Chapter 1
Kidney

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REASONS FOR INTRAOPERATIVE PATHOLOGY CONSULTATION

Intraoperative pathology consultation (IPC) for kidney lesions is relatively infrequent.[1] However, it has a definite role in the surgical management of these lesions.[2] Gross and frozen section (FS) consultations were requested in 10.8% and 12.2%, respectively, for 6,907 radical nephrectomy specimens; whereas the percentages were 11.2% and 53.8%, respectively, for 600 partial nephrectomy specimens.[2] The possible reasons for intraoperative pathology consultation are listed in Table 1.1. The indications for IPC are not well defined and probably reflect personal preference, institutional tradition, and the types of hospitals.[2]

GROSS CONSULTATION

Clinical Background

Request from the surgeon to confirm the presence of a renal tumor is the most frequent type of gross consultation.[2] Most renal tumors are clinically assumed to be renal cell carcinoma (RCC) and are treated by radical nephrectomy, a decision mainly derived from clinical and imaging findings rather than from a tissue diagnosis. Usually only gross consultation is requested to confirm the lesion in the radical nephrectomy specimen. FS diagnosis of the tumor is usually not needed since it does not alter the type of surgical treatment. Gross consultation is also often requested for a predominantly hilar tumor to see whether it is urothelial carcinoma, for which the surgical treatment is different from RCC (*see also* Urothelial Carcinoma below).

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TABLE 1.1 Reasons for intraoperative consultation for 325 consecutive renal specimens (materials from the Methodist Hospital and VA Medical Center, Houston, Texas).

Gross consultation	*62%*
Gross identification of renal or pelvic mass in the nephrectomy specimens	62%
Frozen section consultation	*38%*
Definitive diagnosis for a renal mass	5%
Diagnosis of a solid renal mass in unusual clinical or radiological settings	7%
Clinically suspected urothelial carcinoma and ureteral surgical margin	3%
Diagnosis of a cystic renal mass	5%
Surgical margin and diagnosis for tumors removed by partial nephrectomy	8%
Diagnosis of multiple renal masses	2%
Diagnosis of extrarenal masses or enlarged lymph nodes during nephrectomy	5%
Check for glomeruli in medical renal biopsies	1%
Status of kidneys donated for transplantation	3%

Specimen Handling

The submitted specimen is usually radical nephrectomy specimen. This specimen usually includes kidney, perirenal adipose tissue, Gerota fascia, renal pelvis, and a portion of ureter of variable length. Adrenal gland may or may not be included. We recommend the following way to handle a radical nephrectomy specimen. The intact specimen should be initially inspected for the blood vessels (usually marked with a tie or a metal clip by surgeons in the operating room) at the renal sinus for possible tumor thrombus, followed by identification of an usually short segment of ureter included in the specimen, which should be probed up to the pyelocalyceal system. The specimen is then bivalved through the renal pelvis guided by the ureteral probe for an accurate exposing of the renal sinus with the pyelocalyceal system, the renal parenchyma and the cut surface of the tumor. For an eccentric lesion, the original cut may not suffice, but additional cuts parallel to the original or perpendicular to the original sections should provide gross details. Peeling off the perinephric fat or bivalving the kidney from the perinephric side should be avoided since the relationship of the tumor and adjacent structures and perirenal fat invasion by the tumor may be distorted and cannot be accurately evaluated.

Interpretation

The above approach often clearly reveals the renal lesion with its cut surface as well as its relationship to the adjacent renal parenchyma, renal pelvis, renal sinus, and perirenal soft tissue. As a general rule, the location of the tumor, its gross appearance, and its tinctorial characteristics can often suggest the histological type, even without FS (Table 1.2). The epicenter of the tumor is particularly helpful for the differential diagnoses of tumors that involve predominantly the renal medulla/renal pyelocalyceal area. Tumors in this area raise the question of collecting duct carcinoma and high-grade urothelial carcinoma involving the renal medullary parenchyma. Not uncommonly, large tumors in this area may extend into the soft tissue in the renal sinus, and may involve the renal hilar vessels. The relationship of the tumor to the pyelocalyceal wall should be noted. Low-grade urothelial carcinomas typically appear as shaggy thickening of pelvic wall with protrusion of the tumor into the pelvic lumen (Fig. 1.1).

Gross observation to evaluate all the surgical margins (soft tissue, vascular, and ureteral) for tumor involvement should be done first. Submission of tissue for FS evaluation for these margins will vary depending on the opinion of the surgeon or the pathologist. It is usually not requested since involvement of these margins is very rare and in such case, the margin involvement is usually obvious intraoperatively as well as grossly.

If RCC is confirmed microscopically, additional surgery is usually not performed. However, if urothelial carcinoma is diagnosed, resection of the rest of the ureter with a cuff of bladder wall (nephrourerectomy) will be performed, and the surgeon may request FS for the distal surgical margin of this specimen (*see below*).

FROZEN SECTION TO ESTABLISH A DEFINITIVE DIAGNOSIS OF A RENAL MASS

Clinical Background

Most large and centrally located solid renal tumors are assumed to be RCC and are treated by radical nephrectomy, usually followed by a gross consultation.[3] FS is, however, sometimes requested for the following reasons: (1) To confirm the surgeon's clinical impression and provide the surgeon with additional information about the nature of the tumor for an informative discussion with the patient's family immediately after surgery; (2) To facilitate the decision on nodal dissection.

TABLE 1.2 Differential diagnosis of histological types of renal cell carcinoma.

	Gross features	Frozen section features
Clear cell	Well circumscribed with pseudocapsule; protruding from the renal cortex; variegated cut surface (solid, cystic, myxoid, hemorrhagic); bright yellow areas corresponding to the clear tumor cells; white tan areas corresponding to granular tumor cells	Cells with clear cytoplasm, low nuclear grade, well-defined cell membrane, forming sheets, nests, tubules, acini, ill-defined papillary fronds, and cysts containing red blood cells or eosinophilic fluid, separated by thin-walled blood vessels. Sometimes admixed with cells with granular eosinophilic cytoplasm and higher nuclear grade
Papillary	Well circumscribed with a fibrous capsule; usually confined to the kidney parenchyma; more often multifocal than other types; variegated cut surface, yellow (due to abundant macrophages within tumor), gray-tan, brown; often cystic/hemorrhagic	*Type 1*: Papillary and tubular structures lined by cells with rather scant, partially clear or granular cytoplasm, and low-grade nuclei; macrophages often within the papillary cores *Type 2:* Predominantly papillary structures lined by cells with more abundant eosinophilic cytoplasm, and higher nuclear grade, large nucleoli, without abundant macrophages in the papillary cores
Chromophobe	Well circumscribed; solid homogeneous tan to brown cut surface; focal hemorrhage or necrosis, or central scar in few cases	Three cell types: cells with abundant finely reticulated cytoplasm; cells with less abundant granular eosinophilic cytoplasm, with or without perinuclear halo; all with well-defined cell membrane; often low nuclear grade, irregular nuclear contour, and binucleation; forming solid or trabecular growth separated by thick-walled blood vessels (vs thin-walled blood vessels in clear cell RCC)

Collecting duct	Small tumor usually at medulla; larger tumor at any location; usually large tumor, gray white firm cut surface; indistinct border, often widespread invasion (adrenal gland, perirenal fat, renal sinus, renal pelvis)	Cells with amphophilic cytoplasm, large highly atypical nuclei; prominent nucleoli; forming complex tubulopapillary structures, microcysts with intracystic papillation; constant desmoplastic stroma; extensive infiltration of renal parenchyma; sometimes cytoplasmic mucin; sometimes carcinoma in situ in collecting ducts
Sarcomatoid	Sarcomatoid changes reflect in focal firm, white tan areas, against the background of one of the four above RCC types. The whole tumor may appears that way in case the sarcomatoid component overgrows and obliterates the parental RCC	Spindle or rarely round cells, atypical nuclei; different patterns, e.g., fibrosarcomatous, malignant fibrous histiocytomatous, undifferentiated; rarely heterologous sarcomatous components; often associated with the parental RCC

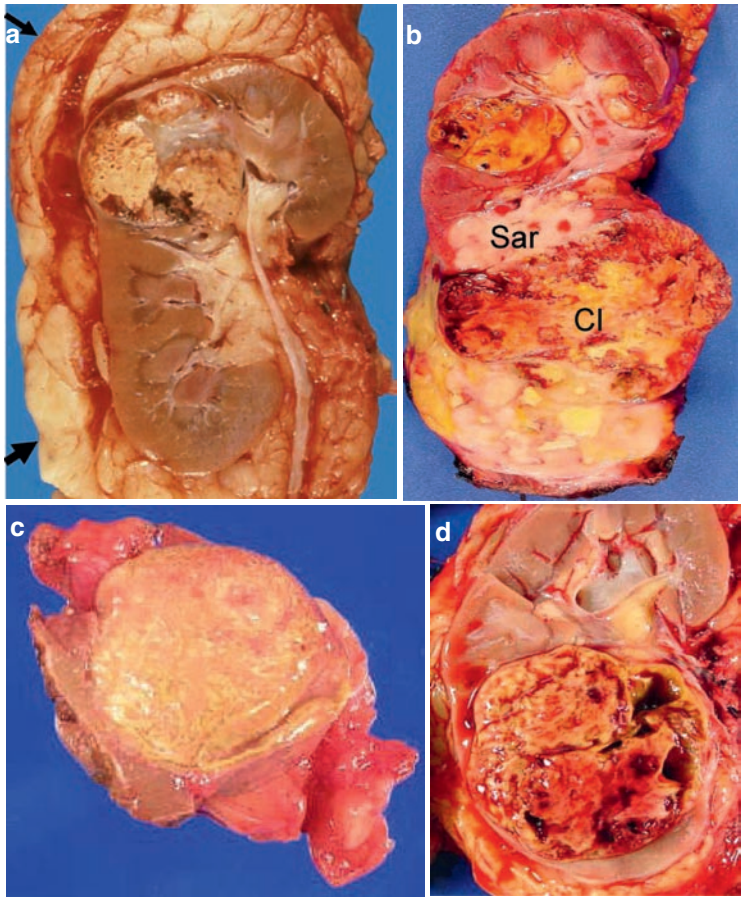


FIGURE 1.1 *Gross appearance of RCC*. (**a**) *Clear cell RCC*. Radical nephrectomy specimen bivalved to show ureter, pyelocalyceal system, renal sinus, kidney, tumor, perirenal adipose tissue, and fascia of Gerota (*arrows*); this fascia encases the specimen but is not grossly apparent due to its thinness. The tumor shows brightly yellow areas, with focal hemorrhagic, cystic, or myxoid changes. (**b**) *Sarcomatoid RCC* [white tan areas (Sar)] arising from a clear cell RCC (Cl). (**c**) *Papillary RCC, type 1* (partial nephrectomy): Circumscribed solid homogeneous tan cut surface. (**d**) *Papillary RCC, type 2*: Encapsulated tumor with yellowish solid areas and cystic changes.

Some features of the primary RCC (high stage, high nuclear grade, large size, a sarcomatoid component, and histological tumor necrosis) may indicate a higher chance of nodal metastasis.

FS may be requested in this context[4]; and (3) To establish a definite diagnosis for a solid renal mass with clinical or imaging features that are unusual for RCC. In the latter situation, lesions other than RCC are not infrequent and, in our experience, may include malakoplakia, xanthogranulomatous pyelonephritis (XGP), renal lymphoma, metastatic tumor, angiomyolipoma (AML), large renal medullary fibroma, leiomyoma, perirenal mesothelial cyst, subcapsular hematoma, adrenal cortical carcinoma extending to kidney, or mixed epithelial and stromal tumor of the kidney[3]; (4) To confirm the diagnosis of renal pelvic urothelial carcinoma, for which excision of the rest of the ureter is indicated (*see below*); (5) To establish a definitive diagnosis of a renal mass, which may dictate the choice among conservative treatment, partial nephrectomy, or radical nephrectomy[5]; and (6) To confirm the involvement of the surgical margins (which is exceptional).

Specimen Handling

The handling is similar to those submitted for gross consultation (*see above*). After the cut surface of the lesion is examined, areas of different gross appearance should be sampled for FS. Attention should be paid to avoid necrotic or hemorrhagic area when choosing tissue for FS.

Interpretation

Discussed below are selected differential diagnostic problems derived from our experience or literature.

The Diagnosis of RCC and Its Histological Subtypes

The 2004 WHO classification recognizes five major types of RCC: clear cell, papillary, chromophobe, collecting duct, and unclassified RCC. Sarcomatoid RCC is not considered a specific histological type and is regarded as a dedifferentiated element of one of these above types, since the sarcomatoid component can be seen in all the above recognizable histological types of RCC.[6] Each of these types of RCC has characteristic features that enable an accurate diagnosis by gross examination alone or combined with FS (Table 1.2 and Figs. 1.1–1.10). Since RCC displays a broad morphological spectrum and there are unclassified RCCs as well as hybrid tumors (two or more recognizable cell types), its histological classification on FS diagnosis may not be possible in some cases. Deferment on histological typing in these cases is appropriate and does not impact patient care. Histological typing of RCC is usually not a

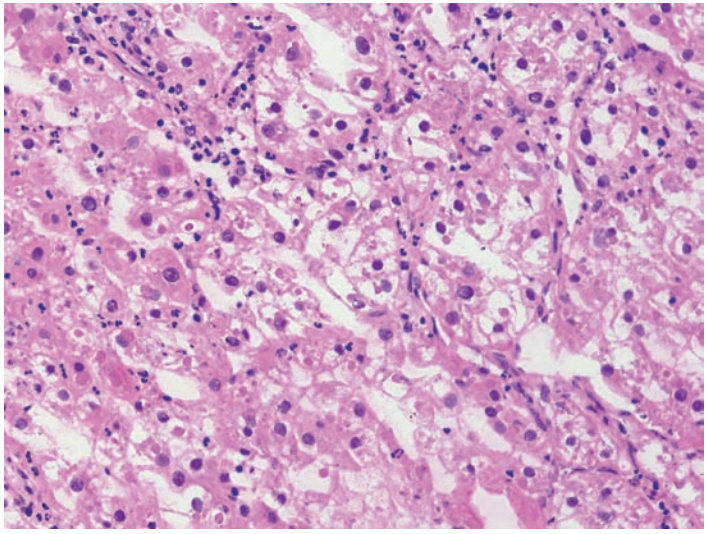


FIGURE 1.2 *Clear cell RCC, high nuclear grade.* Typical tumor cells with abundant granular, clear, or mixed cytoplasm, and large nuclei. Stromal vascularity may not be obvious.

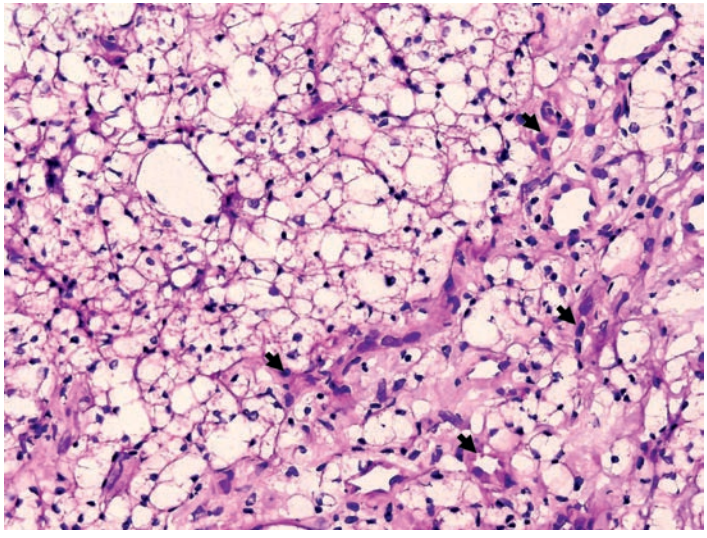


FIGURE 1.3 *Clear cell RCC, low nuclear grade*. Tumor cells with small hyperchromatic nuclei, abundant clear cytoplasm, and well-defined cell border. Prominent stromal vascularity (*arrows*) is characteristic.

