will demonstrate a filling defect in the renal pelvis or collecting system (Murphy et al., 1981; Wagle et al., 1974). Nonvisualization of the affected kidney is noted in 13% to 31% of cases (Grabstald et al., 1971; Murphy et al., 1981). Other common causes of renal pelvic filling defects should be ruled out, including nonopaque stones, blood clots, papillary necrosis with sloughing, crossing renal vessels, and fungus balls.

Cystoscopy in combination with retrograde pyelography is also commonly employed when renal pelvic malignancies are suspected (Fig. 15-28). Cystoscopy may help to localize the bleeding site to the right or left upper tract, as well as in identification of coexisting bladder tumors. Retrograde pyelography is particularly useful when the kidney is not visualized on IVP or when IVP is contraindicated because of renal insufficiency or severe contrast allergy. When properly performed, retrograde pyelography is diagnostic in up to 85% of patients (Murphy et al., 1981). Injec-

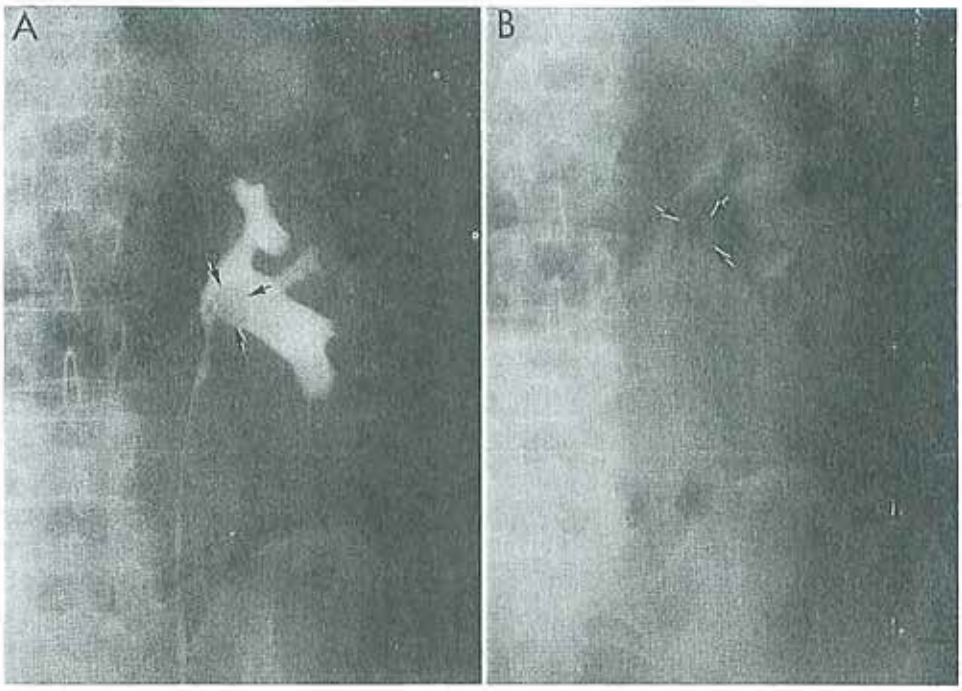


FIG. 15-29
Retrograde pyelogram in a patient with a left renal pelvic urothelial tumor. **A,** Contrast study. **B,** Air study. The tumor is marked by *arrows.*

tion of air and contrast material is sometimes useful (Fig. 15-29).

CT is sometimes used to further delineate renal pelvic filling defects. Although CT is sensitive enough to detect 85% to 90% of urothelial defects (Badalament et al., 1992; Nyman et al., 1992), in general IVP and retrograde pyelography are more practical initial diagnostic studies. CT is useful in differentiating radiolucent stones from urothelial tumors. Because urothelial tumors usually appear hypodense relative to normal renal parenchyma following intravenous contrast administration, CT may also be helpful in differentiating these masses from RCC (Nyman et al., 1992). CT appears to be of limited value in the staging of upper tract tumors (Badalament et al., 1992). The role of magnetic resonance imaging (MRI) is undetermined, but it does not appear to offer any advantages over CT (Milestone et al., 1990).

Renal angiography is not often used for evaluation of suspected renal pelvic tumors. There are some instances in which radiologic evaluation with IVP, retrograde pyelography, and CT fails to reveal a cause of hematuria. Angiography may then be useful in detecting angiomas or arteriovenous malformations. Arteriography may also delineate crossing renal vessels and provides vital information if a segmental resection is indicated.

Urine cytology can be helpful in the evaluation of renal masses, particularly when samples are collected from ureteral catheters following saline barbotage. An accurate diagnosis can be made in approximately 60% to 80% of cases (Highman, 1986; Leistenschneider and Nagel, 1980; Sarnacki et al., 1971). Urine should be collected prior to retrograde pyelography to avoid cellular distortion caused by ionic contrast material (Catalona, 1992). Accuracy of diagnosis is dependent upon the technique of collection, tumor grade, underlying urothelial abnormalities, and skill and experience of the cytopathologist. Higher-grade tumors are accurately diagnosed in 75% to 100% of cases (Highman, 1986; Leistenschneider and Nagel, 1980), whereas grade 1 tumors are correctly diagnosed in only 50% of patients. False-positive diagnoses may result when urothelial inflammation causes exfoliation of abnormal-appearing cells. Addition of fluoroscopically guided brush biopsy of suspicious areas can increase diagnostic accuracy of approximately 80% to 90% (Blute et al., 1981; Sheline et al., 1989).

The development of rigid and flexible ureteroscopes has led to improved diagnostic accuracy in the evaluation of indeterminate renal pelvic filling defects. In several series a correct diagnosis was achieved in 80% to 90% of patients (Andersen et al., 1993; Blute et al., 1989; Streem et al., 1986). Rigid ureteroscopes allow better visualization and larger working ports but are limited in their ability to depict the lower-pole calyces. Flexible ureteroscopes offer improved visualization of the entire collecting system (Bagley et al., 1987). In addition to visualization of the tumor, biopsies may be obtained using either rigid or flexible uretero-

scopes, although in general the characteristic appearance of transitional cell tumors is adequate for diagnosis (Fig. 15-30). Antegrade pyeloscopy has also been advocated but carries a significant risk of tumor seeding into the retroperitoneum (Tomera et al., 1982).

