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Decizie de indexare a faptei de plagiat la poziţia 00086 / 06.04.2014 şi pentru admitere la publicare în volum tipărit

care se bazează pe:

A. **Nota de constatare şi confirmare a indiciilor de plagiat** prin fişa suspiciunii inclusă în decizie.

Fişa suspiciunii de plagiat / Sheet of plagiarism's suspicion		
Opera suspicionată (OS)		Opera autentică (OA)
Suspicious work		Authentic work
OS	SINESCU, I. Tumorile renale parenchimatoase. In: SINESCU, I., (Ed). *Urologie clinică*. Bucureşti: Amaltea, Bucureşti. 1998., p.194-217.	
OA	DREICER, R, WILIAMS, R.D., Renal Parenchymal Neoplams, In: Tanagho, E.A., McAninch, J.W. (Eds.). *Smith's general urology*, 13th edition. Los Altos, California: Lange Medical Book, 1992.	
Incidenţa minimă a suspiciunii / Minimum incidence of suspicion		
p.194: 19s – p.195:13s		p.359: 18s - p.360:26s
p.195: 01d - p.195:43d		p.361: 49s – p.361:44d
p.198: 36d - p.199:10s		p.362: 12d - p.363: 03s
p.206: 19d - p.207: 09		p.366: 18d - p.367: 05s
p.207: 03d – p.207:16d		p.367: 06s – p.367:16s
p.210: 23s – p.210:28s		p.370: 03s – p.370:15s
p.210: 10d - p.210:18d		p.370: 30d – p.370:39d
Fişa întocmită pentru includerea suspiciunii în Indexul Operelor Plagiate în România de la Sheet drawn up for including the suspicion in the Index of Plagiarized Works in Romania at www.plagiate.ro		

Notă: Prin „p.72:00" se înţelege paragraful care se termină la finele pag.72. Notaţia „p.00:00" semnifică până la ultima pagină a capitolului curent, în întregime de la punctul iniţial al preluării.

Note: By „p.72:00" one understands the text ending with the end of the page 72. By „p.00:00" one understands the taking over from the initial point till the last page of the current chapter, entirely.

B. **Fişa de argumentare a calificării** de plagiat alăturată, fişă care la rândul său este parte a deciziei.

Echipa Indexului Operelor Plagiate în România

Asociaţia Grupul pentru Reformă şi Alternativă Universitară (GRAUR)
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Indexul Operelor Plagiate în România
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Fişa de argumentare a calificării

Nr. crt.	Descrierea situaţiei care este încadrată drept plagiat	Se confirmă
1.	Preluarea identică a unor pasaje (piese de creaţie de tip text) dintr-o operă autentică publicată, fără precizarea întinderii şi menţionarea provenienţei şi însuşirea acestora într-o lucrare ulterioară celei autentice.	✓
2.	Preluarea a unor pasaje (piese de creaţie de tip text) dintr-o operă autentică publicată, care sunt rezumate ale unor opere anterioare operei autentice, fără precizarea întinderii şi menţionarea provenienţei şi însuşirea acestora într-o lucrare ulterioară celei autentice.	
3.	Preluarea identică a unor figuri (piese de creaţie de tip grafic) dintr-o operă autentică publicată, fără menţionarea provenienţei şi însuşirea acestora într-o lucrare ulterioară celei autentice.	
4.	Preluarea identică a unor tabele (piese de creaţie de tip structură de informaţie) dintr-o operă autentică publicată, fără menţionarea provenienţei şi însuşirea acestora într-o lucrare ulterioară celei autentice.	
5.	Republicarea unei opere anterioare publicate, prin includerea unui nou autor sau de noi autori fără contribuţie explicită în lista de autori	
6.	Republicarea unei opere anterioare publicate, prin excluderea unui autor sau a unor autori din lista iniţială de autori.	
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8.	Preluarea identică de figuri sau reprezentări grafice (piese de creaţie de tip grafic) dintr-o operă autentică publicată, fără menţionarea provenienţei, fără nici o intervenţie care să justifice exemplificarea sau critica prin aportul creator al autorului care preia şi însuşirea acestora într-o lucrare ulterioară celei autentice.	
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10.	Preluarea identică a unor fragmente de demonstraţie sau de deducere a unor relaţii matematice care nu se justifică în regăsirea unei relaţii matematice finale necesare aplicării efective dintr-o operă autentică publicată, fără menţionarea provenienţei, fără nici o intervenţie care să justifice exemplificarea sau critica prin aportul creator al autorului care preia şi însuşirea acestora într-o lucrare ulterioară celei autentice.	
11.	Preluarea identică a textului (piese de creaţie de tip text) unei lucrări publicate anterior sau simultan, cu acelaşi titlu sau cu titlu similar, de un acelaşi autor / un acelaşi grup de autori în publicaţii sau edituri diferite.	
12.	Preluarea identică de pasaje (piese de creaţie de tip text) ale unui cuvânt înainte sau ale unei prefeţe care se referă la două opere, diferite, publicate în două momente diferite de timp.	

Notă:

a) Prin „provenienţă" se înţelege informaţia din care se pot identifica cel puţin numele autorului / autorilor, titlul operei, anul apariţiei.

b) Plagiatul este definit prin textul legii[1].

> *„ …plagiatul – expunerea într-o operă scrisă sau o comunicare orală, inclusiv în format electronic, a unor texte, idei, demonstraţii, date, ipoteze, teorii, rezultate ori metode ştiinţifice extrase din opere scrise, inclusiv în format electronic, ale altor autori, fără a menţiona acest lucru şi fără a face trimitere la operele originale…".*

Tehnic, plagiatul are la bază conceptul de **piesă de creaţie** care[2]:

> *„…este un element de comunicare prezentat în formă scrisă, ca text, imagine sau combinat, care posedă un subiect, o organizare sau o construcţie logică şi de argumentare care presupune nişte premise, un raţionament şi o concluzie. Piesa de creaţie presupune în mod necesar o formă de exprimare specifică unei persoane. Piesa de creaţie se poate asocia cu întreaga operă autentică sau cu o parte a acesteia…"*

cu care se poate face identificarea operei plagiate sau suspicionate de plagiat[3]:

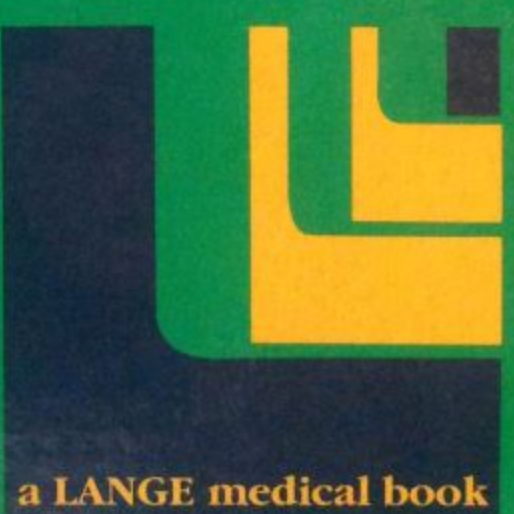
> *„…O operă de creaţie se găseşte în poziţia de operă plagiată sau operă suspicionată de plagiat în raport cu o altă operă considerată autentică dacă:*
> *i) Cele două opere tratează acelaşi subiect sau subiecte înrudite.*
> *ii) Opera autentică a fost făcută publică anterior operei suspicionate.*
> *iii) Cele două opere conţin piese de creaţie identificabile comune care posedă, fiecare în parte, un subiect şi o formă de prezentare bine definită.*
> *iv) Pentru piesele de creaţie comune, adică prezente în opera autentică şi în opera suspicionată, nu există o menţionare explicită a provenienţei. Menţionarea provenienţei se face printr-o citare care permite identificarea piesei de creaţie preluate din opera autentică.*
> *v) Simpla menţionare a titlului unei opere autentice într-un capitol de bibliografie sau similar acestuia fără delimitarea întinderii preluării nu este de natură să evite punerea în discuţie a suspiciunii de plagiat.*
> *vi) Piesele de creaţie preluate din opera autentică se utilizează la construcţii realizate prin juxtapunere fără ca acestea să fie tratate de autorul operei suspicionate prin poziţia sa explicită.*
> *vii) In opera suspicionată se identifică un fir sau mai multe fire logice de argumentare şi tratare care leagă aceleaşi premise cu aceleaşi concluzii ca în opera autentică…"*

[1] Legea nr. 206/2004 privind buna conduită în cercetarea ştiinţifică, dezvoltarea tehnologică şi inovare, publicată în Monitorul Oficial al României, Partea I, nr. 505 din 4 iunie 2004
[2] ISOC, D. *Ghid de acţiune împotriva plagiatului: bună-conduită, prevenire, combatere*. Cluj-Napoca: Ecou Transilvan, 2012.
[3] ISOC, D. *Prevenitor de plagiat*. Cluj-Napoca: Ecou Transilvan, 2014.

thirteenth edition

Smith's General Urology

Emil A. Tanagho
Jack W. McAninch



a LANGE medical book

Renal Parenchymal Neoplasms

21

Robert Dreicer, MD, MS, & Richard D. Williams, MD

BENIGN TUMORS

Prior to routine use of abdominal computed tomography (CT) scans, benign tumors of the kidney were infrequently detected because they rarely cause significant symptoms or morbidity. The liberal use of CT and magnetic resonance imaging (MRI) and the recognition of new syndromes, such as neoplasia associated with acquired renal cystic disease, will increasingly require the clinician to differentiate benign from malignant renal tumors.

Benign renal tumors include adenoma, oncocytoma, angiomyolipoma, leiomyoma, lipoma, hemangioma, and juxtaglomerular tumors.

Renal Adenomas

The adenoma is the most common, benign, solid renal parenchymal lesion (Williams, 1985). These are small, well-differentiated glandular tumors of the renal cortex. They are typically asymptomatic and usually identified incidentally at autopsy after a nephrectomy is performed for an unrelated disease. The true incidence of renal adenomas is unknown; however, 7–22% of patients exhibit them at autopsy (Bonsib, 1985). Despite its classification as a benign tumor, no clinical, histological, or immunohistochemical criteria differentiate renal adenoma from renal carcinoma. Therefore, the incidental finding of a renal adenoma has significant clinical implications for the patient and clinician. Adenomas of any size should be treated as a fortuitous finding of an early renal cancer, and the patient should be evaluated and treated appropriately.

Renal Oncocytoma

Renal oncocytoma has a spectrum of behavior ranging from benign to malignant. Composed of large epithelial cells with finely granular eosinophilic cytoplasm (oncocytes), oncocytomas occur in various organs and organ systems including adrenal, salivary, thyroid, and parathyroid glands as well as the kidney (Klemperl, 1962). An estimated 3–5% of renal tumors are oncocytomas, accounting for approximately 500 cases per year (Lieber and Tsukamoto, 1986). Males are affected twice as often as females.

Renal oncocytomas have a gross appearance significantly different from that of most renal adenocarcinomas. Oncocytomas generally occur within a well-defined fibrous capsule, with tumor tissue rarely penetrating the renal capsule, pelvis, collecting system, or perinephric fat. On cut section, the surface of the tumor is usually tan or light brown. A central stellate scar is often present, especially in larger tumors, but necrosis typical of renal adenocarcinoma is absent. The tumors are usually solitary and unilateral, although several bilateral cases and even multiple sites within one kidney have been reported.

Histologically, well-differentiated oncocytomas are made up of large, uniform cells containing an intensely eosinophilic cytoplasm, which on ultrastructural studies is found to be packed with mitochondria. The cellular origin of renal oncocytes has not been fully elucidated, although some early evidence suggested that oncocytes resemble proximal convoluted tubular cells (Merino and Librelsi, 1982). Recent findings suggest their origin may be a precursor stem cell (Cohen et al, 1988) or the intercalated cells of the collecting ducts (Storkel et al, 1989).

Histological grading of oncocytomas, although a subjective process, has clinical relevance. Grade I neoplasms are composed of closely similar, regular cells possessing rounded smooth nuclei and abundant eosinophilic granular cytoplasm (Fig 21–1). Grade II neoplasms have larger, irregular nuclei and more variation in cell size and configuration (Lieber et al, 1981).

The diagnosis of oncocytoma is predominately pathologic as there are no reliable distinguishing clinical characteristics. Gross hematuria and flank pain occur in less than 20% of patients (Lieber and Tsukamoto, 1986). No characteristic features of the tumors appear on CT, ultrasound (US), intravenous urography (IVU), or MRI. Ambos et al (1978) and Weiner and Bernstein (1977) have described angiographic features of oncocytomas, including the "spoke-wheel" appearance of tumor arterioles, the "lucent rim sign" of the capsule, and a homogeneous capillary nephrogram phase. Unfortunately, these findings are not invariable (Older et al, 1978) and similar findings have been reported in patients with renal cell carcinoma (Maatman et al, 1984).