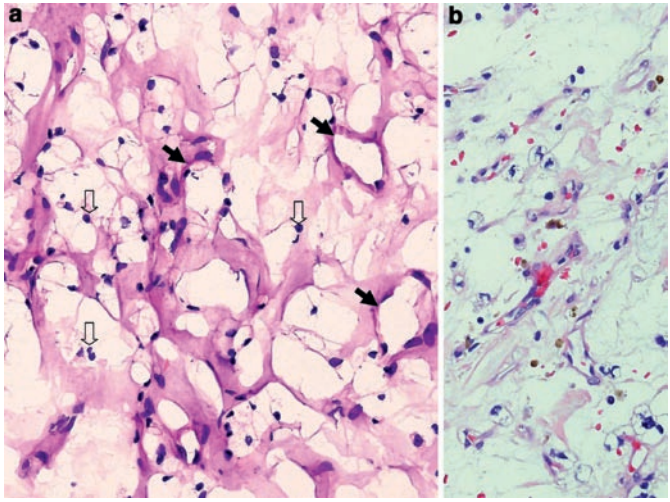


FIGURE 1.4 *Clear cell RCC, low grade*. (**a**) The tumor may be composed mostly of areas with abundant thin-walled blood vessels with prominent endothelial cells (*solid arrows*). Isolated tumor cells may be present (*open arrows*) but are not obvious in FS. This type of stroma strongly suggests the diagnosis of clear cell RCC. (**b**) The corresponding permanent section shows isolated tumor cells with clear cytoplasm.

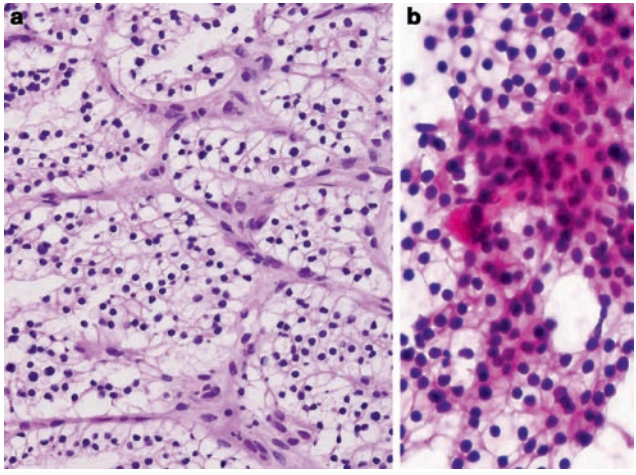


FIGURE 1.5 *Clear cell RCC, low grade*. FS (**a**) and touch prep (**b**). Fixation in formalin, rather than alcohol, and longer staining with hematoxylin enhance the cell membrane and the clear appearance of the cytoplasm.

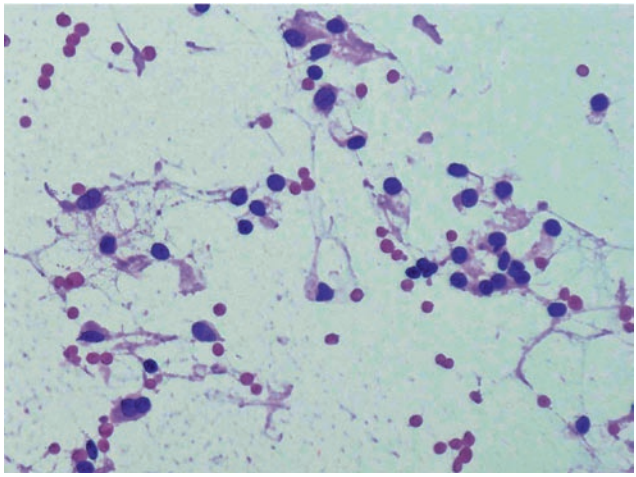


FIGURE 1.6 *Clear cell RCC, low grade*. In touch prep, the tumor cells may appear as bare hyperchromatic nuclei with artifactual loss of the clear cytoplasm. This artifact, which is quite frequent for the cystic variant, is characteristic for low-grade clear cell RCC and should suggest the diagnosis.

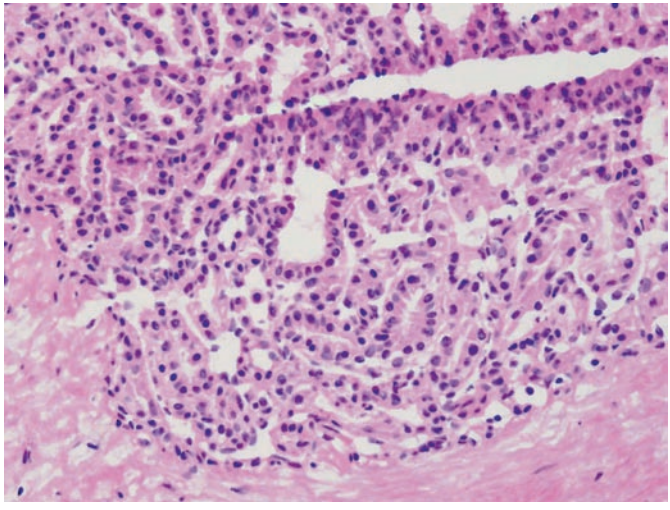


FIGURE 1.7 *Papillary RCC, type 1*. The tumor is encapsulated. In spite of the name, it can be composed mostly of tubules, as seen here. The tumor cells typically display low nuclear atypia, and scant cytoplasm.

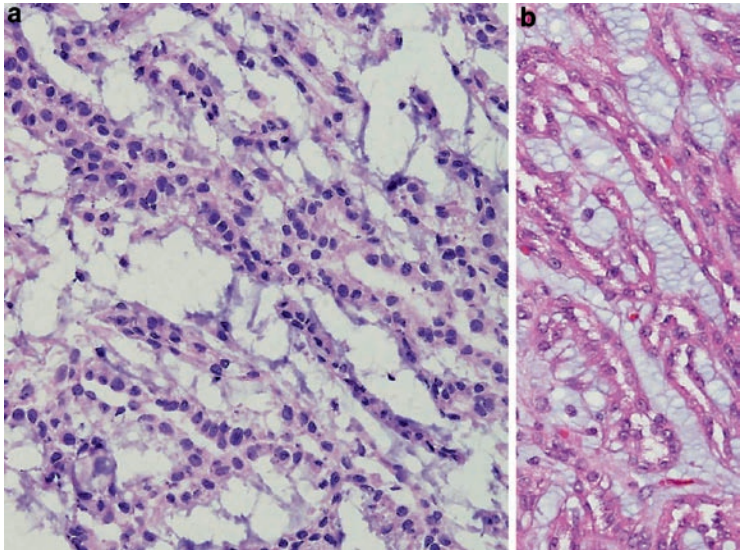


FIGURE 1.8 *Mucinous spindle and tubular cell carcinoma.* (**a**) The tumor cells display low nuclear grade and scant cytoplasm forming tubules, which can simulate papillary RCC, type 1. The stromal mucin is characteristic, but as shown here, may be inconspicuous in FS. (**b**) The corresponding permanent section displays typical features including abundant stromal mucin.

determinant for intraoperative treatment and RCC typing is usually not requested by the surgeon. Nevertheless, one should be familiar with the gross and FS spectrum of various RCC histological types to facilitate their identification and rule out potential mimickers.

The features of RCC histological types in FS reflect their morphological spectrum in permanent sections (Table 1.2 and Figs. 1.1–1.10). FS may create artifacts, leading to diagnostic dilemma. Touch preparation often provides excellent cytological features of tumor cells, complementary to FS (Figs. 1.1–1.10).

Differential Diagnoses of Clear Cell RCC, XGP, and Malakoplakia

Although these entities may show subtle imaging or gross differences among them (Table 1.3 and Figs. 1.11 and 1.15), a definitive diagnosis usually requires FS. An FS diagnosis depends on recognizing the cell type characteristic for each entity.[7,8] The clear cells in solid areas

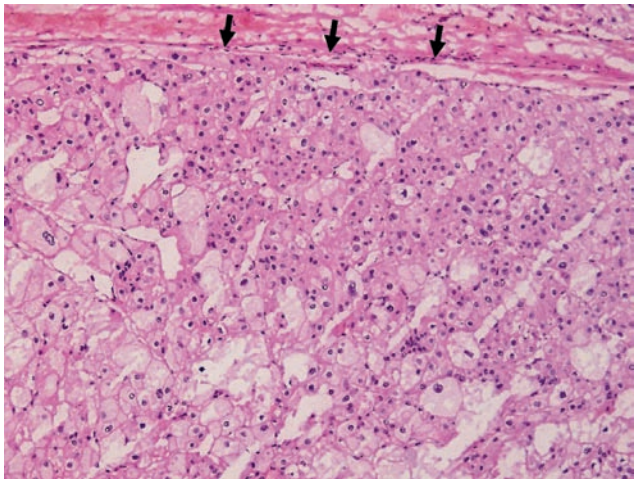


FIGURE 1.9 *Chromophobe RCC*. This field shows all three different cell types (reticular, eosinophilc with perinuclear halo, and eosinophilic without perinuclear halo; *see also* Fig. 1.10) described in chromophobe RCC, but one type may dominate in an individual tumor. Tumor encapsulation (*arrows*) and well-defined cell membrane are characteristic.

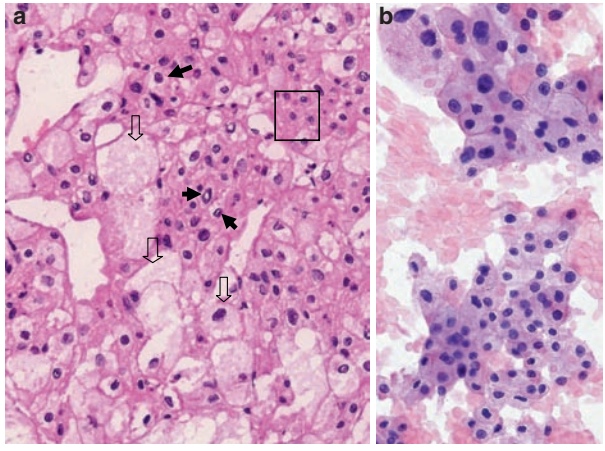


FIGURE 1.10 *Chromophobe RCC*. (**a**) Characteristic features: Three cell types [reticular with abundant cytoplasm (*open arrows*), eosinophilic with perinuclear halo (*solid arrows*), or without perinuclear halo (*square*)], well-defined cell membrane, and irregular nuclear contour. (**b**) Several of these features are seen in touch prep.

TABLE 1.3 Clear cell renal cell carcinoma (*RCC*) vs xanthogranulomatous pyelonephritis (*XGP*) vs renal malakoplakia.

	Gross	Microscopic
RCC	Well circumscribed, yellow cut surface with focal hemorrhagic, necrotic or myxomatous degeneration; +/– perirenal extension; renal parenchyma and pyelocalyceal system usually normal	Clear or clear/granular cells in sheets, with little or no intervening fibrosis or chronic inflammation. Solid, alveolar, cystic, pseudopapillary growth patterns; prominent anastomosing complex vascular stroma
XGP	Rarely circumscribed, often diffuse and poorly demarcated; yellow and white variegated cut surface with often fibroinflammatory changes; constant extension to perirenal or peripelvic soft tissue; renal parenchyma usually atrophic; frequent distortion of the pyelocalyceal system	Sheets of "xanthoma" cells with fine vacuolated cytoplasm admixed with fibrosis, chronic, and acute inflammation
Malakoplakia	Similar to XGP	Sheets of von Hanssemann cells with diagnostic Michaelis-Guttmann bodies; with or without admixed fibrosis and chronic and/or acute inflammation

of RCC usually appear intact with preserved cell membrane and characteristic clear or clear/granular cytoplasm separated by a rich vascular network recognizable in FS (Figs. 1.2–1.6). Difficulty may be encountered when the delicate cytoplasm of the tumor cells disintegrates and results in bare nuclei (Figs. 1. 4 and 1.6); this is especially true for low-grade tumor cells from cystic areas. Alternatively, during FS, the "clear" cytoplasm of tumor cells may display a faint eosinophilia. Fixing the frozen tissue sections in formalin for 1 min and routine staining but with longer staining with hematoxylin (2 min) can better delineate the cell membrane and accentuate the clear cytoplasm (Fig. 1.5).[9] The features of clear cells can be also well recognized in touch preparation (Figs. 1.5 and 1.6).

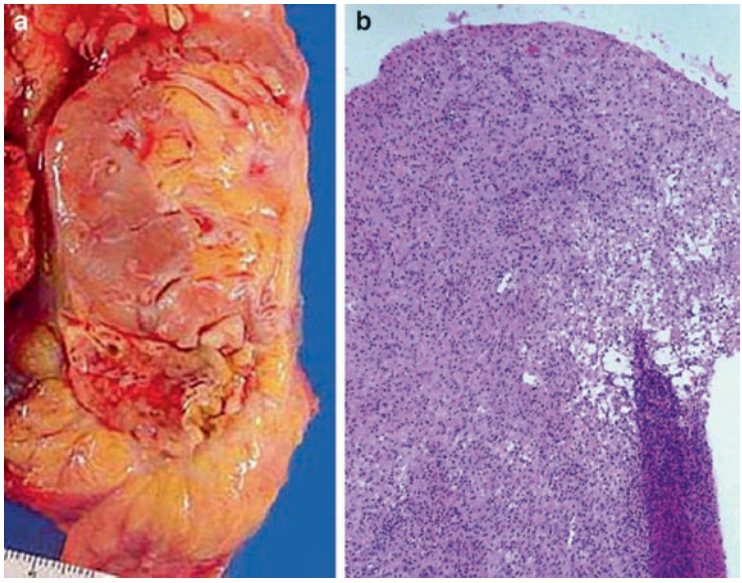


FIGURE 1.11 *Xanthogranulomatous Pyelonephritis*. (**a**) Brightly yellowish partially cystic mass, with perinephric involvement, closely simulating a clear cell RCC. (**b**) Cellular mass lesion with a clear cell area in the right.

The xanthomatous cells of XGP, instead of having a clear cytoplasm, typically display abundant and *finely vacuolated cytoplasm*, which can be recognized in FS. They are often associated with other inflammatory cells (Figs. 1.12 and 1.13). Spindle cells, potentially simulating spindle cell tumors, may be a major component in organized XGP. Residual macrophages admixed with inflammatory cells should raise this possibility (Fig. 1.14). Small clusters of xanthoma cells are frequent in papillary RCC and should not cause diagnostic problem; however, a rare case of papillary RCC may have confluent, grossly visible sheets of xanthoma cells, which can be misleading on FS.[10] In such a situation, careful evaluation of the FS for an epithelial component is necessary.

The von Hanssemann histiocytes typical for malakoplakia may closely simulate RCC cells, especially the granular cells; however, many of these cells contain the pathognomonic Michaelis-Guttmann bodies. In a few cases of malakoplakia personally encountered, the Michaelis-Guttmann bodies, for unknown reason, are deeply basophilic in FS and much easier to recognize in this context than in permanent sections (Figs. 1.15 and 1.16).