Staging and Prognosis

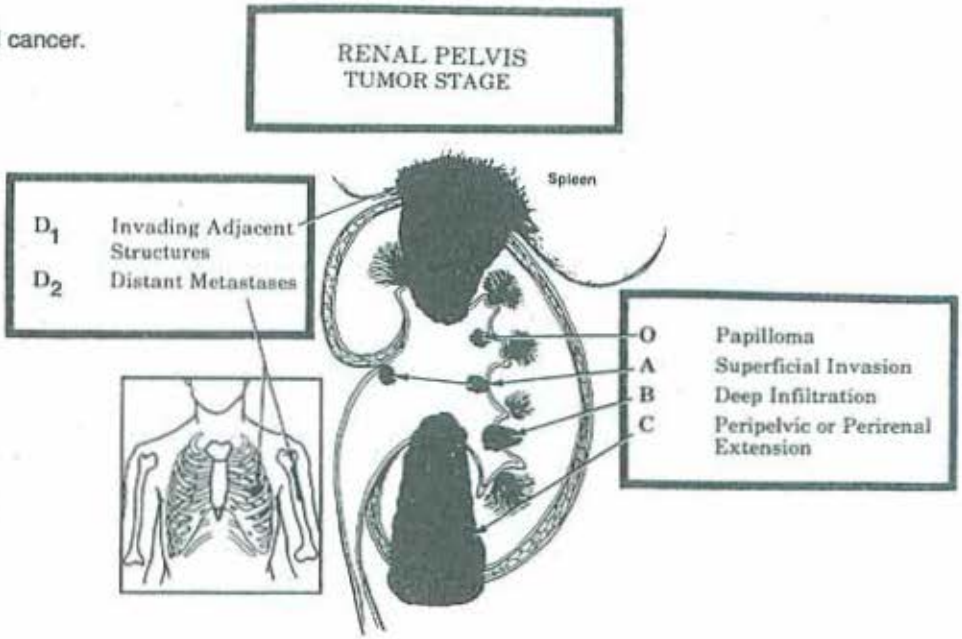
Most urologists in the United States use the staging system proposed by Grabstald and colleagues (1971) and later modified by Cummings (1980). In this system, stage I tumors are noninvasive, stage II tumors invade the lamina propria, stage III tumors involve the muscularis of the renal pelvis or the renal parenchyma but do not extend through the renal pelvic adventitia, and stage IV tumors invade through the full thickness of the renal pelvis or through the renal capsule. Tumors that have invaded into adjacent organs or have metastasized locally or distantly are also considered to be stage IV tumors. An adaptation of the Grabstald-Cummings system is shown in Fig. 15-31.

FIG. 15-30
Ureteroscopic view of a renal urothelial tumor. (Courtesy of Jeffery Huffman, M.D., Department of Urology, University of Southern California, Los Angeles.)

The TNM staging system has also been applied to urothelial tumors of the renal pelvis. In the 1992 edition of this system, T_X tumors cannot be assessed, T_0 denotes no evidence of the primary tumor, T_a tumors are papillary and noninvasive, T_{is} denotes carcinoma in situ, T_1 tumors invade the subepithelial connective tissue, T_2 tumors invade the muscularis, T_3 tumors involve the renal parenchyma or the peripelvic fat, and T_4 tumors invade the perinephric fat or adjacent organs. For nodal metastases, N_X nodes cannot be assessed, N_0 denotes no regional nodal metastases, N_1 denotes a single metastatic lymph node 2 cm or less in size, N_2 denotes multiple metastases in lymph nodes 5 cm or less in size or a single metastatic node between 2 cm and 5 cm in size, and N_3 denotes presence of a single or multiple metastatic lymph nodes greater than 5 cm in size. Metastases are categorized by any site other than the regional lymph nodes and include the M_X category, in which presence of metastases cannot be assessed, the M_0 category, in which no distant metastases are present, and the M_1 category, in which distant metastases are present. Tumors are staged by depth of invasion as denoted by the T classification. Stage IV includes T_4 tumors as well as all tumors with nodal or distant metastases.

Staging studies for urothelial carcinomas of the renal pelvis are mainly useful in the detection of metastatic disease. CT scans are commonly performed and may be quite helpful in detecting tumor extension into the

FIG. 15-31
Staging system for renal urothelial cancer.



renal parenchyma or into the peripelvic or perirenal fat (Badalament et al., 1992; Nyman et al., 1992). Enlarged regional lymph nodes are also seen well on CT, although enlargement was found to correlate with metastases in only 40% of patients in one study (Badalament et al., 1992). The liver, a common site of metastasis from urothelial tumors, can also be evaluated with CT. Following regional lymph nodes, the lungs are the most common site of metastases and should be evaluated with chest x-ray or CT. Finally, a bone scan should be considered, particularly in patients with large or high-grade tumors.

Regardless of the staging system used, tumor stage at diagnosis is the most important prognostic variable (Cummings, 1980; Grabstald et al., 1971; Guinan et al., 1992; Huben et al., 1988; Matsuoka et al., 1991; Raabe et al., 1992). For carcinoma in situ or noninvasive tumors, 5-year survival rates of 75% to 92% are reported (Guinan et al., 1992; Matsuoka et al., 1991). For stage I and II tumors, 5-year survival rates are in the range of 58% to 87% (Cummings, 1980; Guinan et al., 1992; Matsuoka et al., 1991). Five-year survival rates for stage III tumors are 30% to 50% (Cummings, 1980; Grabstald et al., 1971; Guinan et al., 1992). Metastatic disease carries a grim prognosis, with 5-year survivals of only 5% to 10% (Cummings, 1980; Grabstald et al., 1971; Guinan et al., 1992; Huben et al., 1988). Tumor grade also correlates strongly with prognosis. However, most high-grade tumors are also high stage (Huben et al., 1988). DNA flow cytometry has also been proposed as a prognostic indicator. In one study, DNA ploidy offered no additional prognostic information in low-stage, low-grade or high-stage, high-grade tumors. However, a subset of patients with intermediate-grade tumors demonstrated aneuploidy on flow cytometry, and this correlated significantly with poorer survival (Al-Abadi and Nagel, 1992).

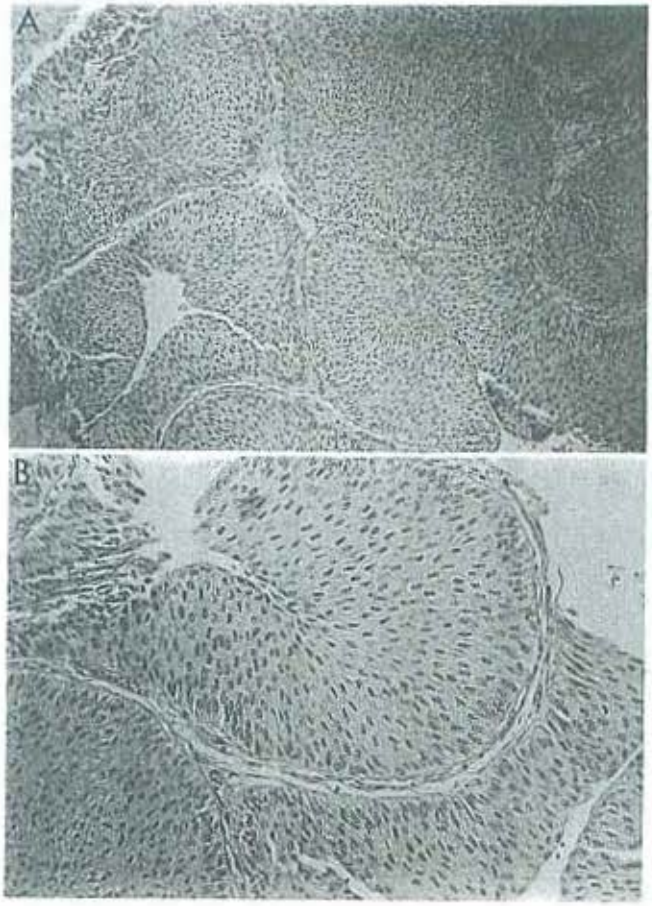


FIG. 15-32
A, Histologic section of a transitional cell carcinoma of the renal pelvis (original magnification, ×80). B, Same section at higher magnification (original magnification, ×157).