Among 100 patients with oncocytomas comprised of entirely grade I tumors, no evidence of metastases or deaths due to tumor has been reported in the literature. Higher grade oncocytomas are frequently intermixed with clear cell elements or spindle-cell ele-

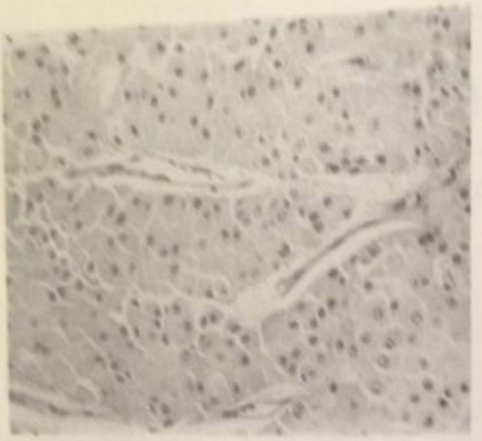


Figure 21–1. Histologic section of a grade I (benign) renal oncocytoma (original magnification, × 100).

ments, which do have metastatic potential and have led to patient demise. This raises the question of whether such tumors are truly oncocytic or are a histological variant of renal cell carcinoma, ie, granular cell carcinoma. The current inability to definitively diagnose oncocytomas preoperatively complicates consideration of renal-sparing surgery (subtotal nephrectomy) in patients with grade I tumors. The use of fine-needle biopsy and flow cytometry have been evaluated, but the results are equivocal (Rodriguez et al, 1984; Rainwater et al, 1986). Therefore, the recommended treatment of the solid renal mass lesion remains radical nephrectomy.

Angiomyolipoma (Renal Hamartoma)

Angiomyolipoma is a rare benign tumor of the kidney seen most often in adults with tuberous sclerosis (adenoma sebaceum, mental retardation, and epilepsy). Approximately 80% of patients with tuberous sclerosis will have angiomyolipomas, typically bilaterally and without symptoms. In patients without tuberous sclerosis, hamartomas usually occur in middle-aged females as solitary, unilateral lesions. As many as 25% of cases can present with spontaneous rupture and subsequent hemorrhage into the retroperitoneum (Wong et al, 1981).

Angiomyolipomas are unencapsulated, yellow-to-gray lesions, typically round to oval, that elevate the renal capsule, producing a bulging smooth or irregular mass (Bennington and Beckwith, 1975). They are characterized by three major histological components: mature fat cells, smooth muscle, and blood vessels. Renal hamartomas may extend to perirenal or renal sinus fat and involve regional lymphatics (Bush et al, 1976) and other visceral organs (Chen and Bauer, 1984). The presence of renal hamartomas in extrarenal sites is a manifestation of multicentricity rather than metastatic potential, as progressive growth and recurrence leading to death has not been described (Mostofi and Davis, 1984).

The diagnosis of renal hamartoma has evolved with the widespread use of US and CT scanning. Arteriography can reveal neovascularity similar to that of renal cancer and is, therefore, not helpful in differential diagnosis. Ultrasonography and CT are frequently diagnostic in those lesions with high fat content. Fat visualized on US appears as very high intensity echoes. Fat imaged by CT has a negative density (−20 to −80 Hounsfield units) which is pathognomonic for angiomyolipomas when observed in the kidney (Fig 21–2) (Pitts et al, 1980). Recently, the use of MRI as a diagnostic tool has been investigated. As with CT scanning, the high fat content makes this lesion suitable for MRI diagnosis (Uhlenbrock et al, 1988); however, as the presence of bleeding in any renal tumor can mimic the typical pattern of angiomyolipoma, MRI should not be considered the diagnostic method of choice until additional clinical experience is gained.

The management of patients with angiomyolipomas is correlated to the presence and severity of symptoms. Patients presenting with life-threatening hemorrhage require immediate nephrectomy. Patients with less severe symptoms or with large tumors should be evaluated by renal angiography prior to consideration of partial nephrectomy, enucleation, or selective renal artery embolization. Asymptomatic patients with unequivocal evidence of a small angiomyolipoma (< 3–5 cm) should only be followed with serial US or CT scans at yearly intervals unless the patient develops symptoms or the tumor enlarges significantly, at which time surgical intervention is warranted (Oesterling et al, 1986).

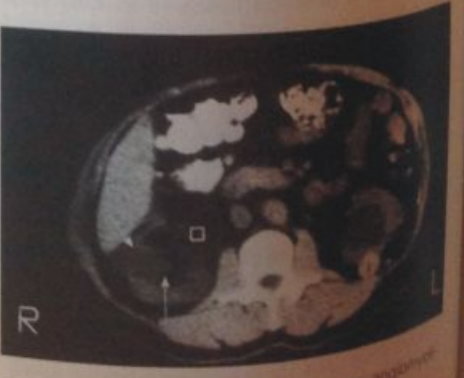


Figure 21–2. Computed tomogram of an angiomyo-

Other Rare Benign Renal Tumors

Several other benign renal tumors are quite rare, including leiomyomas, hemangiomas, lipomas, and juxtaglomerular cell tumors. As a group, the majority of benign tumors are not a diagnostic or therapeutic dilemma since they are rarely encountered during the patient's lifetime. With the exception of juxtaglomerular tumors, there are no features that will unequivocally establish the diagnosis prior to surgery; therefore, the pathologist most often provides the diagnosis following total nephrectomy.

Leiomyomas are the most frequent benign tumors of mesenchymal origin in the renal cortex. These lesions are typically very small (usually several millimeters in diameter) and, thus, are most commonly detected incidentally or at autopsy. Treatment is rarely, if ever, required.

Hemangiomas are small vascular tumors occurring in the kidney with a frequency second only to that in the liver among visceral organs (White and Braunstein, 1946). Multiple lesions in one kidney occur in approximately 12% of cases; however, they are rarely bilateral. They can occasionally be the elusive source of hematuria in an otherwise well-evaluated patient. The diagnosis may be determined by angiography or by direct visualization by endoscopy (Ekelund and Gothlin, 1975).

Renal lipomas are very uncommon deposits of mature adipose cells without evident mitosis that arise from the renal capsule or perirenal tissue. They are seen primarily in middle-aged females and, due to the characteristic CT differentiation of fat, are best detected radiographically on CT scanning.

The juxtaglomerular cell tumor is the most clinically significant member of this subgroup of rare benign tumors because it causes significant hypertension that can be cured by surgical treatment. It is a very rare lesion, with less than 20 reported cases. The tumors originate from the pericytes of afferent arterioles in the juxtaglomerular apparatus and can be shown to contain renin secretory granules. They are typically encapsulated and located in the cortical area. The diagnosis is suspected when there is secondary hyperaldosteronism and is confirmed by selected renal vein sampling for renin (Bonnin et al, 1977). While a subtotal nephrectomy might be possible with adequate radiographic localization, in most reported cases complete nephrectomy has been curative (Bonsib, 1985).