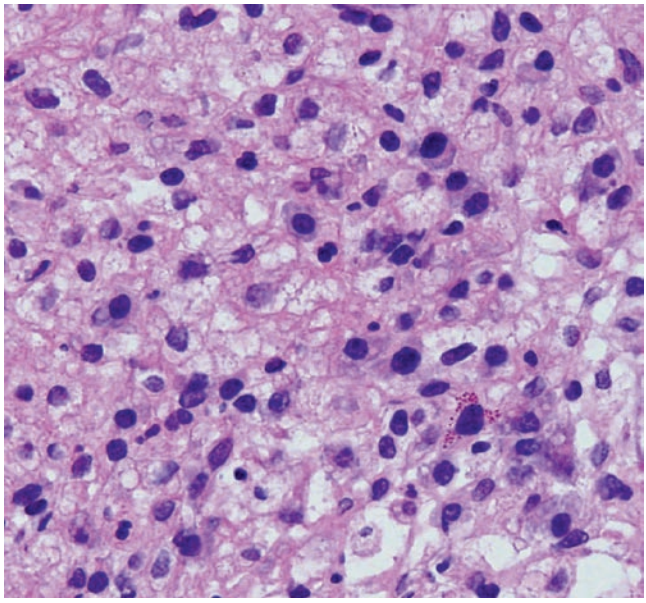


FIGURE 1.12 *Xanthogranulomatous Pyelonephritis*. Xanthoma cells with clear/vacuolated/granular cytoplasm, simulating RCC clear cells. Stromal vascularity, typical for clear cell RCC, is not present. This is a diagnostic clue.

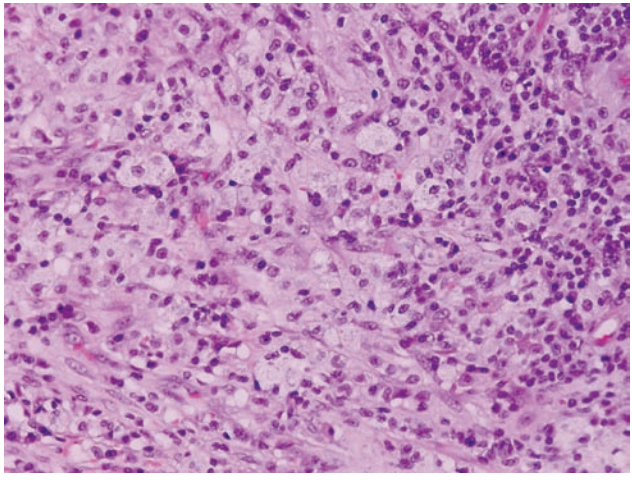


FIGURE 1.13 *Xanthogranulomatous pyelonephritis*. Aggregated xanthoma cells, simulating RCC clear cells. These cells are admixed with inflammatory cells, a diagnostic clue.

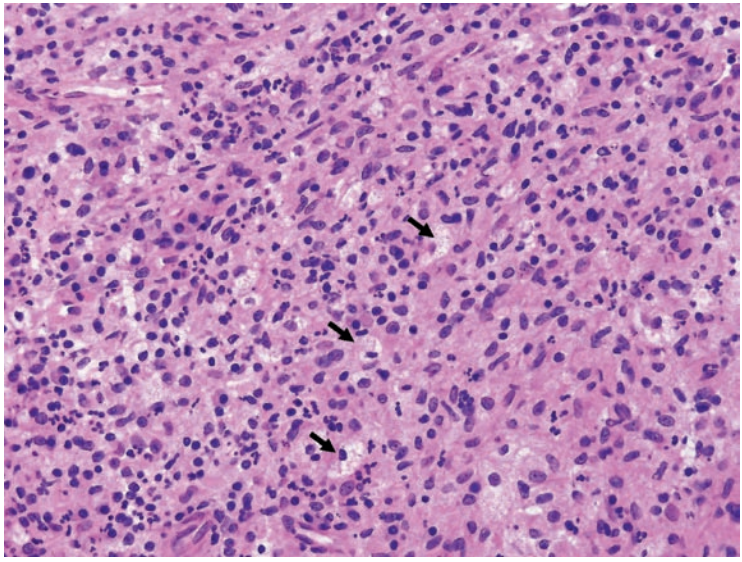


FIGURE 1.14 *Xanthogranulomatous pyelonephritis*. A focal hypercellular area with spindle cells, potentially simulating spindle cell tumors, including sarcomatoid RCC. Residual macrophages (*arrows*) and admixed inflammation should raise the possibility of inflammatory lesions including organized XGP.

Oncocytoma and Chromophobe RCC

These two tumors need to be separated since oncocytoma is benign whereas chromophobe RCC is a carcinoma that is often low grade but may behave aggressively.[11-13] Intraoperative recognition of these tumors is irrelevant in case of total nephrectomy, but may be important in a partial nephrectomy specimen where the margin is critical for a chromophobe carcinoma. FS is needed since their gross appearance can be very similar (Fig. 1.17). Features that help separate them are listed in Table 1.4. Two histological subtypes of chromophobe RCC are recognized, that is typical and eosinophilic.[13] Typical chromophobe RCC can often be separated from oncocytoma by the features listed in Table 1.4 and illustrated in Figs. 1.17–1.20. During FS, the perinuclear halo and/or the well-defined cell membrane typical for chromophobe RCC may not be obvious in tissue sections, especially in suboptimal preparation. However, these features may be better appreciated in touch preparations (Fig. 1.10). The characteristic growth pattern of chromophobe RCC, that is closely packed broad sheets of

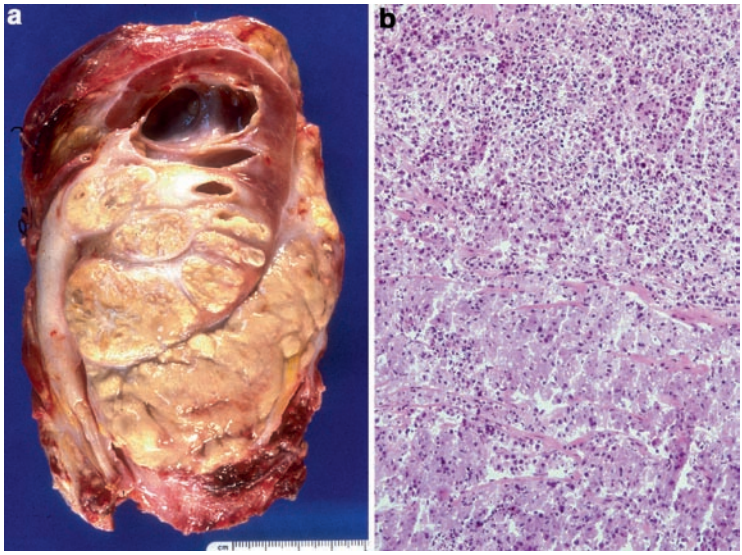


FIGURE 1.15 *Malakoplakia*. (**a**) Renal mass with multinodular brightly yellow cut surface and perinephric extension, simulating clear cell RCC. (**b**) At low magnification, the mass is composed of aggregated cells with variable but often abundant eosinophilic cytoplasm (von Hanssemann cells). Inflammatory cells are not obvious in this case, but can be pronounced in malakoplakia. Prominent stromal vascularity, typical for RCC, is not seen.

tumor cells and abundant cytoplasm, remains helpful since it is maintained in FS and is not seen in oncocytoma (Fig. 1.8). Many of the features that are characteristic for typical chromophobe RCC and help separate it from oncocytoma are not obvious in the eosinophilic variant of chromophobe RCC. Differentiation of this variant from oncocytoma remains problematic, even in permanent sections.[13] The diagnosis of oncocytic renal neoplasm with deferment to permanent sections is appropriate in this situation.

Angiomyolipoma

The utility of FS in the surgical management of angiomyolipoma (AML) is well documented.[14] Accurate FS diagnosis of AML is important since it is rather frequent and can attain large size, but is almost uniformly benign and is being increasingly considered as a good candidate for partial nephrectomy.[15] Indeed, the frequency of benign renal tumors in partial nephrectomy specimens (up to 34%) is higher than that in total nephrectomy specimens (about 10%),[16] and this increase is chiefly due to AML and oncocytoma. In the context

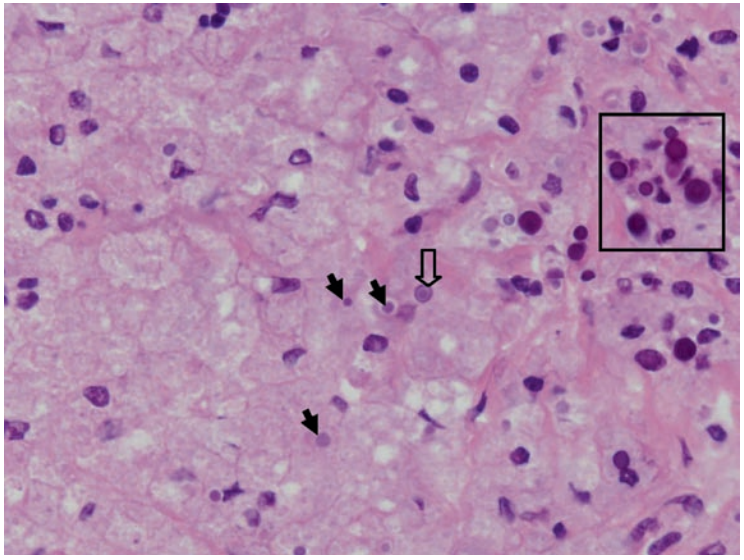


FIGURE 1.16 *Malakoplakia*. Different forms of the diagnostic Michaelis-Guttmann bodies, including basophilic bodies without internal structure (*solid arrows*), with lamellar appearance (*open arrows*) or with calcification (*square*). These bodies are more apparent in FS than in permanent sections, probably due to their more basophilia in the FS.

of laparoscopic partial nephrectomy specimen, if tumor tissue is identified at the surgical margin and if it is malignant, immediate total nephrectomy is usually considered; however, this procedure may not be indicated if the tumor is benign, as in AML.[17,18]

Since AML is composed of adipose tissue, smooth muscle, and blood vessels in various proportions, it has been confused with many other renal tumors during FS.[3,17,18] Imaging study can accurately identify AML if it is composed mostly of adipose tissue, but remains problematic if the other components predominate.[19] *In our experience, touch preparation of AML may not facilitate the diagnosis and may even be misleading since the tumor cell clusters closely simulate those of RCC*. Note that the three components of AML in tissue sections remain essential for diagnosis (Fig. 1.21). The adipose tissue component may display severe frozen artifacts and appear as variably sized and ragged clear spaces interspersed between spindled cells and vessels (Figs. 1.21–1.23). This artifact, however, has a diagnostic value since, in our experience, it is regularly seen and should raise the possibility of AML. One important

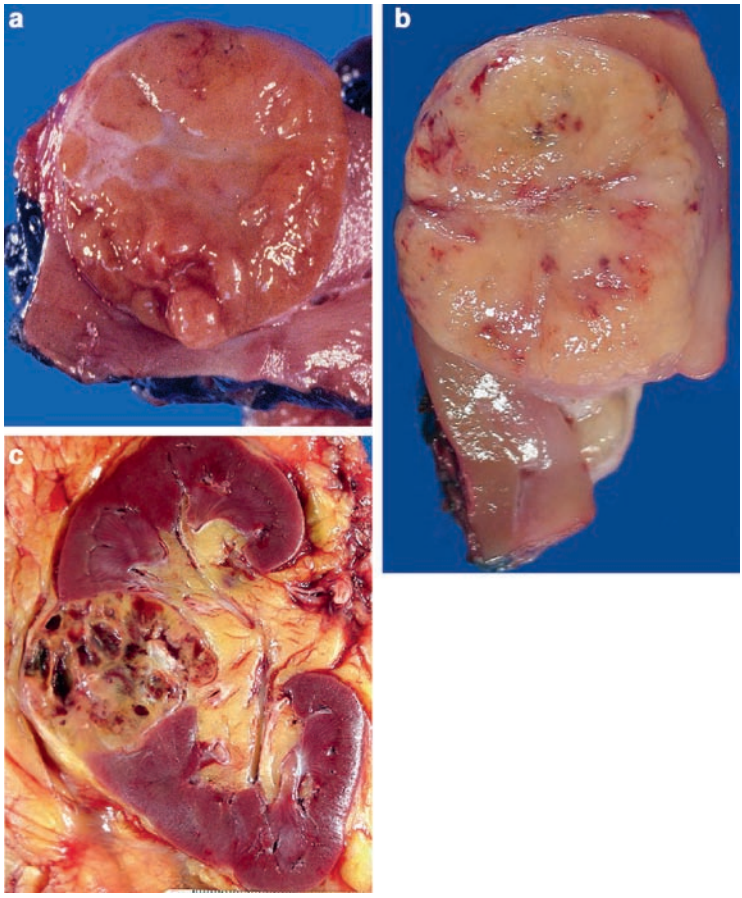


FIGURE 1.17 (**a**) *Oncocytoma*: Encapsulated mass, with a mahogany brown cut surface and a central scar, without necrotic/cystic changes. (**b**) *Chromophobe RCC*: Similar cut surface as oncocytoma, but more tan with a few areas of hemorrhage. (**c**) *Chromophobe RCC:* This tumor has more cystic/hemorrhagic changes. These changes are often not seen in oncocytoma.

clue for a correct diagnosis is abnormal thickened blood vessels with radial array of spindled cells around them (Figs. 1.21–1.23). This feature, characteristic for AML, is not seen in other renal tumors and can be readily appreciated in FS.[19]

AML may be composed predominantly of smooth muscle and vascular components, with significant nuclear atypia as noted in about 8% of AML or in the recently described epithelioid AML[19].

TABLE 1.4 Oncocytoma vs chromophobe renal cell carcinoma (*RCC*).

	Gross	Microscopic
Oncocytoma	Circumscribed, mahogany cut surface, +/– central scar, extrarenal extension rare, possible small hemorrhage, no obvious necrosis	Acini, tubules, small cysts, islands of tumor cells separated by edematous poorly cellular stroma, uniformly eosinophilic cytoplasm, uniform round nuclei, *cell membrane not well defined*, isolated highly atypical cells (5% of cases)
Chromophobe RCC, typical type	As above, but hemorrhage or necrosis possible	Predominantly sheets of tumor cells separated by scant vascularized stroma, abundant reticulated or eosinophilic cytoplasm with *perinuclear halo*, *well-defined cell membrane*, irregular nuclear contour, occasional binucleation
Chromophobe RCC, eosinophilic type	As the typical variant	Tubules or trabeculae separated by scant vascularized stroma; smaller cells with eosinophilic cytoplasm; cell membrane less well defined and perinuclear halo not as obvious as those of the classic type

This variant of AML can be confused with other renal tumors such as *high-grade RCC*, *sarcomatoid RCC*, *dedifferentiated retroperitoneal liposarcoma*, *primary renal sarcomas*, *inflammatory myofibroblastic tumor* (*inflammatory pseudotumor*), or *large cell lymphoma*. A correct FS diagnosis should be achieved by always considering AML in the differential diagnoses of an unusual renal tumor and by recognizing the characteristic perivascular cell array mentioned above (Fig. 1.23). In contrast, sarcomatoid RCC is frequently associated with areas typical for other histological types of RCC recognized by gross or FS.[20] True renal sarcoma is very rare and practically is not a consideration. Other spindle cell tumors such as *leiomyoma*, *inflammatory myofibroblastic tumor*,

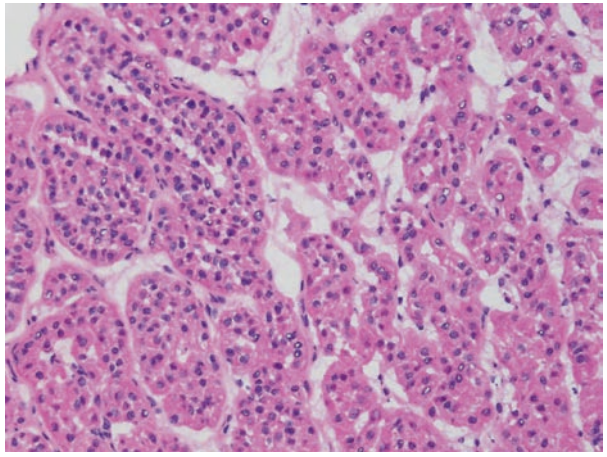


FIGURE 1.18 *Oncocytoma*. Tumor cells with abundant eosinophilic cytoplasm, round nuclei, inconspicuous cell membrane; forming islands, or trabeculae, separated by edematous paucicellular stroma. The tumor cells shown in the left side which have less cytoplasm ("oncoblasts") are characteristic for oncocytoma and may serve as a diagnostic clue.