Pathology

The vast majority (90% or more) of renal pelvic tumors are transitional cell carcinomas (Figs. 15-32 and 15-33). Most of these are papillary tumors, composed of malignant urothelial cells supported by fibrovascular cores (Melamed and Reuter, 1993). Transitional cell carcinomas may also be planar or sessile. Transitional cell carcinoma in situ is also found in the renal pelvis. Squamous cell carcinomas are seen in 5% to 10% of patients with renal pelvic cancers (Melamed and Reuter, 1993). These tumors are often associated with chronic inflammation of the renal pelvis or with urolithiasis. Squamous cell carcinomas are usually of high stage and grade when detected, and thus the prognosis is poor (Nativ et al., 1990). Adenocarcinoma of the renal pelvis is quite rare (fewer than 60 documented cases) and is associated with chronic urolithiasis, hydronephrosis, and pyelonephritis (Spires et al., 1993).

Papillary transitional cell carcinomas are generally

FIG. 15-33
Gross pathology of a renal pelvic transitional cell carcinoma *(arrows)*.

subdivided into three or four grades based on cellular atypia and nuclear anaplasia. As previously mentioned, tumor grade is a strong prognostic indicator. Huben and associates (1988) reported a 69% 5-year survival rate for patients with grade I or II tumors, versus a 24% 5-year survival in patients with grade III or IV disease. Most tumors are of low or intermediate grade (Melamed and Reuter, 1993).

Surgical Treatment

The treatment of choice of carcinoma of the renal pelvis is total nephroureterectomy with excision of a cuff of bladder (Cummings, 1980; Johansson and Wahlqvist, 1979; Johnson et al., 1974). The rationale for this treatment is based on the high incidence of recurrent carcinoma in the ureteral stump following subtotal nephroureterectomy, as well as on studies confirming widespread urothelial abnormalities, including carcinoma in situ, adjacent to frank renal pelvic carcinomas (Kakizoe et al., 1980; Mahadevia et al., 1983). The multifocal nature of urothelial malignancies mandates removal of all tissue at risk. Johansson and Wahlqvist (1979) compared radical nephroureterectomy with excision of bladder cuff to simple nephrectomy with subtotal ureterectomy and found that 5-year survival was increased in patients treated with the more radical approach. This was not a randomized study; nevertheless, the data seem to favor radical surgery.

Nephroureterectomy may be performed through a variety of incisions. Although it is possible to remove the kidney and ureter through a midline or modified flank incision, most surgeons prefer a two-incision technique using a transabdominal subcostal or flank approach to the kidney and proximal ureter and a Gibson incision for the distal ureter and bladder cuff. The kidney is dissected free as for the previously described radical nephrectomy, and then the ureter is dissected away from surrounding structures down to the bladder. Most surgeons prefer to make an anterior cystotomy to remove the intramural ureter and cuff of bladder mucosa. Others feel that an adequate mucosal margin can be achieved without an anterior cystotomy. Occasionally, and especially for larger tumors, a thoracoabdominal approach is indicated (Skinner, 1978). Rarely, transitional cell carcinomas of the renal pelvis will involve the renal vein and inferior vena cava, and in these cases tumor thrombectomy as for RCC has been described (Geiger et al., 1986; Jitsukawa et al., 1985). The prognostic significance of vena cava involvement is unknown. Some authors (Skinner, 1978) advocate a formal regional lymph node dissection, but the benefits of this approach are uncertain.

The results of nephroureterectomy for renal pelvic tumors are dependent upon tumor stage and grade. Charbit and associates (1991) reported an approximate 65% 5-year survival rate in 92 patients treated with nephroureterectomy and found that 90% of the cancer-specific mortalities were in patients with high-grade tumors. In a study of 32 patients with stage I, grade I tumors treated with nephroureterectomy, the 5-year survival rate was 88% (Murphy et al., 1980). Other investigators have reported 90% to 95% 5-year survival rates in patients with low-stage, low-grade disease (Mufti et al., 1989). Survival progressively decreases as tumor stage and grade increase. In patients with stage III or IV, grade III or IV tumors, Murphy and colleagues (1981) found only an approximate 10% 5-year survival.

Some authors have advocated a more conservative approach to renal pelvic tumors, arguing that survival rates following partial nephrectomy or local excision of the renal pelvis for low-stage, low-grade tumors are similar to survival rates following radical nephroureterectomy (Gittes, 1980; Murphy et al., 1980; Wallace et al., 1981; Zincke and Neves, 1984; Bazeed et al., 1986). However, local or distant recurrence rates following a conservative approach are quite high, ranging from 38% to 71% in several collected series (Bazeed et al., 1986; Mazeman, 1976; Mufti et al., 1989; Wallace et al., 1981; Ziegelbaum et al., 1987; Zincke and Neves, 1984). Many of the patients who experienced recurrence in these series did not have low-stage, low-grade tumors, and this points to the risks inherent in the preoperative staging of these individuals. Despite recent advances in cytology and endourologic biopsy, a significant proportion of patients will prove to have tumors of higher stage and grade than suspected preoperatively, or will demonstrate occult multifocality (Seaman et al., 1993). Thus, a conservative approach to renal pelvic tumors seems best limited to those individuals in whom radical nephroureterectomy would result in loss of all functioning renal tissue, i.e., patients with carcinoma in a solitary kidney, bilateral disease, or renal insufficiency. The best results will be achieved in patients with truly unifocal, low-stage, low-grade tumors, but these individuals are rare.

A number of investigators have examined the role of endourology in the treatment of patients with renal pelvic tumors. Huffman and associates (1985) treated two patients with renal pelvic malignancies with ureteroscopic fulguration or resection. One patient subsequently developed five asynchronous recurrences in the renal pelvis or ipsilateral ureter, which were all fulgurated. The other patient had visible tumor remaining following resection. Blute and colleagues (1989) treated five patients with ureteroscopic fulguration of renal pelvic tumors. Only one recurrence was noted, but follow-up periods ranged only from 12 to 48 months. Percutaneous nephroscopy with resection or laser irradiation of renal pelvic tumors has also been reported (Blute et al., 1989; Nolan et al.,

1988; Orihuela and Smith, 1988; Schoenberg et al., 1991; Smith et al., 1987; Tasca and Zattoni, 1990). In the largest series, a recurrence rate of 45% was reported (Orihuela and Smith, 1988). Violation of the collecting system in the face of urothelial malignancy has also raised concerns about tumor seeding along the nephrostomy tract. Tomera and associates (1982) reported two patients with transitional cell carcinoma of the renal pelvis in whom renal fossa recurrences developed following intraoperative pyeloscopy and immediate nephroureterectomy. The pyeloscopy was presumed to be the source of tumor seeding. To date, this complication has not been reported following nephroscopy but should be kept in mind if this approach is contemplated.