ADENOCARCINOMA OF THE KIDNEY (Renal Cell Carcinoma)

In the USA in 1990, an estimated 18,000 new cases of adenocarcinoma of the kidney will be diagnosed and 9000 deaths will occur from this disease. Renal cell carcinoma (RCC) accounts for roughly 3% of adult cancers and constitutes approximately 85% of all primary malignant renal tumors. Renal cell carcinoma occurs most commonly in the fifth to sixth decade and has a male-to-female ratio of 2:1. The incidence of renal cancer is equivalent between whites and blacks. However, Hispanic men and women have kidney cancer rates more than one-third higher than those of white Americans (Paganni-Hill et al, 1988).

Multiple synonyms have been used to describe renal adenocarcinoma, including hypernephroma, clear cell carcinoma, and alveolar carcinoma. This diversity reflects the historical controversy over the histogenesis of RCC. It was not until 1960 that Oberling and associates, using electron microscopy, demonstrated the similarities between cells from the proximal renal tubule epithelium and RCC.

Etiology

The etiology of renal adenocarcinoma is unknown. There are various etiologic hypotheses encompassing a range of environmental and occupational exposures as well as the influence of diet, hormones, chromosomal abnormalities, and oncogenes. There is a rare familial RCC in addition to the well-recognized increased incidence among patients with von Hippel-Lindau syndrome (cerebellar hemangioblastoma, retinal angiomata, and bilateral RCC), horseshoe kidneys, adult polycystic kidney disease, and acquired renal cystic disease from chronic renal failure.

Cigarette smoking is the only risk factor consistently linked to RCC by both epidemiologic case-control and cohort studies (Paganini-Hill, 1988); up to 30% of RCC cases may be directly linked to smoking (Yu, 1985). Analgesic abuse, primarily from phenacetin-containing products and leading to analgesic nephropathy, also strongly correlates with the development of RCC (Lornoy et al, 1986). An increased incidence of renal adenocarcinomas has been reported among shoe workers, leather tanners, and workers exposed to cadmium, various petroleum products, and asbestos (Paganini-Hill, 1988). Coffee consumption, diuretics, obesity, and exogenous estrogens have been associated with an increased incidence of RCC; however, these associations require additional study.

The familial incidence of RCC has a pattern of inheritance consistent with an autosomal dominant gene with the tumor manifesting a specific karyotypic abnormality (Cohen, 1979). Additional studies have demonstrated a translocation of the cellular oncogenes c-myc and c-ras (Drabkin et al, 1985). Current investigation into nonfamilial RCC is focused on the role of alterations in the short arm of chromosome 3 (Yoshida et al, 1986).

Acquired cystic disease of the kidneys (ACDK) is a well-recognized entity of multiple bilateral cysts in the native kidneys of uremic patients (Dunnill et al, 1977; Hughson et al, 1980). Renal cell carcinoma has been reported to occur in 4–9% of patients with

ACDK (Gardner and Evan, 1984; Bretan et al, 1986). Most RCC cases have been described in patients undergoing hemodialysis, although it has also been reported in association with peritoneal dialysis (Smith et al, 1987) and successful renal transplants (Vaziri et al, 1984). Two recent reviews evaluated the reported incidence of RCC associated with ACDK, and both suggested that it is lower than commonly believed (Fallon and Williams, 1989; Katz et al, 1987).

Pathology

As previously noted, RCC originates from the proximal renal tubular epithelium as evidenced by cellular antigen homology (Wallace and Nairn, 1972). These tumors occur with equal frequency in either kidney and are randomly distributed in the upper and lower poles. Renal cell carcinomas originate in the cortex and tend to grow out into perinephric tissue, causing the characteristic bulge or mass effect that aids in its detection on diagnostic imaging studies. These tumors average 7–8 cm in diameter, but can grow to fill the entire retroperitoneum. Grossly, the tumor is characteristically yellow to orange due to the abundance of lipids, particularly in the clear cell type (25%). The granular cell type (25%) contain cells that have large nuclei which stain darker than the clear cell variety and tend to be more gray to white. The rest of the tumors are mixed cell types, with approximately 2% being a sarcomatoid variety that is typically less pigmented and appears gray or tan. Small tumors are homogeneous on a cut surface, but larger tumors can exhibit hemorrhage, necrosis with secondary cystic areas, and, occasionally, calcification. Renal cell carcinomas do not have true capsules, but may have a pseudocapsule of compressed renal parenchyma, fibrous tissue, and inflammatory cells.

Histologically, RCC is most often a mixed adenocarcinoma containing clear cells, granular cells, and, occasionally, sarcomatoid-appearing cells. Clear cells are rounded or polygonal with abundant cytoplasm which contains cholesterol, tryglycerides, glycogen, and lipids (Fig 21–3). Granular cells contain less glycogen and lipids, and electron microscopy reveals that the granular cytoplasm contains large numbers of mitochondria and cytosomes. Sarcomatoid cells are spindle-shaped and form sheets or bundles. This cell type rarely occurs as a pure form and is most commonly a small component of either the clear cell or granular cell type (or both).

Pathogenesis

Renal cell carcinomas are vascular tumors that tend to spread either by direct invasion through the renal capsule into perinephric fat and adjacent visceral structures or by direct extension into the renal vein. Approximately one-third of patients will have evidence of metastatic disease at presentation (Middleton, 1967). The most common site of distant metastases is the lung. However, liver, bone, ipsilateral adjacent lymph nodes, adrenal gland, and the opposite kidney are frequent sites of disease spread.

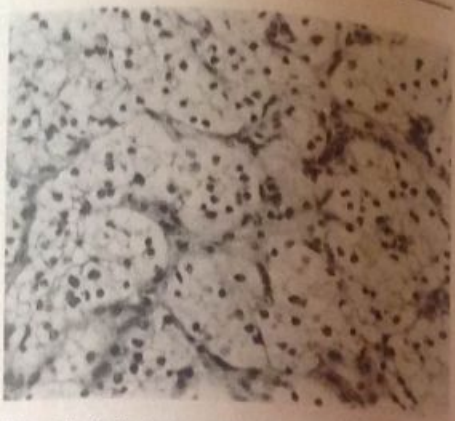


Figure 21–3. Photomicrograph of clear cell renal adenocarcinoma (original magnification, × 125).

Tumor Staging & Grading

A. Tumor Staging: The ultimate goal of staging is to select appropriate therapy and obtain prognostic information. Appropriate studies for a complete clinical staging evaluation include history and physical examination, complete blood count, serum chemistries (renal and hepatic function), urinalysis, chest x-ray (chest CT scan for an equivocal exam), CT scan of abdomen and pelvis, and a radionuclide bone scan (with x-rays of abnormal areas).