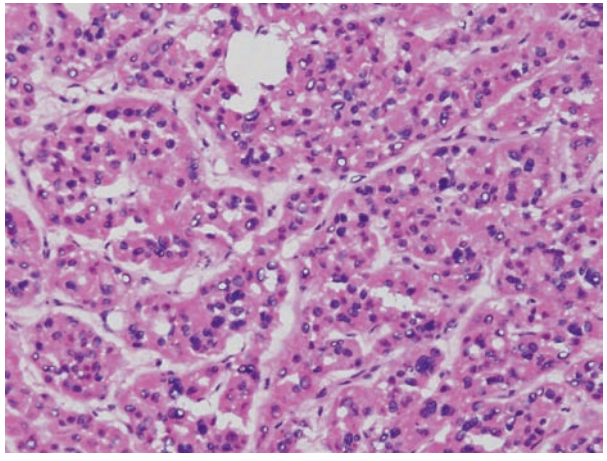


FIGURE 1.19 *Oncocytoma with cytological atypia*. An area with markedly atypical tumor cell nuclei, against a background of otherwise typical oncocytoma elsewhere. These focal changes are infrequent (about 5% of oncocytoma), but they are characteristic for oncocytoma and may even serve as a diagnostic clue. Oncocytoma with these changes remains benign.

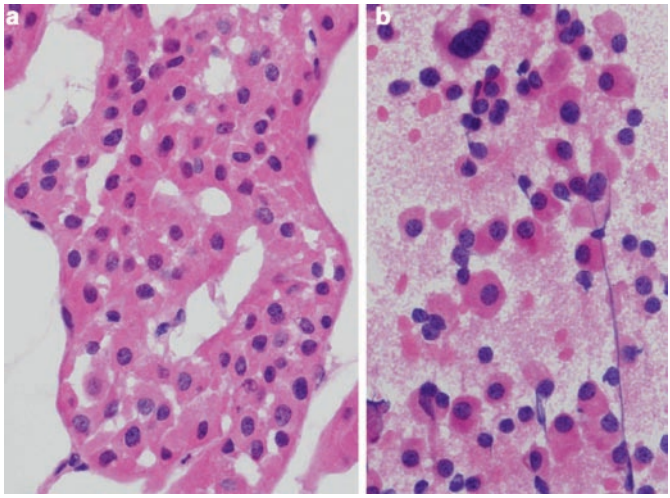


FIGURE 1.20 *Oncocytoma*. (**a**) Tumor cells with abundant eosinophilic cytoplasm, round nuclei, and inconspicuous cell membrane. (**b**) These cytological features are obvious in touch prep. Poor cohesiveness of tumor cells is also characteristic.

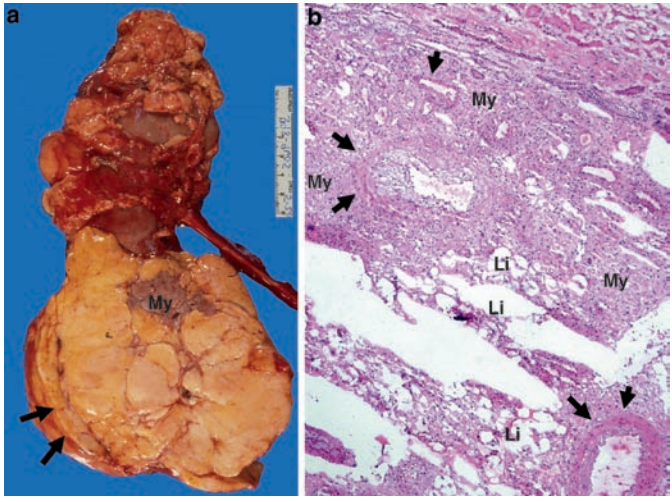


FIGURE 1.21 *Angiomyolipoma*. (**a**) A voluminous tumor with a predominantly extrarenal component, composed mostly of what appears as adipose tissue, with a small brownish area of myoid (*My*) component.

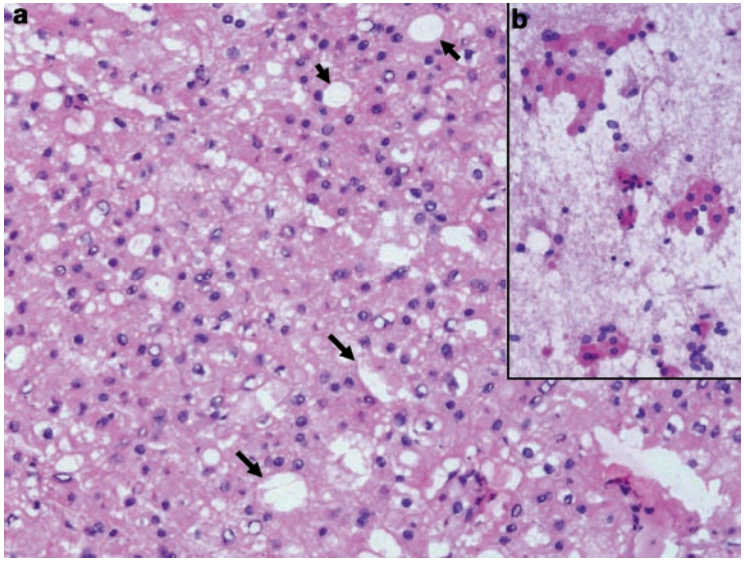


FIGURE 1.22 *Angiomyolipoma*. (**a**) The tumor may be composed almost entirely of the myoid component characterized by cells with abundant clear/vacuolated/granular cytoplasm, simulating RCC. The vascular component characteristic for angiomyolipoma may be inconspicuous in this variant of angiomyolipoma. A diagnostic clue includes clear spaces (*arrows*), which may appear as artifact, but indeed represent lipocytes. This should prompt angiomyolipoma as a diagnostic possibility and further FS sampling for other diagnostic features. (**b**) Touch prep is perhaps misleading since the myoid cells closely simulate cells from other renal cell tumor types.

and *solitary fibrous tumor* are both exceptional and their spindle cell component displays little or no atypia. *Mesoblastic nephroma* or *metanephric stromal tumor* features prominent spindled cells, but these cells are clearly benign and these two tumors are practically limited to the first few years of life.[21]

FIGURE 1.21 (continued) The tumor still respects the boundary of the Gerota's fascia (*arrows*), allowing excision of the tumor along the plane of this fascia, a feature not seen in retroperitoneal liposarcoma. (**b**) Three components may be seen: The myoid component (My) appearing as solid areas on lower magnification, the opened thick-walled blood vessels with apparent replacement of the adventitia by the myoid cells (*arrows*), and the lipomatous component which appears as artifactual clear spaces (*Li*). This artifact is, however, typical for angiomyolipoma and is a diagnostic clue. The presence of all three components is diagnostic for angiomyolipoma, but this may not be seen in every tumor.

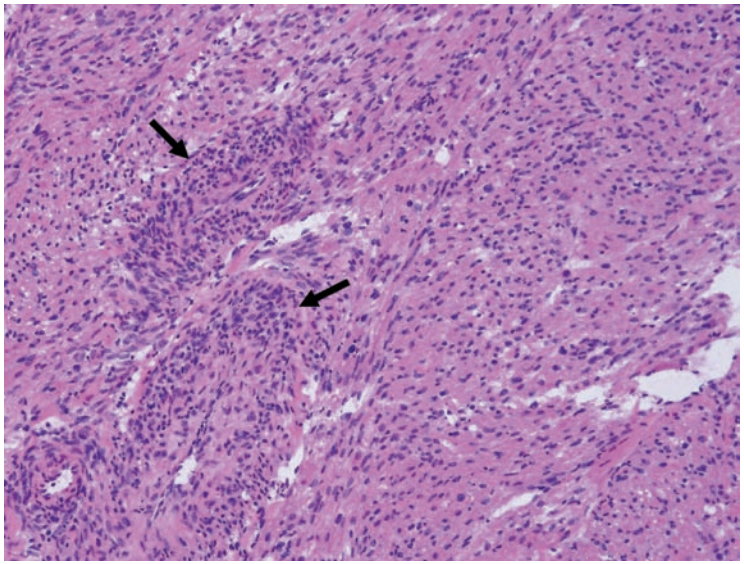


FIGURE 1.23 *Myoid-rich angiomyolipoma*: This tumor is composed almost entirely of ovoid or spindle cells, simulating other renal spindle cell tumors. However, the presence of large thick-walled blood vessels without adventitia (*arrows*) is diagnostic for angiomyolipoma. A peculiar increase in medial cellularity is also noted.

AML composed predominantly of adipose tissue may be confused with well-differentiated retroperitoneal liposarcoma; this is especially true when AML attains large size and consists of a large extrarenal component (Fig. 1.21).[19] The surgeon tends to be aware of the possibility of AML since, even in the above context, AML tends to respect the boundary of Gerota fascia, allowing the surgeon to excise the tumor along the natural tissue plane delineated by this fascia. This is not the case for bulky retroperitoneal liposarcoma. A correct FS diagnosis is also aided by an awareness of this type of AML, the presence of a constant, albeit small, intrarenal component, and microscopic fields of vascular/smooth muscle even in areas which grossly look like adipose tissue (Fig. 1.24).

FS can reveal AML tissue in renal vein or in other organs such as spleen, para-aortic lymph nodes, or liver, but these are considered multifocal disease rather than metastasis.[19,22]

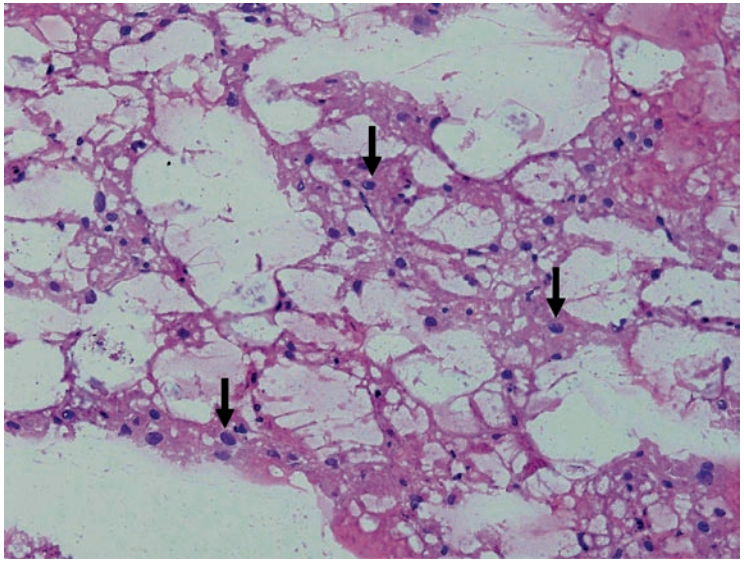


FIGURE 1.24 *Angiomyolipoma*: FS from a grossly "lipomatous" area shows numerous "artifactual" clear spaces, which in fact represent adipose tissue. In addition, few isolated myoid cells (*arrows*) are frequently seen in these areas and represent a diagnostic clue.

FROZEN SECTION FOR CLINICALLY SUSPECTED UROTHELIAL CARCINOMA AND URETER/BLADDER CUFF SURGICAL MARGIN

Clinical Background

If a preoperative diagnosis of renal pelvic urothelial carcinoma is made, the standard treatment is *nephroureterectomy*. This type of specimen may be submitted for confirmation of tumor grossly and FS of the distal surgical margin.

For a centrally located/hilar tumor in which urothelial carcinoma is clinically suspected but not preoperatively diagnosed, *nephrectomy* is usually performed and FS may be requested to confirm the diagnosis. This is important since the diagnosis of urothelial carcinoma mandates removal of the rest of the ureter together with a cuff of bladder wall to prevent tumor recurrence. FS evaluation of the distal surgical margin may also be requested since urothelial carcinoma is often multifocal and may involve this margin.

Specimen Handling

For the *nephrectomy* specimen, the specimen should be bivalved as described above. Successful bivalving of the nephrectomy specimen through the pyelocalyceal system is very helpful, since this often demonstrates in case of urothelial carcinoma that the tumor develops from the pyelocalyceal system, with or without invasion into the kidney (Fig. 1.25). FS diagnosis of urothelial carcinoma is also facilitated by noting that samples taken from the portion which invades kidney may not display typical features of urothelial carcinoma, but those from the pelvic portion of the same tumor often do.[23] (Figs. 1.25–1.28).

The *nephroureterectomy* specimen includes kidney, perirenal adipose tissue, Gerota fascia, the entire ureter, and a cuff of bladder wall. Bivalving the kidney and opening of the ureter should be done as for the nephrectomy specimen. FS to determine

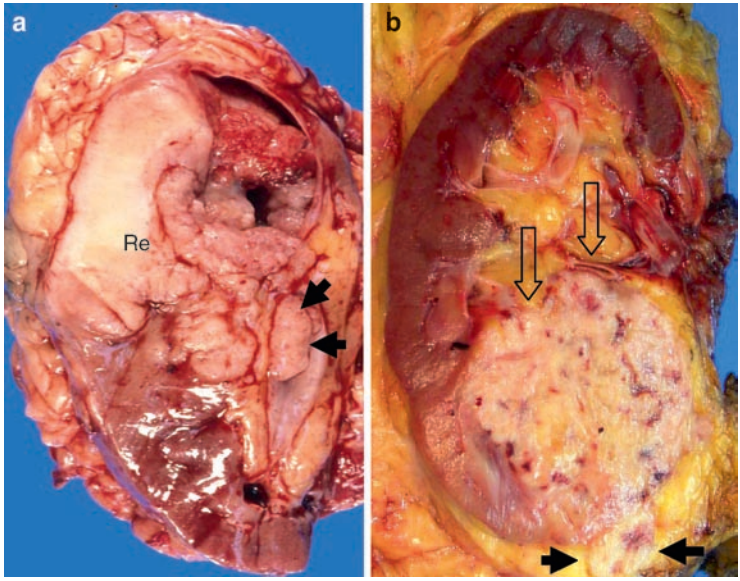


FIGURE 1.25 (**a**) *Urothelial carcinoma*: Bivalving the nephrectomy specimen through the pyelocalyceal system shows a tumor mass that involves the pelvic wall and pelvic lumen (*arrows*), together with a renal component (*Re*). The renal component may simulate other central/hilar renal tumors, but the pelvic component is characteristic for urothelial carcinoma and supports this diagnosis. (**b**) *Collecting duct RCC*: A large central/hilar mass with irregular border and multifocal involvement of both perirenal fat (*solid arrows*) and sinus fat (*open arrows*).

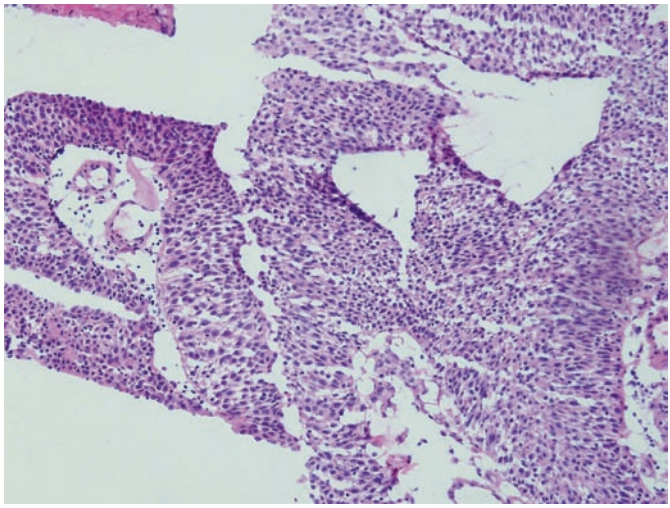


FIGURE 1.26 *Urothelial carcinoma*: Typical features, that is, multilayered atypical urothelial cells forming papillary structures, are seen in the tissue taken from the pelvic wall tumor in Fig. 1.25a.