Various chemotherapeutic and immunologic agents have been instilled into the renal pelvis to treat malignancies following conservative or endoscopic resection (Bellman et al., 1994; DeKock and Bruytenbach, 1986; Eastham and Huffman, 1993; Herr, 1985; Ramsey and Soloway, 1990). Agents may be instilled via retrograde ureteral catheter, via percutaneous nephrostomy, or by reflux through pyeloileal or pyelovesical anastomoses. Early reports are encouraging, but patient numbers are small and follow-up is limited.

Regardless of the surgical approach to carcinomas of the renal pelvis, periodic surveillance postoperatively is critical. Following nephroureterectomy, patients should undergo cystoscopy and examination of urine cytology every 3 months for at least 2 years, then biannually for 1 year, and then annually. Patients in whom conservative treatment has been employed should also undergo imaging studies of the upper tracts (IVP or retrograde pyelography) as well as analysis of ureteral saline barbotage cytology specimens. Ureteropyeloscopy should probably be reserved for patients with suspicious findings on radiographic or cytologic studies, although Gerber and Lyon (1993) have suggested that routine ureteropyeloscopy two to four times a year would not be unreasonable.

In summary, radical nephroureterectomy with excision of a cuff of bladder remains the standard treatment for renal pelvic tumors because of the multifocal nature of urothelial cancer, the inaccuracies of preoperative staging and grading, the significant chance of recurrence in the ipsilateral ureter or bladder when lesser measures are employed, and the very low likelihood of subsequent disease in the contralateral kidney. There is clearly a place for conservative resection or endourologic management in carefully selected patients, but most patients are better served by a more aggressive approach.

Radiation Therapy

Postoperative radiation therapy has been proposed by some authors (Brookland and Richter, 1985; Cozad et al., 1992). Radiation therapy seems to decrease the risk of local recurrence; however, development of metastatic disease and ultimate survival are not affected by this modality. Radiation therapy may also be of benefit in the palliation of patients with painful bony metastases.

Chemotherapy

Various chemotherapeutic agents have been used in the treatment of patients with locally advanced or metastatic carcinomas of the renal pelvis. To date, few patients have been reported, and most series include patients with transitional cell carcinomas of the bladder and ureter. Sternberg and colleagues (1989) reported a 79% complete and partial response rate in 13 patients with renal pelvic cancers treated with methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC regimen). Tannock and associates (1989) treated 9 patients with transitional cell carcinoma of the renal pelvis with M-VAC. Primary tumor site was not specified in the response data, but only 2 of 41 patients overall (5%) demonstrated durable complete responses. The toxicity of this regimen is also considerable. Logothetis and colleagues (1985) used a CISCA regimen (cisplatin, cyclophosphamide, and doxorubicin) to treat patients with metastatic or locally advanced bladder or ureteral cancers and reported a 39% complete remission rate with a median duration of response of 49 weeks. In an effort to avoid the nephrotoxicity associated with cisplatin-based regimens (and that may actually limit entrance into or continuation of these protocols), Boccardo and associates (1994) used carboplatin, methotrexate, and vinblastine to treat 36 patients with locally advanced or metastatic cancers of the renal pelvis or bladder. A 39% complete and partial response rate was achieved. However, 10 patients with creatinine clearances of less than 50 ml/min were able to be treated with this regimen. Further clinical trials of various regimens are currently under way.

Renal Sarcomas

Primary renal sarcomas are quite rare, accounting for only 1% to 3% of primary renal malignancies (Farrow et al., 1968; Srinivas et al., 1984; Vogelzang et al., 1993). These tumors often grow to a large size and present with typical signs and symptoms of other renal tumors, i.e., flank or abdominal pain, hematuria, and palpable mass. Thus preoperative differentiation from renal cell carcinoma is often difficult. Men and women are equally affected, and the mean age at diagnosis is in the sixth decade, although patients may present over a wide age range (Grignon et al., 1990). Many patients present with locally advanced or metastatic disease (Grignon et al., 1990; Srinivas et al., 1984; Vogelzang et al., 1993). These tumors are thought to

arise predominantly from the renal capsule, although any other mesenchymal tissue may be the site of tumorigenesis (Pollack et al., 1987).

Leiomyosarcomas are the most common renal sarcomas, accounting for approximately 50% to 60% of all cases (Farrow et al., 1968; Srinivas et al., 1984; Vogelzang et al., 1993). Grossly, approximately 50% of these tumors are well encapsulated and compress rather than invade the renal parenchyma. The remainder infiltrate into the kidney or adjacent organs (Farrow et al., 1968; Srinivas et al., 1984). The cut surface reveals a firm gray or white mass that appears to be lobulated. Histologically, the tumor cells are spindle shaped with blunted nuclei. Cytogenetic abnormalities appear to be consistent with other intraabdominal leiomyosarcomas (van den Berg et al., 1994). Radiologic studies are generally not helpful in distinguishing leiomyosarcomas from other primary renal tumors, although clear demonstration of a capsular origin on CT or MRI may suggest the diagnosis preoperatively. The treatment for renal leiomyosarcoma has been radical nephrectomy in almost all cases reported. However, local recurrences and distant metastases are common despite aggressive therapy, and few patients are cured (Farrow et al., 1968; Srinivas et al., 1984; Vogelzang et al., 1993). Adjuvant chemotherapy and radiation therapy have been employed with some reports of success, but their true efficacy is unknown (Davis et al., 1992; Rakowsky et al., 1987; Taniguchi et al., 1987).

Liposarcomas are quite rare, accounting for approximately 20% of renal sarcomas (deKernion and Belldegrun, 1992). These tumors appear to arise from the renal capsule. Most tumors do not invade the renal parenchyma and are circumscribed and lobulated (Farrow et al., 1968; Grignon et al., 1990). On CT, fat densities within a large renal mass are seen but are not pathognomonic for this tumor (Shirkhoda and Lewis, 1987). Radical nephrectomy is usually employed, and the value of adjunctive therapy is unknown.

Malignant fibrous histiocytomas have rarely been reported to arise in the kidney. Most of these tumors are quite large when discovered. On cut surface, the tumors appear variegated, with areas of hemorrhage, necrosis, and cyst formation. Clinically and radiographically these tumors cannot be differentiated preoperatively from renal cell carcinomas. Despite radical nephrectomy, the prognosis is poor, with few patients surviving more than a few months (Raghavaiah et al., 1980; Scriven et al., 1984; Vogelzang et al., 1993).

Hemangiopericytomas originate from pericytes, contractile cells that envelop capillaries and assist in regulation of blood flow. Approximately 20 cases have been reported to date (Heppe et al., 1991). The tumors may be well circumscribed or may be multinodular, multifocal, or invasive. Hypoglycemia and hypertension are seen in approximately 20% of cases. Radical nephrectomy may offer a better chance of cure in these patients, and preoperative renal angioinfarction may also be of benefit (Heppe et al., 1991).