Due to the lack of useful diagnostic modalities and effective therapy for metastatic disease, early staging systems were primarily geared to evaluation of operative findings for prognostic information. Flocks and Kadesky (1958) proposed a staging system based on gross physical characteristics of the tumor. Robson (1969) proposed modifications to the Flocks and Kadesky staging scheme taking into account the degree of vascular involvement. It is the latter modified staging system that remains the most widely used system in the USA (Fig 21–4).

Stage I:	Tumor is confined within the kidney parenchyma (no involvement of perinephric fat, renal vein, or regional lymph nodes).
Stage II:	Tumor involves the perinephric fat but is confined within Gerota's fascia (including the adrenal).
Stage IIIA:	Tumor involves the main renal vein or inferior vena cava.
Stage IIIB:	Tumor involves regional lymph nodes.
Stage IIIC:	Tumor involves both local vessels and regional lymph nodes.

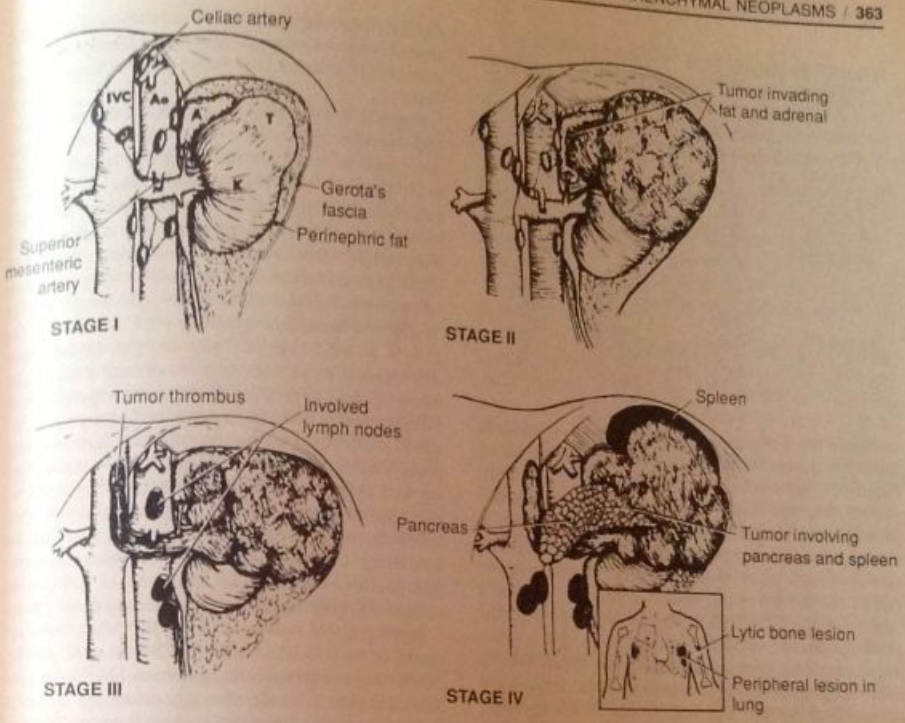


Figure 21–4. Robson staging system for renal cell carcinoma. In stage A, IVC is inferior vena cava; Ao, aorta; A, left suprarenal gland; T, tumor; K, left kidney. (Adapted with permission from Williams RD: Renal, perirenal, and ureteral neoplasms. In: *Adult and Pediatric Urology*, 2nd ed. Yearbook Medical Publishers, 1991.)

Stage IVA: Tumor involves adjacent organs other than the adrenal (colon, pancreas, etc.).

Stage IVB: Distant metastases.

Although the Robson system is easy to use, long-term evaluation of patients, especially with stage III disease, has determined that it does not relate directly to prognosis. Patients with renal vein (or proximal vena cava) involvement (stage IIIA), but without disease extension into perinephric fat and lymph nodes, have survivals comparable to those of patients with disease confined to the kidney (stages I and II) (Siminovitch et al, 1983).

The Tumor-Node-Metastasis (TNM) system more accurately classifies the magnitude of tumor involvement. The TNM classification system for RCC was redefined and simplified in 1987 (Beahrs et al, 1988):

Primary Tumor (T)

(All sizes measured in greatest dimension)

TX: Primary tumor cannot be assessed.

T0: No evidence of primary tumor.

T1: Tumor 2.5 cm or less limited to the kidney.

T2: Tumor more than 2.5 cm limited to the kidney.

T3: Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia.

- **T3a:** Tumor invades adrenal gland or perinephric tissues but not beyond Gerota's fascia.
- **T3b:** Tumor grossly extends into renal vein(s) or vena cava.

T4: Tumor invades beyond Gerota's fascia.

Regional Lymph Nodes (N)

NX: Regional lymph nodes cannot be assessed.

N0: No regional lymph node metastasis.

N1: Metastasis in a single lymph node 2 cm or less.

N2: Metastasis in a single lymph node, greater than 2 cm but not more than 5 cm or multiple nodes none greater than 5 cm.

N3: Metastasis in a lymph node greater than 5 cm.

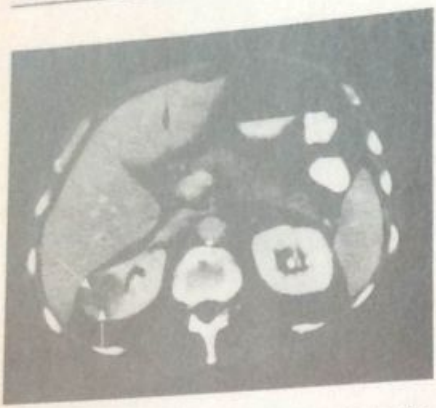


Figure 21–6. Computed tomograph (contrast enhancement) of a renal cell carcinoma **(*arrows*)**.

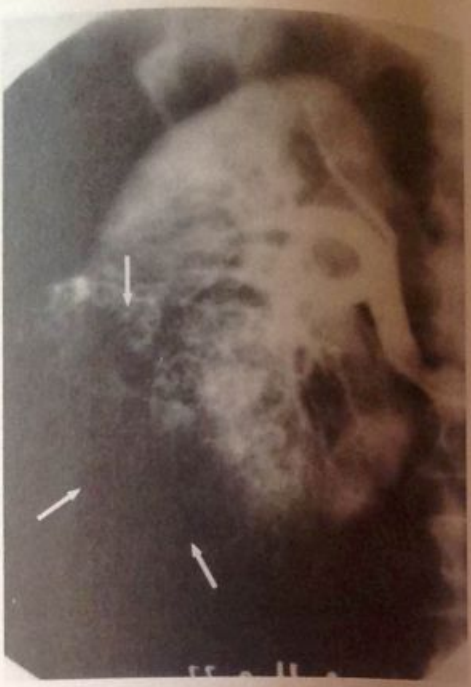


Figure 21–7. Right renal angiogram showing typical neovascularity **(*arrows*)** in a large lower pole renal cell cancer.

on US or IVU, CT scanning has been shown to be at least as accurate as renal angiography in the diagnosis of RCC (Mauro et al, 1982) and in the detection of renal vein and inferior vena cava involvement (Weyman et al, 1980). A typical finding of RCC on CT is a mass that enhances with the use of intravenous contrast media. In general, RCC exhibits an overall decreased density in Hounsfield units as compared to normal renal parenchyma, but will show a heterogenous pattern of enhancement or increased attenuation (slightly decreased from the surrounding parenchyma) when contrast is used (Fig 21–6) (Kosko et al, 1984). In addition to defining the primary lesion, CT scanning is also the modality of choice in staging the patient by visualizing the renal hilum, perinephric space, renal vein and vena cava, adrenals, regional lymphatics, and adjacent organs. In the patient with equivocal chest x-ray findings, a CT scan of the chest is indicated. Patients who present with symptoms consistent with brain metastases should be evaluated with either CT or MRI.