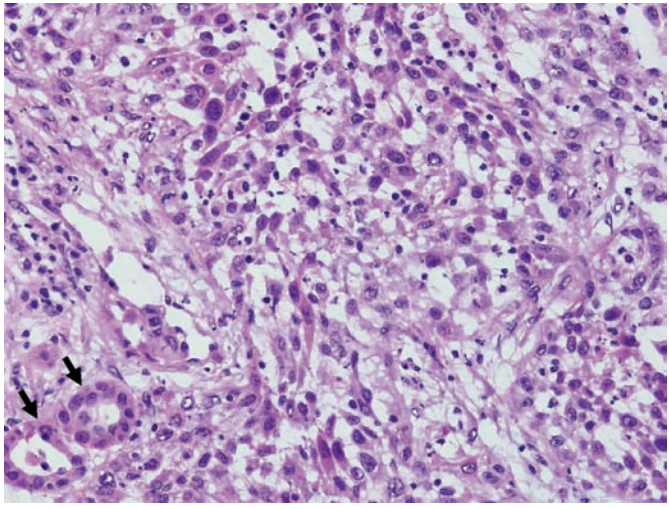


FIGURE 1.27 *Urothelial carcinoma*: Spindle and cuboidal cells not readily diagnostic for urothelial carcinoma in the tissue taken from the renal component of the tumor in Fig. 1.25a. Residual renal tubules are seen (*arrows*).

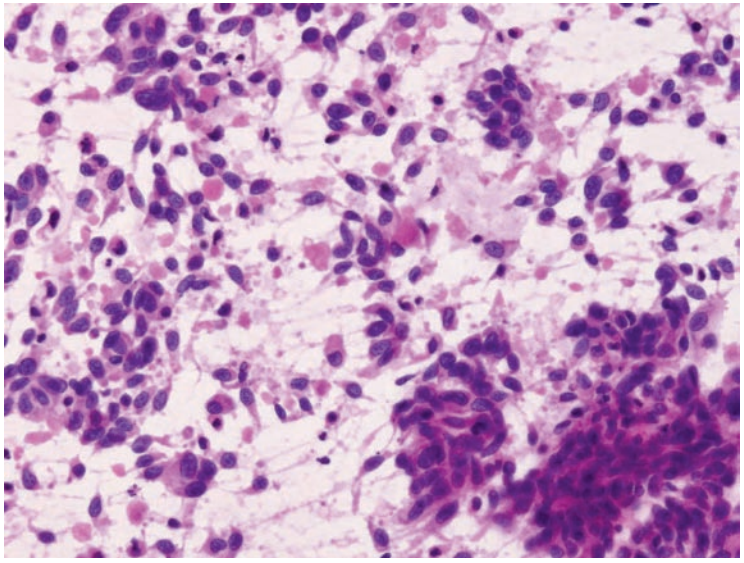


FIGURE 1.28 *Urothelial carcinoma*: In touch prep, the tumor cells typically display cuboidal or spindle shape cytoplasm with a "solid" eosinophilic appearance. They form papillary structures, small clusters, or isolated cells.

whether the distal surgical margin is involved by in situ or invasive urothelial neoplasm may be requested. The entire bladder cuff margin should be submitted. Whether tissue sampling should be circumferential (parallel to the surgical resection plan) or radial (perpendicular to the surgical resection plan) is probably optional, depending on the gross examination of the distal margin.

1.4.3. Interpretations

Urothelial carcinoma must be differentiated from other tumors, which may involve renal medulla predominantly or share some histological features with urothelial carcinoma. They include *collecting duct RCC*,[24,25] *primary renal pelvic adenocarcinoma*,[26] *metastatic adenocarcinoma*,[26] and *high-grade papillary RCC* (Table 1.5) This differential diagnosis can be problematic since urothelial carcinoma of renal pelvis is often of high grade (70%) and may display focal unusual growth patterns such as undifferentiated, micropapillary, spindle cell, clear cell, or gland-like formation (40%).[23]

Urothelial carcinoma may be confused with either papillary RCC or collecting duct RCC since papillary structures may predominate

TABLE 1.5 Differential diagnoses of renal pelvic urothelial carcinoma.

	Gross	Microscopic
Urothelial carcinoma	Tumor involvement of renal pelvic wall and lumen, +/– renal parenchymal extension, not encapsulated or circumscribed	Features of high- or low-grade urothelial carcinoma; squamous or glandular differentiation possible, but the urothelial carcinoma component always present. Features of urothelial carcinoma usually obvious in the pelvic component but less so in the renal invasive component; urothelial carcinoma in situ may be present
Collecting duct RCC	Tan white tumor mass predominantly in renal medulla, usually large tumor, gray white firm cut surface; indistinct border, often widespread invasion (adrenal gland, perirenal fat, renal sinus, renal pelvis)	Cells with amphophilic cytoplasm, large highly atypical nuclei; prominent nucleoli; forming complex tubulopapillary structures, microcysts with intracystic papillation; constant desmoplastic stroma; extensive infiltration of renal parenchyma; sometimes cytoplasmic mucin; sometimes carcinoma in situ in collecting ducts
Papillary RCC	Red brown tumor mass within kidney, no involvement of pelvic wall or lumen, often well circumscribed, usually cystic with areas of necrosis and hemorrhage	Usually low-grade tumor cell nuclei but may be high grade. Papillary structures with a single cell layer (*vs* multiple layers in the papillary structures of urothelial carcinoma), less often growth pattern including tubular, trabecular, or solid. Desmoplastic stroma not pronounced. Foamy macrophages frequent in the papillae of lower grade tumor

in all these three tumor types. Primary renal pelvic adenocarcinoma or metastatic adenocarcinoma may closely simulate collecting duct RCC, but they are rarely submitted to FS, since the former is exceptional whereas the latter is usually diagnosed by other means such as fine needle aspiration, and is not subjected to surgery.[6] Features that may facilitate these differential diagnoses are listed in Table 1.5 and Figs. 1.25–1.28.

FROZEN SECTION TO EVALUATE A CYSTIC RENAL MASS

Clinical Background

Up to 15% of renal tumor may be predominantly cystic. The Bosniak classification (Bosniak Class I–IV) is often used to classify renal cystic tumors on imaging. Class I tumors represent a unilocular mass with smooth and thin wall; Class IV tumors represent a multilocular mass with thick, shaggy wall and solid areas[27]; and Class II or III tumors are in between. The Class I tumor is thought to be benign and is usually not subjected to surgery. The Class II–IV tumors may histologically represent a large variety of lesions, including simple cyst with superimposing hemorrhage or infection, cystic nephroma, multilocular cystic RCC, and RCC with marked cystic changes secondary to necrosis or hemorrhage.[27,28] The treatment for these lesions is quite different and may depend on a specific diagnosis, which is usually not obtainable preoperatively, in spite of sophisticated renal imaging techniques or even fine needle aspiration.[28] FS is therefore may be requested before definitive treatment. Nevertheless, diagnostic failure of FS (often a false negative result) in this context has been often reported, reflecting sampling limitation or interpretational difficulty. These considerations limit the use of FS in the surgical treatment for cystic renal lesions.

Sometimes mass lesions develop in a kidney with diffuse cysts. The two most common conditions which cause bilateral diffuse renal cystic changes are *autosomal dominant polycystic kidney* and *acquired cystic kidney*, a condition associated with chronic dialysis. Symptomatic mass lesion including cyst infection, hematoma, or RCC may develop in these kidneys. Since the true nature of these masses may not be established by clinical or imaging findings, total nephrectomy may be needed and an intraoperative consultation may be requested.[29,30]

Specimen Handling

For a localized cystic renal mass, the submitted specimen may be a wedge biopsy of the cyst wall, the diagnosis of which may dictate a conservative approach for a benign lesion or radical resection for a malignant one. The entire specimen should be submitted for FS and, in case a diagnosis is not achieved, additional tissue should be requested.

Interpretation

The major differential diagnoses for a localized cystic mass include simple cyst, simple cyst with superimposing hemorrhage or infection, cystic nephroma, multilocular cystic RCC, RCC with marked cystic

changes secondary to necrosis or hemorrhage, and mixed stromal and epithelial tumor.[28,31] Some features helpful for their differentiation are listed in Table 1.6. This table does not include cystic partially differentiated nephroblastoma which is also predominantly cystic, but is practically limited to the first two years of life.[31] These cystic lesions usually have distinctive gross features, which facilitate the differential diagnoses (Table 1.6 and Figs. 1.29–1.35). Some practical caveats pertinent to FS are emphasized. Identifying the epithelial cells lining the cyst wall is essential for a correct diagnosis. These cells, however, may be necrotic and replaced by inflammatory fibrous tissue as often seen in cystic papillary RCC (Fig. 1.35). Indeed, necrosis is an important clue for RCC and its presence should prompt an attempt to confirm this diagnosis. The presence of clear cells lining cyst wall, usually more than one layer, and/or clusters of clear cells within septa are required for diagnosing multilocular cystic RCC and differentiating it from other cystic tumors including cystic nephroma. During tissue preparation, these cells may be completely lost or appear only as mildly atypical bare nuclei reminiscent of lymphocytes, an artifact probably due to their delicate cytoplasm devoid of well-developed organelles or cytoskeleton (Figs. 1.31 and 1.32**)**. In these situations, however, the highly vascularized and edematous stroma of the cyst wall or the septa, characteristic for clear cell RCC, is still present and, in our experience, is an important diagnostic clue (Figs. 1.31 and 1.32). The diagnostic pitfalls are highlighted by personally encountered cystic tumors diagnosed as "benign cyst" in FS since only fibrous wall is identified but, on permanent sections, show rare cyst lining cells characteristic for either clear or papillary RCC. These considerations imply a need for careful specimen sampling and for additional biopsies for FS if the subtle clues for RCC, as described above, are encountered in the initial FS slides (Figs. 1.29d and 1.35).

In the context of a mass lesion in a kidney with diffuse cystic changes, RCC is rare in autosomal dominant polycystic kidney and most renal masses in this condition represent intracystic hematoma or, less frequently, infection.[30] In contrast, RCC is very frequent and usually multifocal in acquired cystic kidney and, in about a third of cases, is associated with hemorrhage, which may be massive and mask the RCC.[29] Indeed, the presence of renal hematoma in the context of acquired cystic kidney should prompt a thorough search for RCC. In contrast, large hematoma may be "organized" at its periphery and appears as aggregations of atypical spindle cells, reminiscent of sarcomatoid RCC. The presence of admixed inflammatory cell including macrophages and hemosiderin granules may offer diagnostic clues.

TABLE 1.6 Differential diagnoses of cystic renal tumors.

	Gross	Lining epithelium	Septal stroma	Intraseptal epithelium
Simple cyst with infection or hemorrhage	*Unilocular*, usually in cortex, hemorrhagic, cheesy material in cyst wall or lumen	Flat or cuboidal non-clear cells in single layer; focal replacement of epithelium with fibrin, degenerated red blood cells, and fibroinflammatory tissue but NO necrosis	No septa	Not applicable
Cystic nephroma	Single *multilocular* mass, circumscribed or encapsulated, extension to perirenal or peripelvic soft tissue possible, smooth and thin wall molding to the cyst contour without solid mass, serous, gelatinous or serosanguinous cyst content, NO necrosis	Flat, cuboidal, or hobnail cells in single layer; rare clear cells (cyst lining cell may be focally clear, but this finding alone does not indicate renal cell carcinoma)	Vascularized fibrous tissue of variable celllularity; focal myxoid or myoid areas in some cases	Microcysts, complex branching tubules resembling renal tubules
Multilocular cystic RCC	Virtually identical to cystic nephroma	Almost always clear cells with low nuclear grade, in singe or multiple layers; focal loss of epithelium frequent	Fibrous and commonly calcified; focal myxoid and highly vascularized areas	Focal clusters of clear cells similar to cyst lining cells

RCC with extensive cystic necrosis	*Multilocular* (usually clear cell RCC) or *unilocular*(usually papillary RCC) cyst due to necrosis and hemorrhage, solid tumor areas frequent	Cysts filled with hemorrhagic and necrotic debris, without tumor cell lining; cyst with mural nodules or microscopic clusters of clear or papillary RCC of variable nuclear grades	Thick, shaggy; myxoid and highly vascularized areas admixed with dense fibrotic areas	Tumor cells with necrosis and hemorrhage
Mixed stromal and epithelial renal tumor	Single *multilocular mass*, circumscribed but not encapsulated; frequent extension to peripelvic soft tissue, cysts always present but with different extent; some cases with pronounced solid areas and thick cyst wall	Cuboidal cells with focal intracystic papillary projection	Fibrous stroma with variable cellularity, thick-walled blood vessels, smooth muscle bundles	Microcysts, complex branching, tubules resembling renal tubules

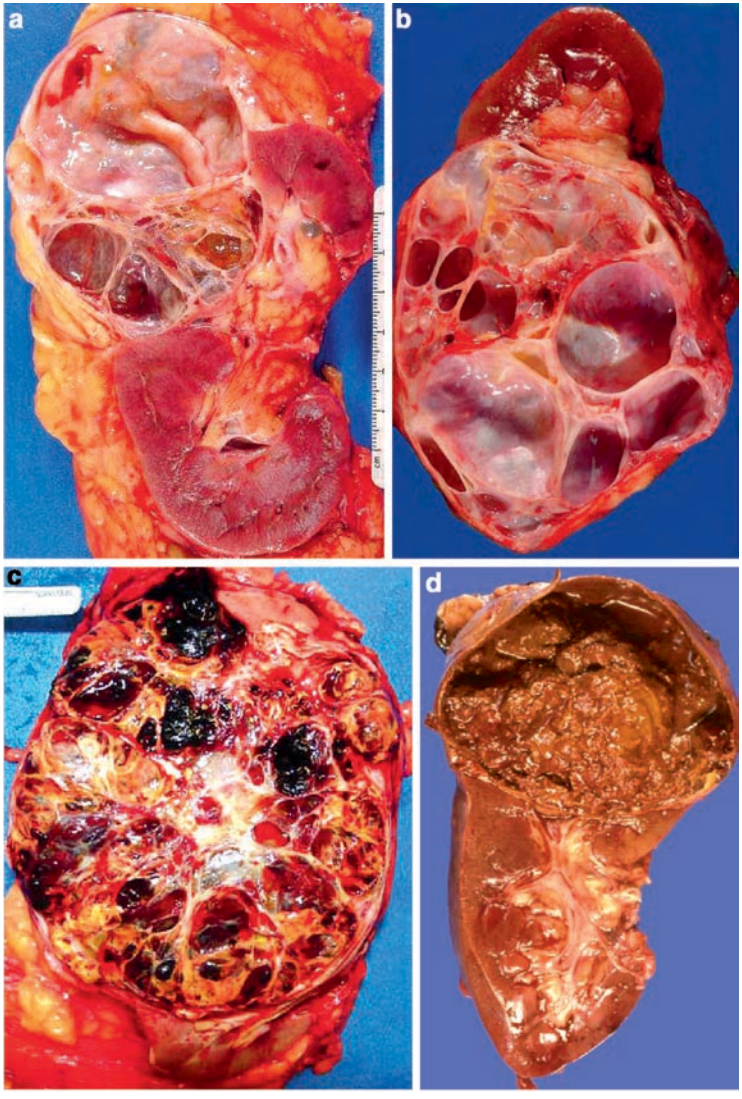


FIGURE 1.29 *Cystic renal neoplasm*. (**a**) *Cystic nephroma*: A single multilocular, circumscribed mass composed of locules with smooth thin wall, without obvious necrosis or septal nodules. (**b**) Multilocular cystic clear cell RCC: Similar appearance as cystic nephroma. (**c**). *Clear cell RCC, with extensive cystic changes:* Cysts due to extensive necrosis and hemorrhage with multiple septal tumor nodules. (**d**) *Papillary RCC with cystic changes*: unilocular cystic tumor with necrosis of the wall.