Fibrosarcomas are quite rare but are frequently confused with the more common leiomyosarcomas (Kansara and Powell, 1980). These tumors may have a pale or fleshy appearance. Radical nephrectomy offers the only known chance of cure, but few survivors are reported (Kansara and Powell, 1980; Grignon et al., 1990).

Various other types of primary renal sarcomas have been described. Rhabdomyosarcomas are large, multilobulated tumors that seem to have a poor prognosis despite nephrectomy and intensive neoadjuvant and adjuvant therapy (Srinivas et al., 1984; Grignon et al., 1990). Carcinosarcomas and angiosarcomas have been reported and are also associated with a grim prognosis (Allred et al., 1981; Rao et al., 1977). Primary renal osteosarcomas are extremely rare, and the precise histogenesis is unclear. Extensive calcification is common and may suggest the diagnosis preoperatively. As with other sarcomas, the prognosis is poor, but nephrectomy followed by adjuvant chemotherapy may be of some benefit (Biggers and Stewart, 1979; Micolonghi et al., 1984; Moon et al., 1983).

SECONDARY MALIGNANT RENAL TUMORS

Secondary malignant renal tumors may involve the kidney via direct extension or hematogenous spread. In theory, a tumor originating from any retroperitoneal organ or structure could directly invade the kidney, but such occurrences are rare. Bloodborne metastases, whether from solid or hematologic malignancies, are much more common.

Renal metastases from solid tumors are found in approximately 7% to 12% of patients in combined autopsy series (Bracken et al., 1979; Mayer, 1982; Barbaric, 1994). These tumors are almost always discovered at autopsy, with only 40 cases diagnosed prior to death reported in the literature (Petersen, 1992). In general, renal metastases are clinically silent, although pain or hematuria may occur. Walther and associates (1979) reported a case of life-threatening hematuria caused by renal metastases from an adenocarcinoma of the lung, which was successfully treated by renal angioinfarction. Primary tumors of the lung, breast, and gastrointestinal tract are the most common sources of renal metastases (Table 15-10). Renal metastases are generally small, bilateral, and multifocal (Choyke et al., 1987; Petersen, 1992), although large solitary tumors do occur and may present difficulties in diagnosis (Fig. 15-34). Choyke and colleagues (1987) found that renal masses in patients with other known primary tumors were four times as likely to be met-

TABLE 15-10
Solid Tumors Metastatic to the Kidney

Primary Site	%
Lung	27
Breast	14
Stomach	12
Pancreas	7
Colon	6
Cervix	5
Esophagus	4
Prostate	4
Gallbladder, testis, thyroid, bladder, or melanoma	2-3
Endometrium, kidney, ovary, head and neck, or bone	1-2

Adapted from Mayer RJ: Infiltrative and metastatic disease of the kidney, in Rieselback RE, Garnick MB (eds): *Cancer and the Kidney*. Philadelphia, Lea & Febiger, 1982, p 707.

astatic as a primary renal tumor; however, if the primary disease was discovered at the same time as the renal mass or was in remission, the renal mass was equally likely to represent a metastatic site or a primary renal tumor. In general, there are no characteristic radiologic findings to distinguish renal metastases from primary renal cell carcinomas (Barbaric, 1994). Percutaneous fine-needle aspiration cytology may assist in diagnosis. Because renal metastases are almost always present in the context of multiple other metastases, the prognosis for most patients is extremely poor.

Hematogenous metastases from hematologic malignancies are also common but are usually clinically silent. Renal infiltration from leukemia is found in 50% to 67% of patients in autopsy series (Barbaric, 1994; Mayer, 1982). Leukemic involvement is characterized by diffuse bilateral cortical infiltration, although grossly apparent nodules may occasionally be seen (Petersen, 1992). Gross enlargement of the kidneys may result, but renal function is usually unimpaired.

Renal involvement from lymphoma is found in approximately 35% of patients in autopsy series (Barbaric, 1994; Mayer, 1982; Petersen, 1992). Primary renal lymphoma has also been reported but is probably a transient manifestation of systemic disease (Kandel et al., 1987). Lymphomatous infiltrates may be nodular or diffuse. Solitary renal masses and direct renal invasion from adjacent lymph nodes are also seen (Heiken et al., 1983). Renal involvement is usually bilateral. Patients are usually asymptomatic, although azotemia, palpable mass, or hypertension is occasionally noted (Mayer, 1982). CT is the imaging modality of choice when renal involvement by lymphoma is suspected, but the usual appearance of lymphoma on CT scans is nonspecific, and percutaneous or open renal biopsy may be necessary to confirm the diagnosis (Fig. 15-35). CT does appear to be useful in monitoring progression of disease and response to therapy (Hei-

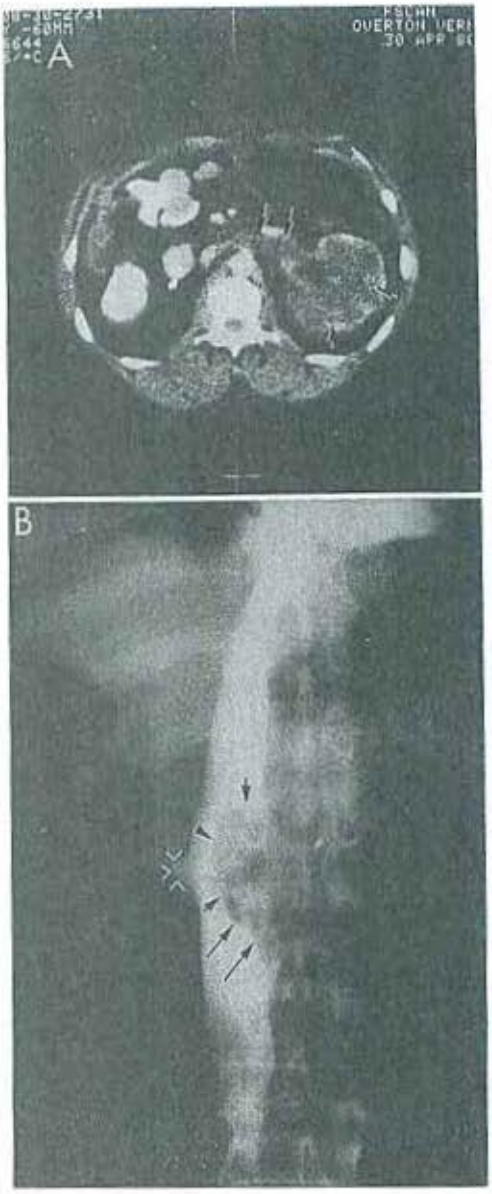


FIG. 15-34
Patient with colon carcinoma metastatic to the kidney with atypical findings. **A,** CT showing enhanced tumor diffusely invading the left kidney *(short arrows)* and left renal vein *(long arrows)*. **B,** Inferior venacavogram of the same patient showing tumor occluding the left renal vein and involving the vena cava *(short arrows)*. The tumor was invading the wall of the vena cava predicted by inferior growth of the tumor below the left renal vein *(long arrows)*. Backflow of contrast into the normal right renal vein is seen *(arrowheads)*. (From Carroll PR, Pellegrini C, Hedgcock MW, et al: Microscopic hematuria, left renal mass with renal vein obstruction and elevated serum level of carcinoembryonic antigen in a 56-year-old man. *J Urol* 1983:129:569-570. Used by permission.)