G. Renal Angiography: With the widespread availability of CT scanners, the role of renal angiography in the diagnostic evaluation of RCC has markedly diminished. Angiography is capable of demonstrating neovascularity and arteriovenous fistulae as well as renal vein and vena caval tumor involvement, but is of limited utility in the approximately 10% of patients whose tumors are not hypervascular (Fig 21–7). In addition, angiography is invasive and carries a small but real risk of complications, including hemorrhage, pseudoaneurysm formation at the puncture site, arterial emboli, and contrast-related nephrotoxicity. Furthermore, renal angiography is relatively expensive and may require hospitalization. There remain specific clinical situations where angiography may be of significant utility, for example, guiding the operative approach in the patient with an RCC in a solitary kidney where attempts to perform a partial nephrectomy may be indicated.

H. Radionuclide Imaging: Radionuclide renal scans may occasionally be useful in the evaluation of patients unable to receive contrast material for IVU. Determination of metastases to bones is most accurate by radionuclide bone scan, although the study is nonspecific and requires confirmation with bone x-rays of identified abnormalities to verify the presence of the typical osteolytic lesions. While there is evidence that patients without bone pain and with a normal alkaline phosphatase have a very low incidence of bone metastases (Campbell et al, 1985), the prognosis for patients with osseous metastases is so poor that the discovery of such lesions would almost always contraindicate surgical intervention. Thus, the use of a staging bone scan is still recommended.

I. Magnetic Resonance Imaging (MRI): Experience with MRI in the diagnosis of RCC is limited. In a relatively small, early study in the evaluation of renal masses, Hricak et al (1985) demonstrated MRI to be equivalent to CT in the diagnosis of RCC but more accurate than CT in staging renal cancer, particularly with respect to perinephric extension and degree of renal vein and vena caval involvement (Fig 21–8). Advantages of MRI over CT include the fact

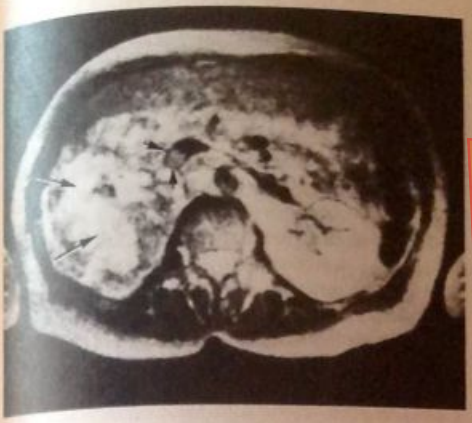


Figure 21–8. Transaxial magnetic resonance image (T_2) of a renal cell carcinoma (***long arrows***) with vena caval tumor thrombus (***short arrows***).

that MRI does not utilize ionizing radiation or require iodinated contrast material. However, MRI is currently more expensive, has specific patient limitations (no pacemakers, etc.), and has not been rigorously compared to other radiologic modalities.

J. Percutaneous Needle Aspiration and Biopsy: Cystic-appearing lesions that remain equivocal after CT scanning should be evaluated by needle aspiration. Cytology is the only reliable test of cyst fluid. Bloody aspirates are not diagnostic, but are associated with malignancy in approximately 25% of patients (Lang et al, 1972). Needle aspiration and biopsy in the preoperative evaluation of patients with an unequivocal solid renal mass is unnecessary unless the patient has another malignancy that could have metastasized to the kidney.

K. Instrumental and Cytologic Examination: Patients presenting with hematuria should be evaluated with cystoscopy. Blood flow from the ureteral orifice identifies the origin of bleeding from the upper tract. Most renal pelvis tumors can be distinguished radiographically from RCC; however, endoscopic evaluation of the bladder, ureters, and renal pelvis is occasionally helpful in making a diagnosis. Additionally, while urine cytology is rarely helpful in the diagnosis of RCC, cytology of urine and renal pelvis washing is frequently diagnostic in renal pelvis tumors.

L. Tumor Markers: As noted above, RCC is associated with numerous biologically active substances. However, at present there are no clinically relevant tumor markers to aid in screening, diagnosis, or evaluating response to therapy.

Differential Diagnosis

When a patient presents with clinical findings consistent with metastatic disease and is found to have a renal mass, a diagnosis of RCC can be straightforward. The majority of patients present with a renal mass discovered after an evaluation of hematuria or pain, or as an incidental finding during a workup of an unrelated problem. The differential diagnosis of RCC includes other solid renal lesions. The great majority of renal masses are simple cysts. Once the diagnosis of a cyst is confirmed by US, no additional evaluation is required if the patient is asymptomatic. Equivocal findings or the presence of calcification warrants further evaluation by CT. There are a wide variety of pathologic entities that appear as solid masses on CT scans and differentiation of benign from malignant lesions is frequently difficult. Findings on CT scan that suggest malignancy include amputation of a portion of the collecting system, presence of calcification, a poorly defined interface between the renal parenchyma and the lesion, invasion into perinephric fat or adjacent structures, and the presence of abnormal periaortic adenopathy or distant metastatic disease (Kosko et al, 1984).

Some characteristic lesions can be defined using CT criteria in combination with clinical findings. Angiomyolipomas (with large fat components) can easily be identified by the low attenuation areas classically produced by substantial fat content. A renal abscess may be highly suspected in a patient presenting with fever, flank pain, pyuria, and leukocytosis, and an early needle aspiration and culture should be performed. Other benign renal masses (in addition to those previously described) include granulomas and arteriovenous malformations. Renal lymphoma (both Hodgkin's disease and non-Hodgkin's), transitional cell carcinoma of the renal pelvis, adrenal cancer, and metastatic disease are additional diagnostic possibilities that may be suspected based on CT and clinical findings.