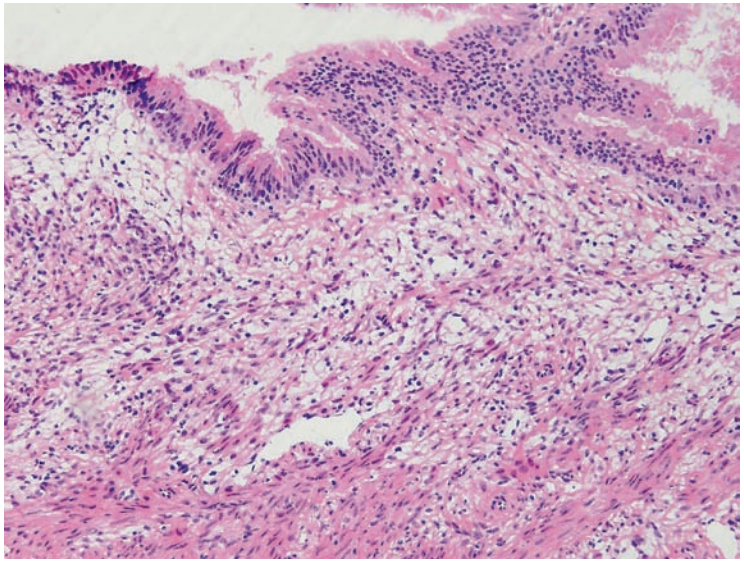


FIGURE 1.30 *Cystic nephroma*: The cyst is lined by cuboidal/columnar cells with intact eosinophilic cytoplasm. The stroma is fibromyxoid and vascular. Bundles of smooth muscle cells can be seen in both cystic nephroma and mixed stromal and epithelial tumor.

PARTIAL NEPHRECTOMY SPECIMENS

Clinical Background

Partial nephrectomy for renal tumors becomes more frequent due to increased detection of small and asymptomatic renal masses by imaging and the recently recognized importance of maintaining renal function for improving survival in patients with RCC maintaining renal function for long term-survival.[15] The later consideration is especially true for elderly patients, whose renal function may already be impaired by frequently associated conditions such as hypertension and diabetes. Its indications include (1) conditions where total nephrectomy renders the patient anephric.[32] These conditions include solitary kidney, bilateral synchronous RCC, genetic predisposition to multiple synchronous or sequential tumor as in von Hippel-Lindau (VHL) disease, hereditary papillary renal carcinoma syndrome, Birt-Hogg-Dube syndrome, and tuberous sclerosis; (2) small RCCs (usually <4 cm) confined to kidney, and (3) inflammatory masses or some benign renal tumors such as multilocular cystic nephroma, AML, and oncocytoma.[14]

Partial nephrectomy specimen is traditionally submitted for FS evaluation of *surgical margin* since complete tumor resection is

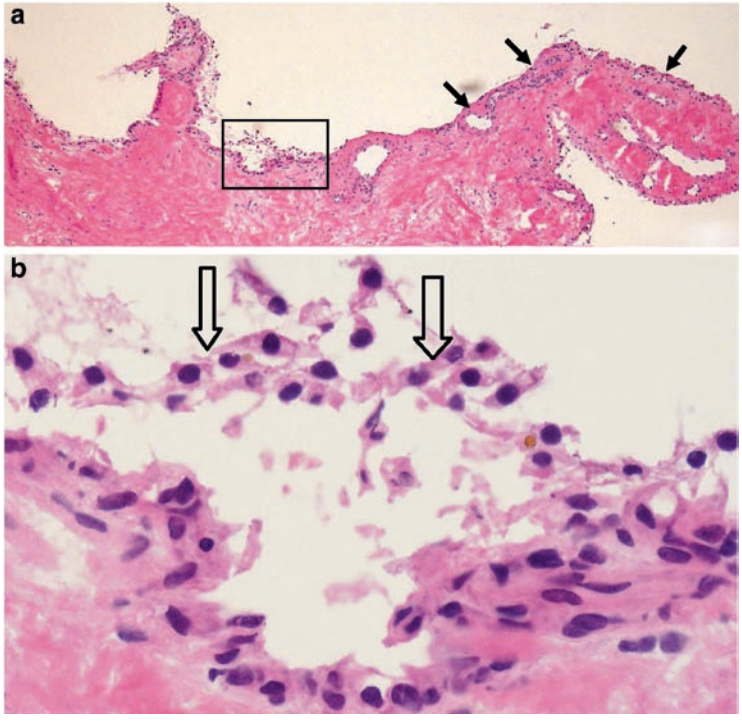


FIGURE 1.31 *Multilocular cystic RCC*. (**a**) A locule lined by fibrous stroma with superficial stromal vascularity (solid arrows) that can be recognized under low-power view, a characteristic feature, and a diagnostic clue. Most of the times, tumor cell lining is not obvious. (**b**) High-power view of the rectangle area in (**a**). The findings at low magnification should prompt careful examination and, in rare situation, inconspicuous tumor cells detached from the underlying wall can be found (*open arrows*). Touch prep usually yield a few bare small hyperchromatic nuclei, a characteristic feature of this tumor type (*see also* Fig. 1.6).

thought to be essential for successful treatment. However, refrain from routine FS consultation for surgical margin has been suggested by several more recent studies, citing rather frequent FS misinterpretation and more importantly, a lack of correlation of the surgical margin status with subsequent tumor recurrence, metastasis, or patients' survival.[33,34]

Partial nephrectomy can be performed by open surgery or laparoscopy. The implication of FS for surgical margin is somewhat different between these two approaches. This difference is

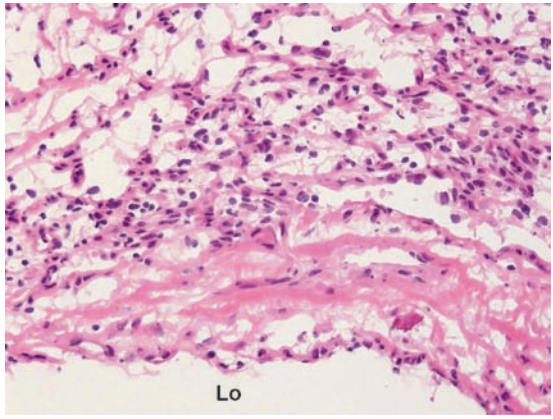


FIGURE 1.32 *Multilocular cystic RCC*. Septum of a locule (*Lo*) with vascularized stroma characterized by interconnecting thin-walled blood vessels lined by prominent endothelial cells set against an edematous background. Although there are no obvious tumor cells lining the locule or within the septum, this type of stroma is characteristic for multilocular cystic RCC. It presence should prompt further consideration for this diagnosis, including additional tissue sampling or request for more biopsies.

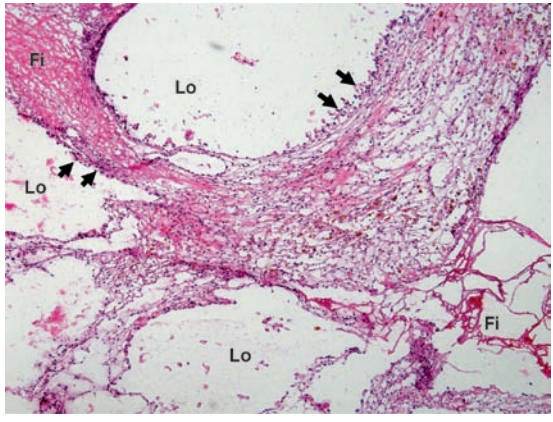


FIGURE 1.33 *RCC with extensive cystic necrosis*. The locules (*Lo*) are lined by tumor cells with clear cytoplasm (*solid arrows*). The same types of tumor cells may be present in the septa also, but these cells may be artifactually distorted with loss of the clear cytoplasm and may not be obvious. Hemorrhage and fibrin (*Fi*) are also noted within the septa or the lumens of the locules.

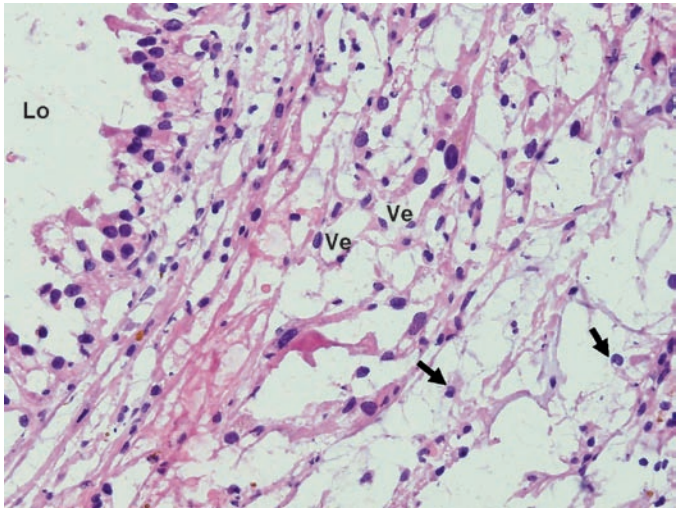


FIGURE 1.34 *RCC with extensive cystic necrosis*. Higher view of the Fig. 1.33. This locule (*Lo*) is lined by tumor cells with clear cytoplasm. The same type of tumor cells may be present in the septum also, but these cells may be artifactually distorted with loss of the clear cytoplasm and may not be obvious (*solid arrows*). Stromal thin-walled blood vessels with prominent endothelial cell lining are present (*Ve*).

related to the observation that during either procedure, the renal pedicle including the hilar blood vessels is often clamped to control bleeding, but the clamping time should usually be less than 30 min to avoid renal ischemia. For open partial nephrectomy, a positive surgical margin by FS calls for additional resection to achieve complete tumor resection with free surgical margins. This is technically possible in most cases since the time required for open partial nephrectomy is often less than the threshold for renal artery clamping. This scenario may not be the case for laparoscopic partial nephrectomy, which may be more time consuming that the open approach.[32] Thus, when an FS diagnosis of positive surgical margin is rendered in the context of laparoscopic approach, the threshold for renal ischemia was already reached and further excision of the surgical margin may not be feasible. The surgeon then can either complete the laparoscopic procedure regardless of the surgical margin status or proceed immediately to total nephrectomy.[32] Information on the tumor type provided by FS may influence this choice. Sometimes the surgical margin is evaluated not only by FS of the partial nephrectomy specimens but also by biopsy of the surgical bed.[35]

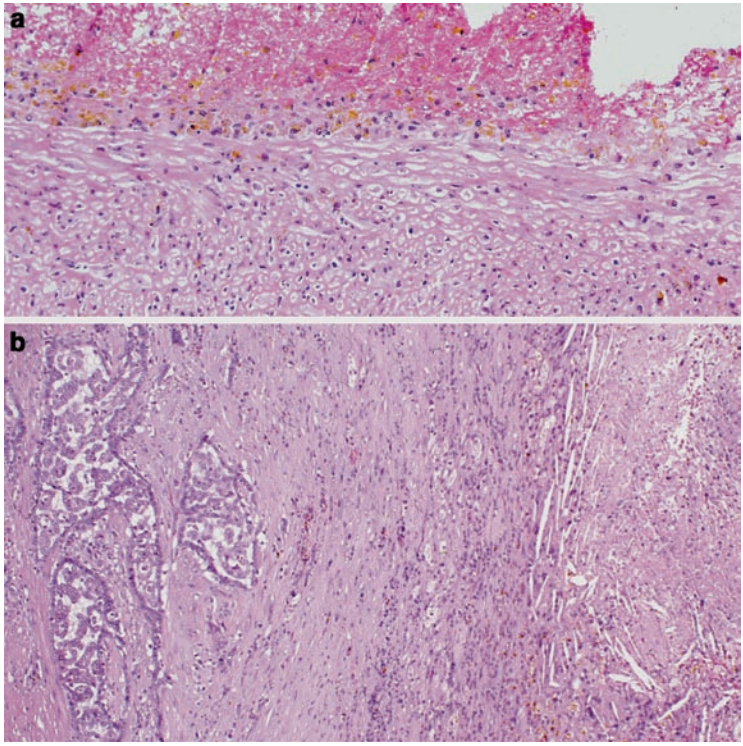


FIGURE 1.35 *Unilocular cystic papillary RCC*. (**a**) Most areas of the cystic tumor shown in Fig. 1.29d show necrotic material and macrophages lining a fibrous wall. These changes, however, strongly suggest the diagnosis of cystic papillary RCC. (**b**) Additional samplings for FS show an area of papillary carcinoma in the wall.

FS may be also requested for a *specific diagnosis* during partial nephrectomy, since tumor type may be one of the factors that determine whether partial nephrectomy is appropriate.[15] Furthermore, when the surgical margin is positive during laparoscopic partial nephrectomy, a specific diagnosis of a benign tumor such as AML or oncocytoma may negate the need for immediate total nephrectomy.[17,18]

Specimen Handling

Since partial nephrectomy is preferred for small peripheral and polar tumors, the resected specimen often includes renal tissue and perirenal adipose tissue. Central tumors, defined as those

with extension to the collecting system or renal sinus by imaging,[36] are increasingly considered for partial nephrectomy. These resected specimens may also include renal sinus soft tissue and pyelocalyceal tissue, in addition to renal tissue and perirenal adipose tissue.[34,36]

Because of the complex anatomy of the kidney and the excretory system, the partial nephrectomy specimen is often disoriented or even disrupted, with the surgical margins difficult to identify. *In such case, orientation by the surgeon is essential*. The surgical margins may include perirenal soft tissue, renal parenchyma, pyelocalyceal tissue, and renal sinus soft tissue including blood vessels. Since RCCs chosen for partial nephrectomy are usually small (<4 cm) and remain confined to the kidney, the renal parenchymal margin is the most critical one, but other margins should also be evaluated.[34] The margins should be inked, followed by serial sectioning perpendicular to the renal parenchymal surgical margin to demonstrate the tumor and its relation to this margin.

Sometime, rather than submitting the partial nephrectomy specimen for evaluating surgical margin, biopsies of the remaining tumor bed after partial nephrectomy are separately submitted to evaluate surgical margin.[35] These biopsies are usually small and should be entirely submitted for FS. Misinterpretation is frequent in this situation (*see below*).[37]

Interpretation

Since the tumors selected for partial nephrectomy are usually circumscribed and even encapsulated, gross impression of a negative margin is usually accurate. However, Li et al. have shown that for clear cell or papillary RCC of 4 cm or less, microscopic extension of tumor tissue beyond the gross confine of the tumor can be seen in 19.5% of tumor at a distance of 0–5 mm (0.5 ± 1.3 mm).[38] These data speak against tumor enucleation and support the need for microscopic examination for the surgical margin. The minimum accepted surgical margin clearance has not been established.[34] Although a clearance of 1 cm was previously suggested, recent studies suggest that the size of the margin is not related to recurrence, and thus even a microscopic absence of tumor tissue at the inked surgical margin is adequate.[18,34] These observations are important since they facilitate the most essential goal of partial nephrectomy, that is maintaining as much functioning renal tissue as technically possible. Moreover, a large surgical margin clearance, for example 1 cm is evidently not possible for hilar/central tumors.[33,36] These complicated considerations withstanding, a positive surgical margin is indeed relatively rare (0–7.4%, mean 2.4%).[18,34]

Satellite tumor nodules may be encountered in up to 25% of all RCCs but in about 5–7% for those suitable for partial nephrectomy. In the latter instance, these nodules measure 0.1–2.8 cm and are situated 0.2–6.0 cm from the main RCC.[38,39] These data suggest that satellite nodules are not usually included in the partial nephrectomy specimens and are not a problem in FS.