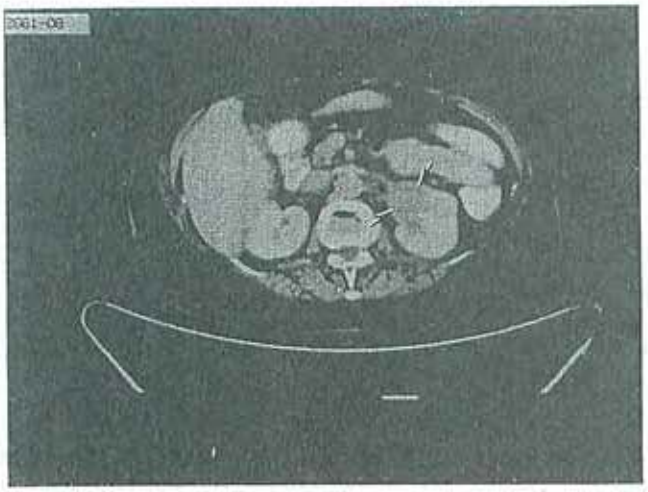


FIG. 15-35
CT of a patient with metastatic lymphoma to the left kidney *(arrows)*.

ken et al., 1983; Jafri et al., 1982). As is the case with leukemia, prognosis is dependent upon the status of the primary disease, and surgical intervention is discouraged.

PRIMARY RETROPERITONEAL TUMORS

Primary retroperitoneal tumors are malignant in approximately 80% of patients (Kutta et al., 1992; Storm and Mahvi, 1991). Benign masses are generally counterparts of related malignant processes and include lipomas, leiomyomas, and other tumors of mesenchymal or neural chest origin, as well as cysts originating from the urogenital ridge (Smith, 1990). The majority of malignant retroperitoneal tumors (75% to 95%) are composed of lymphomas and sarcomas (Smith, 1990; Storm and Mahvi, 1991). The lymphomatous tumors are considered to be systemic processes and are treated accordingly, although aspiration or open biopsy may be necessary to confirm the diagnosis. Retroperitoneal sarcomas are estimated to occur in approximately 100 patients each year (Storm and Mahvi, 1991). Liposarcoma is the most common histologic type, followed by fibrosarcoma, leiomyosarcoma, and other rare types (Storm and Mahvi, 1991). However, the precise histologic type is far less important than tumor grade in determining the prognosis of these patients (Smith, 1990; Sondak et al., 1991).

Most retroperitoneal sarcomas do not produce symptoms until they have become quite large. Poorly localized abdominal pain associated with an abdominal mass or enlargement is typical (Sondak et al., 1991; Storm and Mahvi, 1991). Systemic manifestations such as fever, weight loss, and malaise are common but generally are associated with advanced disease (Smith, 1990). Although various radiologic modalities are used to evaluate patients with suspected retroperitoneal sarcomas, CT is the most valuable single study for determination of tumor size, composition, local extent, and presence of intraabdominal metastases (Sondak et al., 1991; Storm and Mahvi, 1991). MRI scans frequently add complementary information and are particularly useful in the delineation of vascular structures. Angiography and venacavography are also commonly performed. A CT scan of the chest to evaluate the patient for lung metastases should also be done.

The only known effective treatment for retroperitoneal sarcomas is radical resection with wide margins of normal tissue. Frequently, adjacent organs or vascular structures must be resected to achieve normal margins. Only 50% of patients are able to be resected completely, and partial resection or debulking procedures are not effective (Sondak et al., 1991; Storm and Mahvik, 1991). Preoperative chemotherapy or radiation therapy may be useful to reduce tumor size and improve resectability (Fernandez-Trigo and Sugarbaker, 1993; Smith, 1990; Sondak et al., 1991). Adjuvant radiotherapy and chemotherapy have not been shown to be of any benefit either in local control or in survival (Sondak et al., 1991; Storm and Mahvi, 1991). The use of radiotherapy is limited by associated toxicity of the bowel and other intraabdominal organs, and chemotherapy is often poorly tolerated following major resection of multiple organs (Sondak et al., 1991).

The results of surgical therapy are dependent upon tumor grade and extent of resection. Tumors of all grades that are able to be completely resected are associated with a 5-year survival rate of approximately 50% (Storm and Mahvi, 1991). Patients with low-grade (grade I) tumors fare much better following complete resection than those with grade II or III tumors, with 5-year survivals of 74% and 24%, respectively. Unfortunately, even patients who undergo complete resection manifest local recurrence by 10 years in over 90% of cases, and this is the usual cause of death (Storm and Mahvi, 1991). Innovative strategies such as intraperitoneal chemotherapy (Fernandez-Trigo and Sugarbaker, 1993) may ultimately prove to be of benefit, but for the moment only complete surgical extirpation is effective.

BENIGN URETERAL TUMORS

Primary ureteral tumors are rare, accounting for approximately 1% of all upper tract neoplasms (Fein and McClennan, 1986). Of these tumors, approximately 75% to 80% are malignant. The most common benign ureteral tumor is the fibroepithelial polyp (Psihramis and Hartwick, 1993). These benign growths tend to arise from the upper third of the ureter and may resemble a smooth nodule or may be pedunculated, often with a long stalk (Melamed and Reuter, 1993). Histologically they are composed of a

central fibrous core surrounded by normal or hyperplastic benign urothelium (Fein and McClennan, 1986; Melamed and Reuter, 1993). Flank pain and hematuria are the usual presenting symptoms, although prolapse of the polyp through the urethral meatus has been reported (Schiotz, 1990). Radiographically, polyps appear as smooth filling defects that may change position if the tumor is pedunculated. Varying degrees of hydroureteronephrosis are seen, and ureteral intussusception has been described (Fiorelli et al., 1981; Fukushi et al., 1983). Ureteroscopy is often necessary to confirm the diagnosis (Bahnson et al., 1984). Ureteroscopic resection, open ureterotomy with polypectomy, or partial ureterectomy are all viable conservative treatment options if the diagnosis can be confirmed preoperatively; nevertheless, many patients undergo nephroureterectomy for suspected malignancy (Bahnson et al., 1984; Debruyne et al., 1980; Oesterling et al., 1989).