Treatment

A. Specific Measures:

1. Localized disease–Surgical removal of the early stage lesion remains the only potentially curative therapy available for RCC patients. Appropriate therapy depends almost entirely on the stage of tumor at presentation and, therefore, requires a thorough staging evaluation. The prognoses of patients with stages I, II, and IIIA (renal vein only) are very similar after surgical removal of the kidney and enveloping fascia are accomplished (Skinner et al, 1972a).

Radical nephrectomy is the primary treatment for localized RCC. Its goal is to achieve the removal of tumor to take a wide margin of normal tissue. Radical nephrectomy (Robson 1963) entails en bloc removal of the kidney and its enveloping fascia (Gerota's) including the ipsilateral adrenal, proximal one-half of the ureter, and lymph nodes up to the area of transection of the renal vessels (Fig 21–9).

Various incisions provide optimal access for the

status, referral to institutions with ongoing clinical trials is a preferable approach.

c. Chemotherapy: Renal cell carcinoma is one of the most chemotherapy-resistant solid tumors. Vinblastine is generally believed to be the most active single agent, with response rates (typically short-term partial responses) reported in the 15% range (Harris, 1983). Combination chemotherapy has not been shown to have any significant benefit over single-agent therapy. Impressive single-institution reports of responses to new agents or new combinations of old drugs must be evaluated with caution as experience has consistently demonstrated that the initial high response rates are rarely confirmed when these studies are repeated in multi-institutional trials.

d. Biological response modifiers: The use of metastatic RCC as a model for the investigation of various biological response modifiers (BRMs) is both a consequence of the lack of effective therapy and the long-recognized biologic "eccentricities" of this tumor. Spontaneous regression of metastatic RCC is a well-recognized, albeit rare, event (Freed et al, 1977). While no specific evidence exists, many believe this phenomenon to be immunologically mediated.

A variety of clinical approaches to the immunotherapy of RCC have been tested, including the administration of bacillus Calmette-Guerin (BCG), infusion of autologous tumor cells, and immune RNA. The results from these and other early trials led to the more recent experience with interferons (alpha, beta, gamma) and adoptive cellular therapy with LAK cells and tumor-infiltrating lymphocytes (TIL) plus the lymphokine IL-2.

Studies with various types of alpha interferons have provided evidence for reproducible response rates in 15–20% of patients (Krown, 1987; Quesada et al, 1985). The characteristics of patients responding to interferon include a minimal tumor burden (ie, primary kidney tumor removed), lung metastases only, and an excellent performance status. The observation that most responses are seen in patients with small tumor burdens has led to an ongoing multi-institutional randomized trial comparing adjuvant alpha interferon to no therapy after nephrectomy in patients who are at high risk for disease recurrence (perinephric fat invasion, positive lymph nodes, renal vein involvement). The experience with beta and gamma interferons has been less impressive, although a recent report of a 30% overall response rate in patients receiving low-dose gamma interferon is of interest (Aulitzky et al, 1989).

In the mid-1980s, early reports of impressive responses to IL-2 with and without LAK cells generated a great deal of excitement and clinical activity. At the surgery branch of the National Cancer Institute (NCI), patients with metastatic RCC were treated using IL-2 with and without LAK cells. A recent update of their experience demonstrated overall response rates of 35% and 21%, respectively (Lineham et al, 1989). The IL-2/LAK Extramural Working group using the same dose and schedule of IL-2 and LAK, however, reported a 16% response rate (Fisher et al, 1988). The disparity in results may relate to patient selection factors. In an attempt to define the role of LAK cells in the therapy of metastatic RCC, the NCI is currently conducting a randomized trial comparing IL-2 plus LAK cells to IL-2 alone.

Areas of active investigation include defining populations of more potent and specific lymphocytes (TIL cells, etc.) and combinations of BRMs (IL-2 plus interferons, tumor necrosis factor) as well as work with murine and human monoclonal antibodies.

B. Follow-Up Care: There is no universal agreement on the frequency or studies required in the follow-up care of patients with RCC. Patients who have undergone radical nephrectomy should be seen at regular intervals (3-month periods in the first year is suggested) to evaluate progress and screen for metastatic disease. These follow-up examinations should include a history and physical examination as well as a chest x-ray, complete blood count, and serum chemistries to assess liver and renal function. Additional studies such as CT and bone scans should be done only when clinically indicated (ie, flank or bone pain). Patients with metastatic disease not undergoing therapy need continued follow-up to provide appropriate supportive care.

Prognosis

The prognosis of patients is most clearly related to the stage of disease at presentation. Recent studies report 5-year survival for patients with T1 disease in the 88–100% range and approximately 60% for stages T2 and T3a. As previously noted, patients with stage IIIb have a markedly worsened 5-year survival (15 to 20%). Patients presenting with metastatic disease have a dismal prognosis with 0–20% 5-year survivals (Cherrie et al, 1982; Selli et al, 1983; Bassil et al, 1985; Golimbu et al, 1986). Various other prognostic factors such as the sex of the patient, tumor size, grade, and histological type have been correlated with outcome; however, they are clearly secondary in importance to the stage of disease at presentation.

NEPHROBLASTOMA (Wilms' Tumor)

Nephroblastoma, also known as Wilms' tumor, is the most common solid renal tumor of childhood, accounting for roughly 5% of childhood cancers. Approximately 350 new cases are reported annually. The peak age for presentation is during the third year of life and there is a 1:1 sex ratio. The disease is seen worldwide with a similar age of onset and sex distribution. Tumors are commonly unicentric, but occur in either kidney with equal frequency. In 5% of cases the tumors are bilateral.

Wilms' tumor occurs in familial and nonfamilial forms. The National Wilms' Tumor Study (NWTS) group documented the occurrence of a familial Wilms' tumor in approximately 1% of cases (Breslow and Beckwith, 1982). This tumor is associated with a variety of congenital anomalies including a range of genitourinary abnormalities (eg, cryptorchidism and hypospadias), aniridia, and hemihypertrophy.

Etiology

The mode of inheritance for the familial form of Wilms' tumor is thought to be autosomal dominant with variable penetrance. Knudson and Strong (1972) postulated that the pathogenesis of the nonhereditary form of Wilms' tumor results from two postzygotic mutations in a single cell. In contrast, the hereditary form of the disease arises after one prezygotic mutation and a subsequent mutation resulting in malignant transformation. Cytogenetic characterization of tumor cells from patients with Wilms' tumor has identified the location of this gene to be at the p13 band of chromosome 11 (Francke et al, 1979).

Pathogenesis & Pathology

Wilms' tumors are thought to arise from the metanephric blastema. While a variety of histological elements may be present, the typical Wilms' tumor consists of blastemal, epithelial, and stromal elements in varying proportions (Fig 21–11). Tumors composed of blastema and stroma or blastema alone have been described.