Recognizing a free parenchymal surgical margin is usually straightforward when the partial nephrectomy specimen is submitted (Fig. 1.36). However, misinterpretation has been documented (Fig. 1.37), and this is rather often in case of small biopsy from the tumor bed.[37] Normal proximal renal tubules may closely simulate the tubular growth pattern in oncocytoma, a frequent tumor type in the context of partial nephrectomy (Fig. 1.38). Atrophic renal tubules often seen at the periphery of tumor may display enough structural distortion and reactive nuclear atypia, creating potential confusion with tumor tissue in FS (Fig. 1.39). Neoplastic tubules of low-grade RCC may look similar to benign renal tubules. The presence of glomeruli in tissue with misleading

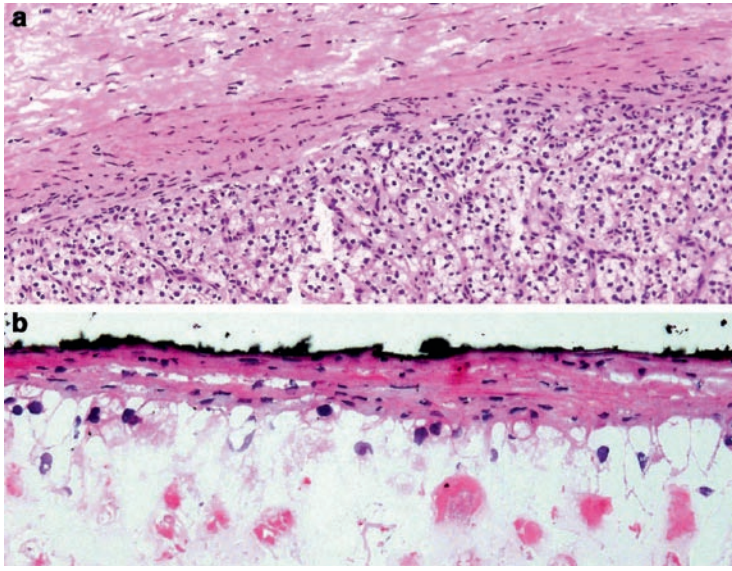


FIGURE 1.36 *Partial nephrectomy specimen*. (**a**) The tumor types selected for partial nephrectomy often are circumscribed or encapsulated, as seen in this low-grade clear cell RCC. (**b**) This observation supports the view that even a microscopic absence of tumor cells at the ink margin is acceptable as "free margin."

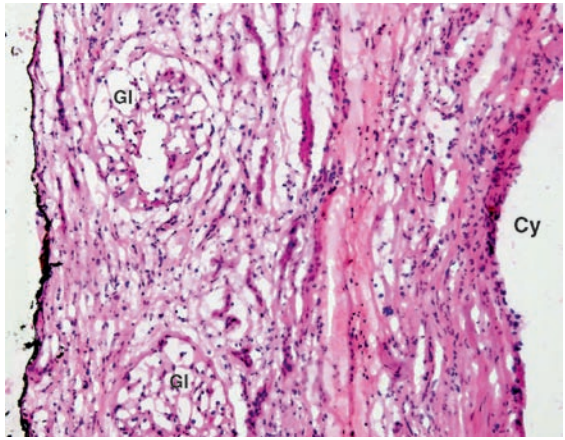


FIGURE 1.37 *Partial nephrectomy for a cystic clear cell RCC*. The tumor cyst (*Cy*) is not obviously lined by tumor cells. Whether tumor cells are present in the pericystic tissue is debatable, since, as mentioned previously, clear tumor cells in this context may be isolated and artifactually loose their clear cytoplasm, and are not readily identified. However, the presence of glomeruli (*Gl*) confidently indicates the absence of tumor tissue and thus a "free" surgical margin.

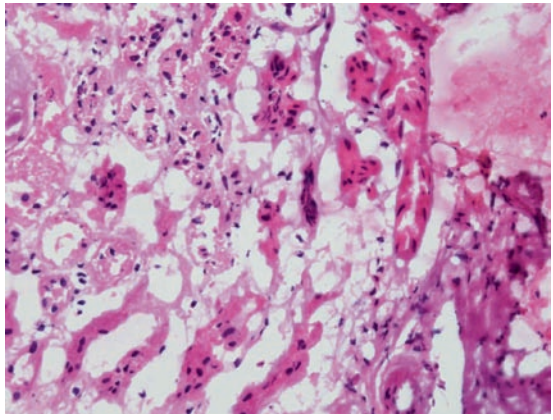


FIGURE 1.38 *Biopsy of the tumor bed during partial nephrectomy*. The submitted tissue is often distorted with artifactual changes. The proximal tubules may simulate oncocytoma. Identifying glomeruli admixed with these tubules confidently indicates the absence of tumor tissue. Even in case glomeruli are not obvious, the uniform tubular structures and nuclear regularity are compatible with proximal tubules (*see also* Figs. 1.18 and 1.20 for comparison with oncocytoma).

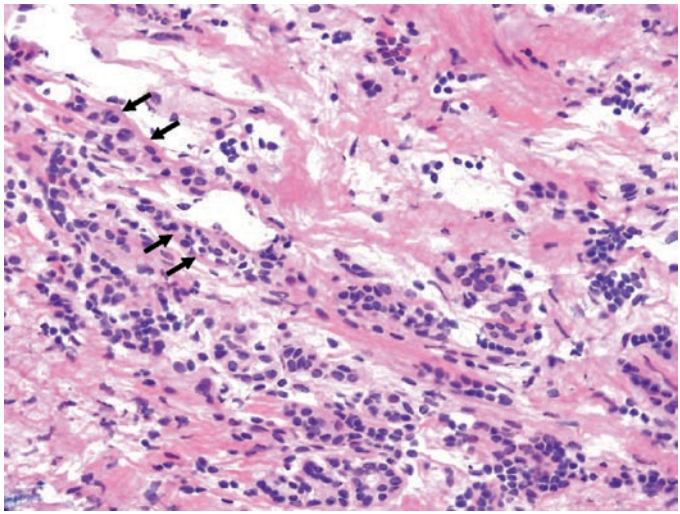


FIGURE 1.39 *Biopsy of the tumor bed during partial nephrectomy*. The peritumoral tissue may show tubular atrophy and interstitial fibrosis, simulating tumor tissue. A correct diagnosis should be facilitated by awareness of this type of changes, the uniform tubular appearance and thickened tubular basement membrane (*arrows*).

changes such as fibrosis or distorted tubules suggests the absence of tumor involvement (Fig. 1.37)

MULTIPLE RENAL MASSES AND EXTRARENAL MASSES

Clinical Background

FS may be requested for specific diagnoses when *multiple masses* are identified in one or both kidneys, or when *extrarenal masses*, including enlarged lymph nodes, are unexpectedly encountered during surgery for renal tumors.

Interpretation

Up to 10% of renal tumors are multiple or bilateral.[39] As listed in Table 1.7, these tumor masses may represent the *same* or *different* histological types.

Satellite Tumor Nodules in RCC

Up to 25% of sporadic RCCs show satellite tumor nodules of the same histological type as the main tumor, but the specific frequency depends on factors such as size, grade, or type of the index tumor.[40]

TABLE 1.7 Types of multiple renal masses.

Same histological types	Different histological types
Sporadic RCC	Clear cell RCC and angiomyolipoma
Clear cell RCC in the context of von Hippel-Lindau disease	Clear cell RCC and collecting duct RCC
Lymphoma	RCC and lymphoma
Angiomyolipoma	RCC, urthelial carcinoma, and lymphoma
Papillary RCC	Angiomyolipoma and cystic nephroma
Oncocytoma	Oncocytoma and chromophobe RCC

RCC = renal cell carcinoma

Since most of these satellite nodules are small and not obvious by renal imaging or during operation, they are not submitted to FS and are usually detected by permanent sections.

Multiple Renal Masses of the Same Histological Type

They may be encountered in the following situations: (1) multiple or bilateral AML seen in up to 70–85% of tuberous sclerosis patients,[19] (2) papillary RCC, which may be multifocal in up to 39% of cases,[41] and (3) oncocytoma, which may be multifocal in up to about 13% of cases.[11] Another condition that features mutifocal oncocytoma is renal oncocytosis, a recently described condition in which multiple oncocytomas, chromophobe RCCs, and tumors with hybrid features are found in the same kidney.[42] FS may be requested for these situations and awareness of them is the key to a correct diagnosis.

Multiple Renal Masses of Different Histological Types

They can be rarely seen in the same kidney, as listed in Table 1.7.[43,44] The gross and histological features of these lesions are similar to those of their respective isolated counterparts.

Renal Tumors in VHL Syndrome

Renal tumors develop in up to 70% of VHL patients during their life span. They display a morphological spectrum that includes variably sized, uni- or multilocular cysts, cysts with solid mural nodules, and solid tumors ranging from microscopic to unequivocal RCC.[45] They are almost always composed of clear cells of low-grade nuclei and simultaneously or sequentially present in the kidneys in various combinations, with RCC encountered in about 50% of patients at an age much younger than for sporadic RCC.[45]

These tumors are usually treated by conservative surgery including tumor enucleation and partial nephrectomy,[46,47] because (1) all of them are now known to be precursors of RCC, (2) new lesions continue to develop in both kidneys throughout life, which may require repeated surgery, and (3) this approach helps delay dialysis dependency until all renal tissue is removed. The renal lesions may be submitted to FS "to rule out RCC." It should be emphasized that all renal lesions in VHL patients have the same cytological features (being composed of clear cells with a low nuclear grade) and represent a morphological continuum within which the demarcation of RCC from the rest may be subjective and, indeed, has not been defined.[45] Since RCC metastasizes in 30–50% of VHL patients and this is the cause of death in 15–50% of them, *a more critical question with FS relevance is at what point RCC in this context can give rise to metastasis*.[45] In this aspect, Walther et al. noted that no patients with a solid tumor smaller than 3 cm left untreated for a median of 60 months developed metastasis.[46] These considerations should facilitate interpretation, when either a cystic or a solid renal tumor in a patient with VHL disease is submitted for FS.

Primary tumors of organs other than kidney often develop in VHL patients and, if encountered during renal surgery, must be differentiated from metastatic RCC. The most frequent problems in this context is *metastatic RCC* versus *pheochromocytoma* of the adrenal (Figs. 1.40 and 1.41), and *metastatic RCC* versus *a variety of primary cystic or solid pancreatic neoplasms*, all of which may feature a prominent clear cell component.[48]

Primary Renal Lymphoma

This tumor, defined as isolated renal involvement without systemic disease, is not rare. Six out of 200 renal tumors initially thought to be RCC were primary renal lymphoma.[49] Primary renal lymphoma may be identical to RCC on imaging studies, but up to a third of them may have unusual features, including multiple masses, predominantly perirenal plaque, or uni- or bilateral diffuse renal enlargement. In contrast, a renal mass in patients with systemic lymphoma may be RCC since a tenfold increase in the incidence of RCC is noted in these patients.[50] FS for a specific diagnosis may be requested since the treatment of choice for renal lymphoma is radiation/chemotherapy, whereas that for RCC is nephrectomy. The FS diagnosis of renal lymphoma is usually not problematic, even in a small biopsy, if the clinical context is aware of. The lesion is composed of compact lymphoid cells, which "crowd out" renal tissue and form nodules, or insinuate between intact renal tubules at the periphery of the nodules (Fig. 1.42).[49]

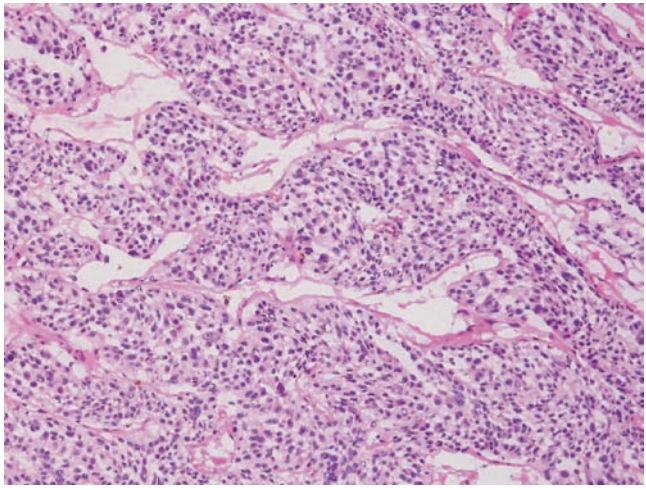


FIGURE 1.40 *Pheochromocytoma*. A large tumor involving both adrenal gland and kidney. Nests of tumor cells with abundant clear or faintly granular cytoplasm separated by dilated thin-walled blood vessels can simulate clear cell RCC.

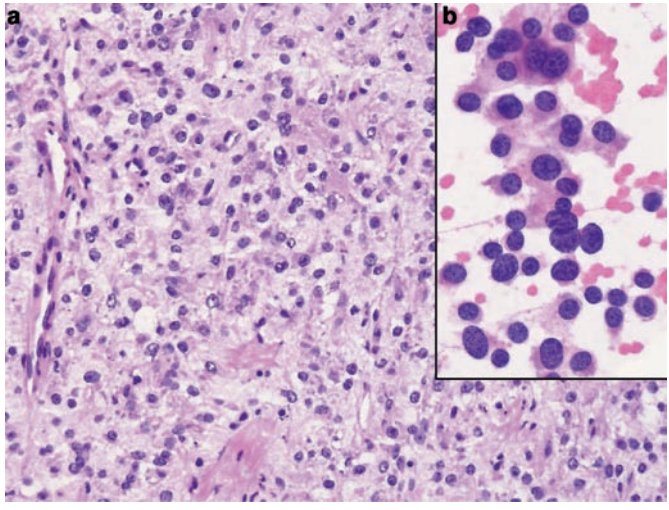


FIGURE 1.41 *Pheochromocytoma*. (**a**) Another area simulating clear cell RCC. (**b**) The touch prep, however, shows typical cytological features of pheochromocytoma, that is, small clusters and isolated cells or bare nuclei, with round nuclear contour and clumpy chromatin.

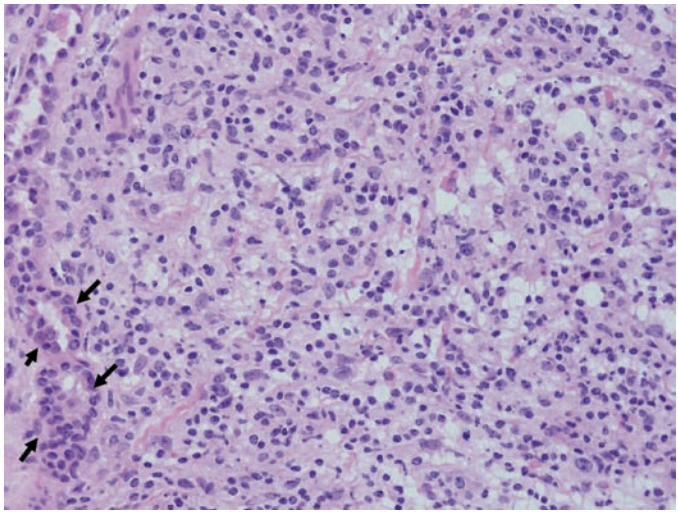


FIGURE 1.42 *Primary renal lymphoma*. Interstitial infiltration by lymphoid cells, several of which show atypical features, that is, large irregular nuclei and prominent nucleoli. Differentiation from interstitial inflammation is possible due to the presence of atypical lymphoid cells, and aggregation of the lymphoid cells to form gross or microscopic nodules, "crowding out" renal tubules (*arrows*).