Inverted papillomas of the ureter are rare tumors that are found predominantly in males (Page et al., 1991). These tumors may be asymptomatic or may cause hematuria or flank pain. Grossly, inverted papillomas appear to be smooth or lobulated solid masses and may be pedunculated. Histologically, these tumors are characterized by an endophytic proliferation of benign urothelium surrounding a fibrovascular core (Grainger et al., 1990). The overlying mucosa appears to be normal or attenuated (Melamed and Reuter, 1993). Radiographically, a smooth ureteral filling defect is seen and may be pedunculated (Stower et al., 1990; Page et al., 1991). Ureteral intussusception has also been reported (Duchek et al., 1987). Several reports of inverted papillomas with malignant components have recently been documented, but the significance of these generally low-grade malignant changes is unclear (Grainger et al., 1990; Risio et al., 1988; Stower et al., 1990). If the diagnosis of inverted papilloma without malignant transformation or without stromal invasion can be made preoperatively or at time of surgery, partial ureterectomy is indicated, but continued surveillance is mandatory (Kimura et al., 1987; Stower et al., 1990). Evidence of more extensive malignant transformation should be treated more aggressively.

PRIMARY MALIGNANT URETERAL TUMORS

Primary malignant ureteral tumors account for approximately 1% of all malignancies of the upper urinary tracts (Babaian and Johnson, 1980; Bloom et al., 1970). In multiple series, the peak age of incidence is in the seventh decade, and males are affected two to three times more frequently than females (Anderstrom et al., 1989; Babaian and Johnson, 1980; Batata et al., 1975; Bloom et al., 1970; Hawtrey, 1971; Zoretic and Gonzales, 1983). Ureteral carcinomas are located in the distal third of the ureter in approximately 65% to 70% of cases. Ureteral carcinoma is associated with bladder cancer (synchronous or asynchronous) in approximately 30% to 50% of cases (Ghazi et al., 1979; Kakizoe et al., 1980).

Etiology

The etiologic factors involved in the development of ureteral carcinoma are unknown but are presumed to be similar to those associated with renal pelvic malignancies. Cigarette smoking appears to be a major risk factor, with significant dose-response associations (Jensen et al., 1988; McLaughlin et al., 1992). Abuse of phenacetin-containing analgesics (Jensen et al., 1989; Mahony et al., 1977) and Balkan nephropathy (Cukuranovic et al., 1991; Petronic et al., 1991) are also associated with the development of ureteral carcinomas.

Clinical Presentation and Diagnosis

Gross hematuria is the most common presenting symptom, noted in approximately 60% to 80% of patients (Anderstrom et al., 1989; Bloom et al., 1970; Murphy et al., 1981). Flank or abdominal pain occurs in approximately 20% to 30% of patients, alone or in conjunction with hematuria (Babaian and Johnson, 1980; Bloom et al., 1970; Zoretic and Gonzales, 1983). The pain is usually colicky in nature and is presumed to be due to passage of blood clots or to ureteral obstruction by tumor. Urinary frequency or dysuria occurs in 20% to 50% of patients (Batata et al., 1975; Bloom et al., 1970). A palpable abdominal mass is present in fewer than 10% of patients (Ghazi et al., 1979; Murphy et al., 1981).

Diagnostic modalities employed for suspected ureteral carcinomas are similar to those employed for renal pelvic tumors. On IVP, typical findings include a ureteral filling defect or nonvisualization of the ipsilateral kidney, each seen in approximately 25% to 45% of cases (Anderstrom et al., 1989; Batata et al., 1975; Murphy et al., 1981). Hydroureteronephrosis is seen in 10% to 30% of patients (Batata et al., 1975; Murphy et al., 1981). A normal IVP is seen in a small minority of patients (Anderstrom et al., 1989; Murphy et al., 1981). Again, other common causes of ureteral filling defects should be eliminated.

Cystoscopy in conjunction with retrograde pyelography and collection of cytology specimens by saline barbotage or brush biopsy is crucial in the setting of suspected ureteral carcinoma. Cystoscopy alone is necessary to evaluate the bladder for concurrent urothelial tumors. Occasionally, a tumor may be seen protruding from a ureteral orifice, or hematuria may be localized to one ureter. Retrograde pyelography commonly shows a filling defect within the ureter (Fig. 15-36), complete obstruction of the lumen by tumor,

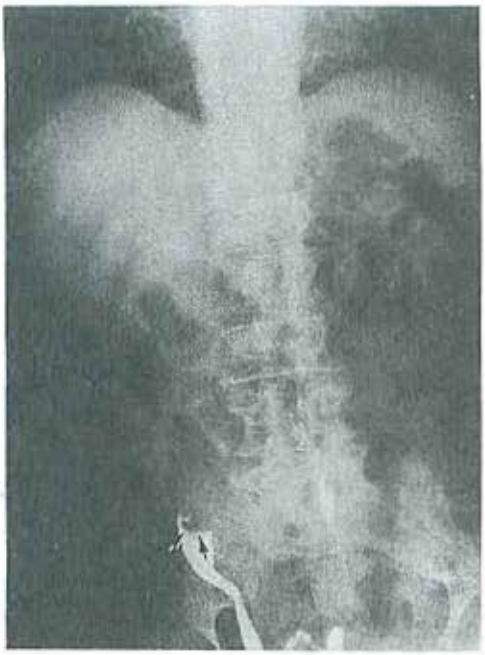


FIG. 15-36
Retrograde ureterogram showing a "wine goblet" sign of a typical low-grade transitional cell carcinoma *(arrows)* of the right ureter. (From Williams RD, Tanagho EA: *Current Surgical Diagnosis and Treatment.* Los Altos, Calif, Lange Medical Publications, 1985, p 864. Used by permission.)

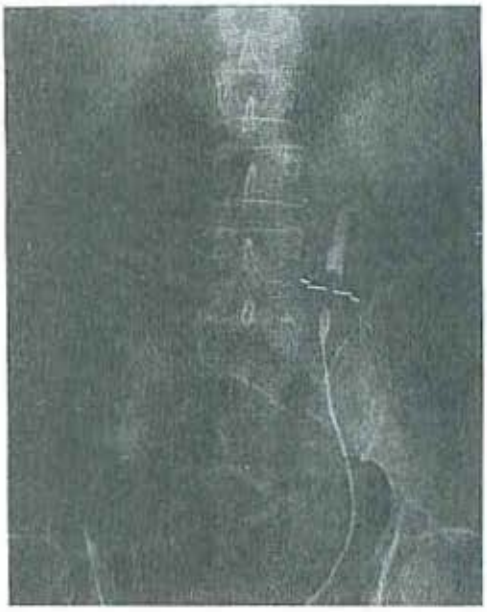


FIG. 15-37
Retrograde ureterogram showing a strictured area *(arrows)* in a patient with a high-grade undifferentiated primary ureteral cancer. The filling defects below the tumor are air bubbles.

or diffuse narrowing or stricture (Fig. 15-37). In combination with IVP, retrograde pyelography can determine the precise site and extent of ureteral involvement in 80% to 100% of patients (Anderstrom et al., 1989; Batata et al., 1975; Bloom et al., 1970; Hawtrey, 1971; Murphy et al., 1981). As previously mentioned in the section on renal pelvic tumors, cytologic examination of saline barbotage or brush biopsy specimens may be diagnostic, particularly for high-grade tumors. Rigid or flexible ureteroscopy is useful for visualization and biopsy of indeterminate ureteral masses (Andersen et al., 1993; Bagley et al., 1987; Blute et al., 1989).