Figure 21–11. Wilms' tumor with characteristic tubular/glomerulid structures and blastema (original magnification, × 40).

The NWTS correlated pathologic specimens with clinical outcome and divided various histological features into favorable and unfavorable prognostic groups. The unfavorable subgroup includes tumors that contain focal or diffuse elements of anaplastic cells, clear cell sarcoma, or malignant rhabdoid tumors (Beckwith and Palmer, 1978; Beckwith, 1983). Anaplastic tumors are characterized by extreme nuclear atypia, hyperdiploidy, and numerous complex translocations.

Grossly, Wilms' tumors are generally large, multilobulated, and gray or tan in color with focal areas of hemorrhage and necrosis. A fibrous pseudocapsule is occasionally seen.

Tumor dissemination can occur by direct extension through the renal capsule, hematogenously via the renal vein and vena cava, or via lymphatic spread. Metastatic disease is present at diagnosis in 10–15% of patients, with the lungs (85–95%) and liver (10–15%) the most common sites of involvement. Regional lymphatics are involved in as many as 25% of patients. Metastases to bone and brain are uncommon.

Tumor Staging

The NWTS staging system is most widely used and is based upon surgical and pathological findings. The original classification was used in the first and second NWTS trials and was modified for NWTS III (D'Angio et al, 1989).

Stage I: Tumor limited to kidney and completely excised. The surface of the renal capsule is intact. Tumor was not ruptured before or during removal. There is no residual tumor apparent beyond the margins of resection.

Stage II: Tumor extends beyond the kidney but is completely removed. There is regional extension of the tumor, ie, penetration through the outer surface of the renal capsule into perirenal soft tissues. Vessels outside the kidney substance are infiltrated or contain tumor thrombus. The tumor may have been biopsied or there has been local spillage of tumor confined to the flank. There is no residual tumor apparent at or beyond the margins of excision.

Stage III: Residual nonhematogenous tumor confined to abdomen. Any one or more of the following occur:

a. Lymph nodes on biopsy are found to be involved in the hilus, the periaortic chains or beyond.

b. There has been diffuse peritoneal contamination by tumor such as spillage of tumor beyond the flank before or during surgery, or by tumor growth that

...that incorporates surgery, radiation therapy, and chemotherapy.

A. Surgical Measures: For patients with unilateral kidney involvement deemed surgically resectable (tumors not crossing the midline or involving adjacent visceral organs), radical nephrectomy via a transabdominal incision is the procedure of choice.

Retroperitoneal lymph node dissection is not of proven value and is not recommended. However, biopsy of regional lymphatics (renal hilum and paraaortic nodes) and careful examination of the opposite kidney and the remainder of the abdomen provide crucial data for staging and prognosis. Tumor extending into the vena cava should be removed unless there is evidence of total obstruction. A major point of emphasis during surgical extirpation is to avoid spillage as there is evidence that this increases abdominal recurrence of disease.

The child with bilateral Wilms' tumor, like the adult with bilateral RCC, requires an individualized approach. Patients with favorable histology (FH) tumors can frequently be managed with preoperative chemotherapy followed by renal-sparing surgery. In those patients for whom preoperative chemotherapy is planned, a biopsy for diagnosis and staging is indicated (Blute et al, 1987). In some centers, needle aspiration biopsy has proven to be a reliable diagnostic tool when evaluated by experienced pathologists (Hanash et al, 1989). In patients with unfavorable histology (UH), the therapeutic approach consists of aggressive surgery followed by chemotherapy and radiation therapy.

B. Radiation Therapy: Wilms' tumor has long been recognized as a radiosensitive tumor. However, despite the proven efficacy of radiation therapy in children, its use is complicated by its potential for growth disturbances and recognized cardiac, pulmonary, and hepatic toxicities. The development of effective chemotherapy combinations has practically replaced radiation therapy in the preoperative setting. The first and second NWTS trials demonstrated that postoperative radiotherapy was not required for patients with favorable histology stage I disease. The recently published NWTS III failed to show an advantage for postoperative radiotherapy in patients with favorable stage II disease and demonstrated that the relapse rate of patients with stage III disease was no different for patients receiving 1000 cGy compared to the traditional 2000 cGy (D'Angio et al, 1989). Postoperative radiation is recommended for patients with unfavorable histologies of any stage and for stage IV disease.

C. Chemotherapy: Wilms' tumor is a chemosensitive neoplasm and is responsive to various single agents including actinomycin D, vincristine, doxorubicin, cyclophosphamide, and cisplatin. The first NWTS study demonstrated that the combination of actinomycin D plus vincristine was more effective in reducing the risk of relapse than either drug used alone (D'Angio et al, 1976). In an orderly fashion, the NWTS has utilized each successive study to evaluate new approaches to improving response and decreasing toxicity. Summarized below by stage and histology are the results of the NWTS III and the standard therapy arms used in the NWTS IV currently in progress:

Stage I FH/UH:	Chemotherapy with actinomycin D plus vincristine for 6 months. No radiotherapy.
Stage II FH:	Chemotherapy with actinomycin D plus vincristine for 15 months. No radiotherapy.
Stage III FH:	1000 cGy postoperative radiotherapy followed by actinomycin D, vincristine, and doxorubicin for 15 months.
Stage IV FH:	2000 cGy to flank, 1200 cGy to lungs postoperatively followed by actinomycin D, vincristine, and doxorubicin for 15 months.
Stage II–IV UH:	Randomization from NWTS continues. Evaluating the benefits of adding cyclophosphamide to actinomycin D, vincristine, and doxorubicin after postoperative radiotherapy.
Stage V FH/UH:	Therapy is individualized (see text).

Prognosis

The multimodality approach to the treatment of children with Wilms' tumors has significantly improved outcomes. The NWTS III reported overall relapse-free survival and survival to be 85% and 92.4%, respectively. The most important negative prognostic factors remain the unfavorable histological subtypes (clear cell sarcoma, rhabdoid, and anaplastic tumors). While the addition of doxorubicin in NWTS III significantly improved the 2-year survival for patients with clear cell sarcomas (61.5 to 90.3%), it did not impact the survival of children with rhabdoid tumors. Analysis of patients with bilateral Wilms' tumors registered with NWTS II and III revealed a 3-year survival rate of 82% (Blute et al, 1987).

Future challenges include improvements in therapy for patients with anaplastic tumors (stages II–IV) and rhabdoid tumors, and efforts to improve outcomes in favorable histology tumors while decreasing both short-term and late toxicities.

SARCOMA OF THE KIDNEY

Primary sarcomas of the kidney are rare, with a reported incidence ranging from 1 to 3% of all malignant renal neoplasms (Farrow et al, 1968; Srinivas et al, 1984). Renal sarcomas are most commonly