Staging and Prognosis

The staging of ureteral carcinomas is similar to systems used for other urothelial malignancies. Stage O tumors are limited to the ureteral mucosa, stage A (or I) tumors are confined to the submucosa, stage B (or II) tumors invade the ureteral musculature, stage C (or III) tumors involve the periureteral fat, and stage D (or IV) tumors invade adjacent organs or have metastasized locally or distantly (Babaian and Johnson, 1980; Batata et al., 1975). A TNM staging system has also been proposed but has not received widespread acceptance in the United States.

Staging studies for ureteral carcinomas are primarily useful in the determination of locally advanced or metastatic disease, which tends to occur in lung, liver, and bone (Huben et al., 1988). CT scans are commonly performed and may accurately depict tumor extension through the ureteral wall, as well as demonstrate enlarged local lymph nodes or hepatic metastases (Badalament et al., 1992). Consideration should be given to chest CT and bone scans for evaluation of pulmonary or osseous metastases.

As in renal pelvic carcinomas, tumor stage and grade are the most important prognostic indicators in ureteral carcinomas (Babaian and Johnson, 1980; Batata et al., 1975; Bloom et al., 1970; Heney et al., 1981; Huben et al., 1988; Matsuoka et al., 1991). Overall 5-year survival rates for patients with stage O and A tumors are excellent, ranging from 90% to 100% in selected series (Babaian and Johnson, 1980; Batata et al., 1975; Heney et al., 1981). For stage B tumors, 5-year survival rates range from 40% to 80% (Batata et al., 1975; Heney et al., 1981; Matsuoka et al., 1991). Stage C tumors are associated with 5-year survival rates of 15% to 30% (Batata et al., 1975; Heney et al., 1981; Huben et al., 1988; Matsuoka et al., 1991). Metastatic ureteral carcinoma carries a grim prognosis, with several series reporting no 5-year survivors (Babaian and Johnson, 1980; Batata et al., 1975; Heney et al., 1981). Similarly, low-grade tumors are associated with 5-year survival rates of 90% to 100%, compared with 25% for high-grade tumors (Heney et al., 1981; Huben et al., 1988; Matsuoka et al., 1991). Most patients in these series had intermediate-grade tumors, and DNA flow cytometry may offer additional

prognostic information in this setting (Al-Abadi and Nagel, 1992).

Pathology

Transitional cell carcinoma is by far the most common histologic type of primary ureteral carcinoma, accounting for over 90% of tumors. The majority of these are papillary tumors, although solid or sessile tumors and carcinoma in situ are also seen (Melamed and Reuter, 1993). Squamous cell carcinomas are seen in 5% to 10% of patients (Batata et al., 1975; Babaian and Johnson, 1980; Zoretic and Gonzales, 1983). Primary ureteral adenocarcinomas account for approximately 1% of cases. Like renal pelvic carcinomas, ureteral carcinomas are graded by degree of cellular atypia and nuclear anaplasia.

Surgical Treatment

The standard therapy for localized ureteral carcinoma is radical nephroureterectomy with excision of a cuff of bladder mucosa (Gerber and Lyon, 1993). As in carcinoma of the renal pelvis, concerns regarding the multifocality of urothelial tumors, the high rate of recurrence following less than total resection, and the very low incidence of contralateral renal involvement have led to the acceptance of this form of therapy (Seaman et al., 1993). Although no randomized studies have been performed comparing radical nephroureterectomy with more conservative therapies, a more aggressive approach is justifiable in the majority of patients. Advocates of conservative approaches argue that tumor stage and grade are more important prognostic variables than extent of surgical therapy, and that patients with low-grade, low-stage tumors do well with radical or conservative treatment (Babaian and Johnson, 1980; Heney et al., 1981). In particular, patients with noninvasive tumors of the distal ureter managed by distal ureterectomy and ureteral reimplantation may benefit from a conservative approach (Babaian and Johnson, 1980). Clearly, patients with compelling indications such as a functionally or anatomically solitary kidney or bilateral disease are best served with a conservative approach, and this may represent the optimal treatment for patients with low-grade, low-stage tumors of the distal ureter. Patients with higher-grade or higher-stage tumors or with tumors of the upper or middle ureter are best managed by nephroureterectomy. The possibility of undergrading or understaging must also be considered in planning surgical intervention.

Besides partial ureterectomy, a number of endourologic treatment options are available for conservative management of ureteral carcinomas. Ureteroscopic fulguration or resection of ureteral tumors is well established (Gerber and Lyon, 1993). Recently, several investigators have utilized neodynium:YAG or argon lasers to treat selected patients with ureteral carcinomas (Grossman et al., 1992; Johnson, 1992; Kaufman and Carson, 1993; Schmeller and Hofstetter, 1989). Early results are favorable, but it is unclear whether laser irradiation is preferable to fulguration (Gerber and Lyon, 1993). Laparoscopic ureterectomy or nephroureterectomy has also been performed in carefully selected patients (Chandhoke et al., 1993; Kerbl et al., 1993). Again, early results are encouraging, but further follow-up is necessary to assess the benefits and potential complications of this form of therapy. Chemotherapeutic and immunologic agents may also be used topically in the treatment of ureteral carcinomas (Amano et al., 1993; Eastham and Huffman, 1993; Smith et al., 1987).

Periodic surveillance is crucial following therapy for ureteral carcinomas, and is similar to regimens employed for renal pelvic cancers. Regular cystoscopy and examination of urine cytology specimens should be performed in all patients. Following conservative management, patients should undergo imaging studies of the upper tracts, as well as collection of ureteral saline barbotage specimens for cytologic analysis. Periodic ureteroscopy with biopsy should also be considered (Gerber and Lyon, 1993).

Adjuvant Therapy

The results of adjuvant radiation therapy and chemotherapy are similar to those reported for renal pelvic carcinomas. Radiation therapy is capable of decreasing local recurrence rates but has no effect on overall survival (Cozad et al., 1992). Chemotherapeutic regimens are similar to those employed for bladder and renal pelvic cancers. At the present time, too few patients have been treated for meaningful statements regarding efficacy to be made.

SECONDARY MALIGNANT URETERAL TUMORS

The ureters may be secondarily involved by direct extension of tumors originating in contiguous organs or by hematogenous spread. The breast is the most common primary site, followed by the stomach, bladder, colon, cervix, and prostate (Petersen, 1992). Most cases are asymptomatic and are discovered at autopsy (Cohen et al., 1974). Low back pain is the most common presenting symptom (Richie et al., 1979). Hematuria is present in a minority of patients. Evidence of renal insufficiency, usually due to an obstructive nephropathy, is the most significant laboratory finding (Cohen et al., 1974; Richie et al., 1979). There are no pathognomonic radiologic findings. Bilateral obstruction is noted in approximately 30% of cases and usually occurs in the lower third of the ureter. Treatment is predominantly aimed at alleviation of obstruction, both to decrease symptoms and to optimize renal func-

tion for planned adjuvant therapies. Indwelling ureteral stents or percutaneous nephrostomies may be indicated, but more aggressive surgical intervention is discouraged, in light of the overall grim prognosis usually associated with widespread metastases.

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