Lymph Nodes

Nodal dissection is not routinely performed during total nephrectomy since this procedure does not improve survival, and clinically unsuspected nodal metastasis occurs in less than 5% of cases. Clinically recognized nodal metastasis often calls for nodal dissection for tumor staging and debulking purposes. Nodal metastasis is often suspected preoperatively by imaging, thus obviating the need for FS in most instances.[51] However, the enlarged lymph nodes may be due to *metastatic RCC*, *reactive lymphoid hyperplasia*, or *lymphoma*. Thus, FS may be requested. Ectopic adrenal cortex may appear as an isolated nodule in the hilar soft tissue, which may be confused with nodal metastasis on FS (Fig. 1.43).

Metastatic RCC often displays the same histological spectrum as the primary tumor; the primary tumor, however, may not be available for comparison since nodal FS may be performed prior to nephrectomy. Noting that nodal tumor tissue often show high-grade clear cell, papillary or sarcomatoid features may help with FS interpretation.[4] Micrometastasis may coexist with reactive lymphoid hyperplasia.

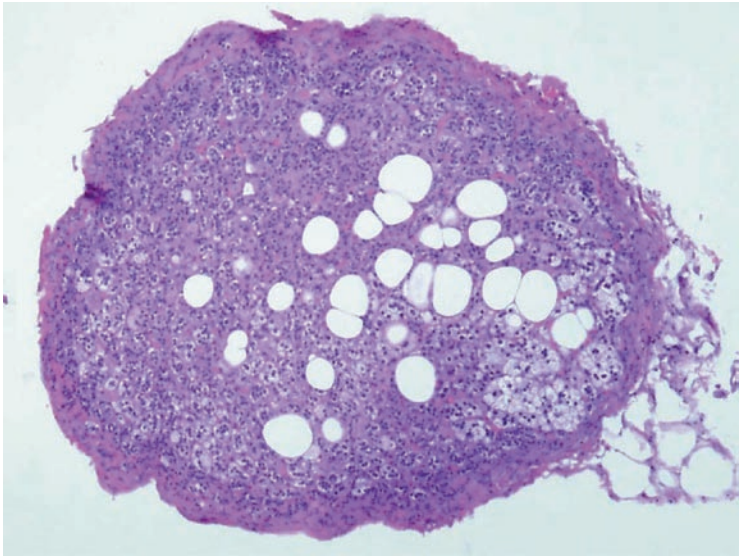


FIGURE 1.43 *Ectopic adrenal cortex* in permanent section. This nodule of ectopic adrenal cortex is detected in the nodal resection specimen for renal cell carcinoma. Other lymph nodes show reactive lymphoid hyperplasia. This type of lesion can simulate nodal metastasis of RCC in FS.

Since a tenfold increase in the incidence of RCC is recently reported in patients with lymphoma,[50] enlarged lymph nodes in the context of nephrectomy for RCC may be due to associated lymphoma. Awareness of this association aids in the differential diagnoses and ensures proper tissue triage for special studies, including flow cytometry and gene rearrangement. AML tissue may be encountered in lymph nodes but this represents multifocal tumor rather than metastasis.[19]

Extrarenal Masses

These masses may be encountered during surgery for a primary renal tumor and are often submitted for FS. These often include *adrenal masses* or *masses of other organs including peritoneum.*

Masses of other organs may be metastatic RCC or incidental lesions unrelated to RCC. In our experience, adrenal masses are most frequent and may include *RCC extending* or *metastatic to adrenal gland*, *adrenal cortical adenoma* or *nodule, adrenal cortical carcinoma extending to the kidney*, and *pheochromocytoma* (Figs. 1.40 and 1.41).

NEEDLE BIOPSY OF NATIVE OR TRANSPLANTED KIDNEYS

Clinical Background

These biopsies are usually "signed out" by a renal pathologist from specialized in-house units or referral laboratories. However, initial handling of these biopsies may require *immediate attention* of a general pathologist to determine whether the biopsy is adequate, so if additional tissue is needed, it can be obtained during the same procedure.

Specimen Handling

A spring-loaded biopsy device attached to a needle is currently used in most institutions. Although the needle can be of 14, 16, or 18 gauge, of which the smaller ones are usually preferred. Usually two or three tissue cores obtained by needle biopsy are submitted in saline or a preservative medium (usually a tissue culture fluid). How to divide these tissue cores for different studies is well described,[52] but is beyond the scope of this monograph. However, as mentioned above, requests may be made during the biopsy procedure to determine whether the biopsy is adequate.

Most native kidney biopsies are done for glomerular diseases. Many of the diseases accounting for renal allograft dysfunction are best represented in renal cortical tissue. *Therefore, the first goal of adequacy check is identifying renal cortical tissue including glomeruli*. Among various reported methods, we found the following accurate and technically feasible method, regardless of individual laboratory setting.[53] The tissue cores should be placed on a regular glass slide within a drop of preservative medium and examined under a regular light microscope.

Interpretation

The above procedure usually allows accurate identification of soft tissue (fat, skeletal muscle, fibrous tissue) and renal tissue including cortical tissue, glomeruli, larger blood vessels, and medullary tissue (Fig. 1.44). *Open* glomeruli are usually easily and accurately identified owing to the presence of red blood cells within the glomerular capillary lumens. Gently putting a glass coverslip on top of the cores will flatten them and enhance glomerular visualization. Sclerotic glomeruli or glomeruli with marked hypercellularity may not be visualized by this technique.

How much cortical tissue is considered adequate for a native kidney biopsy has not been established. The glomerular involvement in a specific renal disease may be patchy [segmental (a portion of the glomerular capillaries affected), global (all glomerular capillaries

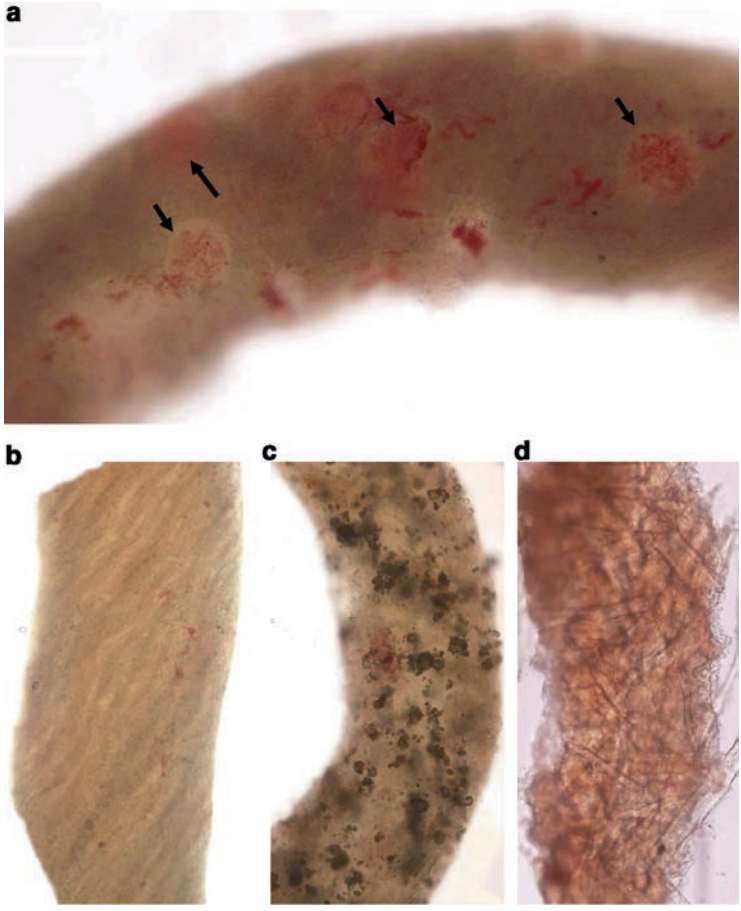


FIGURE 1.44 *Needle renal biopsy examined by regular light microscopy*. (**a**) Cortical tissue with several open glomeruli (arrows). (**b**) Medullary tissue characterized by a parallel distribution of renal tubules and an absence of glomeruli. (**c**) Cortical tissue with abundant crystalline deposition. The permanent sections show calcium oxalate nephropathy. (**d**) Skeletal muscle fibers.

of a glomerulus affected), focal (only some glomeruli affected), or diffuse (all glomeruli affected)]. Thus, a few glomerular capillaries are adequate for a global diffuse disease process, but a large number of them are needed for a focal segmental disease process. For example, for a disease process with an expected involvement

of 10% of glomeruli, the chance to detect the lesion in a renal biopsy with ten glomeruli is 65%. This chance will increase to 95% for a disease process with an expected involvement of 35% of glomeruli.[54] These numbers, however, are derived from studies of tissue sections. How the number of glomeruli recognized by the above technique (three-dimensional) correlates with the number of glomeruli seen in the corresponding tissue sections (two dimensional) has not been determined, but the former is significantly higher in our experience. *We therefore empirically set the threshold for adequacy to include at least two cores of renal tissue with at least a half of the total tissue area being cortical tissue.*

For renal transplant biopsy, a retrospective study shows that the sensitivity for the diagnosis of rejection is 90% for one core and 99% for two cores.[55] The increasingly accepted Banff scheme for renal transplant biopsy stipulates that an adequate renal transplant biopsy should contain two tissue cores, with at least seven nonsclerotic glomeruli and two small artery profiles.[56] These numbers are intended for tissue sections. How to translate this threshold into immediate adequacy check of tissue cores is not clear. *We therefore empirically set the threshold for adequacy the same as for native kidney biopsy, that is, at least two cores of renal tissue with at least a half of the total tissue area being cortical tissue.*

DONORS' KIDNEYS

Clinical Background

Clinical criteria (no history of renal disease or hypertension, normal renal function, and normal urinalysis) are traditionally used to determine whether a donated kidney is accepted for transplantation. However, in response to the increasing shortage of donated kidney, kidneys from donors who do not meet these stringent criteria (expanded criteria donors) are *considered* for transplantation. *Biopsies from these kidneys with FS consultation* may play an important role in the clinical decision of whether these kidneys are accepted or rejected.[57] The possible indications for FS of a donated kidney are listed in Table 1.8. Morphological changes can be more sensitive than clinical parameters in predicting parenchymal injury and they may be pronounced even when renal function is normal.[58] This discrepancy usually encountered in kidneys from expanded criteria donors. These donors are often affected with conditions that may promote renal scarring and these conditions are best demonstrated by FS.[58] In USA, about 75% of the kidneys from these donors are biopsied, and about 41% of them were discarded, basing in part on the biopsy findings at FS.[57]

TABLE 1.8 Donors' kidneys: Reasons for frozen section consultation.

Conditions that may promote renal scarring
Donors older than 60 years
History of diabetes mellitus
History of hypertension
Cerebrovascular accident as the cause of death
Conditions that may promote renal necrosis
Hypotension at time of renal harvesting
Acute tubular necrosis
Disseminated intravascular coagulation
No heart beat at time of renal harvesting
Abnormal intraoperative observations
Small kidney
Granular renal surface
Petechial renal hemorrhage
Renal tumor
Abnormal laboratory findings during renal harvesting
Serum creatinine greater than 1.5 mg/dl
Hematuria
Proteinuria
Rapid deterioration of renal function

Specimen Handling

Either wedge or needle biopsy may be submitted. Wedge biopsy provides more tissue but may sample subcapsular cortical scars where globally sclerotic glomeruli may be overrepresented, a fact that should be taken in consideration during FS.[58] Needle biopsy may be more representative but may not provide enough tissue. In our practice, up to four pieces (less than 1 mm each) are obtained from the biopsies and saved for possible electron microscopy. The remaining tissue is divided into two portions and entirely submitted for FS. At the completion of FS, one block will be submitted for light microscopy and the other for immunofluorescent study. Permanent sections of the previously frozen tissue may show artifacts, which hamper precise interpretation. We, however, believe this limitation is well compensated for by the more accurate and timely available information if the entire specimen is submitted to FS. The exact definition for an adequate sampling has not been established. We empirically ask for cortical tissue with at least 25 glomeruli.[52,58] Additional tissue should be requested if this criteria is not met.

Interpretation

The following types of lesions should be sought: chronic parenchymal injury, intravascular coagulation, cortical necrosis, and glomerulonephritis.

TABLE 1.9 Grading of chronic renal injury in donors' kidneys.

Glomerulus	
Number of glomeruli in the biopsy	
Percentage of sclerotic glomeruli	
Tubulointerstitium (percentage of cortical areas with tubular atrophy, interstitial fibrosis, and interstitial inflammation)	
Normal	0–5%
Mild	6–25%
Moderate	26–50%
Blood vessels (fibrotic or hyaline intimal thickening of small arteries or arterioles as percentage of the original vascular lumen)	
Normal-Mild	<25%
Moderate	26–50%
Severe	>50%

Evaluating *chronic parenchymal injury* should include separate evaluation of glomerular, tubulointerstitial, and vascular injury as listed in the Table 1.9. Although these parameters are separately evaluated, their severity roughly correlates with one another.[58] In FS, normal renal tissue may show tubular retraction associated with apparent expanded and edematous interstitium, which may be confused with chronic injury (Fig. 1.45). Chronic injury, however, should also include tubular atrophy, fibrous stroma, and increased stromal cellularity including inflammatory cells (Fig. 1.46). As mentioned above, subcapsular scar should be ignored in evaluating the extent of chronic tubulointerstitial injury (Fig. 1.47). Sclerotic glomeruli may be difficult to identify in FS and a longer exposure to eosin may be helpful (Figs. 1.47 and 1.48). The vascular changes most often include arteriolar hyalinosis and arterial fibrointimal thickening (Table 1.9 and Figs. 1.49 and 1.50) *The morphological threshold of chronic injury for accepting or rejecting a donor's kidney has not been established*.[58,59] We therefore accurately report the observed changes together with their respective severity, so that the transplant surgeon can incorporate them in their preferred final decision scheme. For example, one group declines to transplant the donated kidney when significant injury (defined as more than 20% glomeruli with global sclerosis or more than mild tubulointerstitial or vascular injury) is noted in any compartment.[58,60]

Intravascular coagulation may be seen in up to 10% of unselected donor renal biopsies and this incidence may be as high as 30% in those who died of brain trauma (probably due to sudden

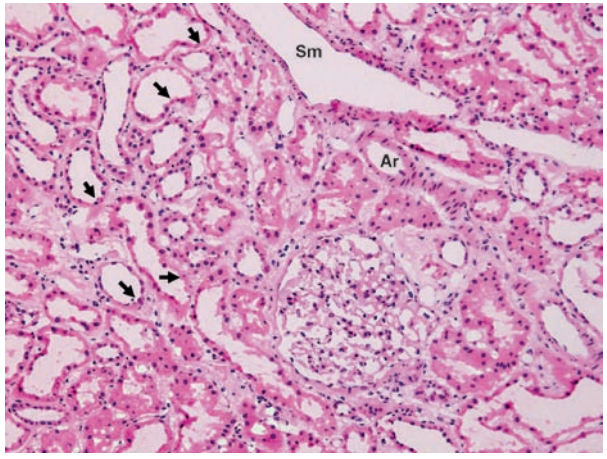


FIGURE 1.45 *Donor kidney*. No pathological alteration. The tubules are not "back-to-back" but are separated by a widened interstitial space: This is an almost constant artifactual change. The tubules have normal sizes and shapes. There is focal flattening of the tubular epithelial cells (*solid arrows*), which may represent artifact or acute tubular cell injury, but should not affect the decision to accept or deny the donor kidney. The small artery (*Sm*) and arteriole (*Ar*) are normal with an inconspicuous intima.

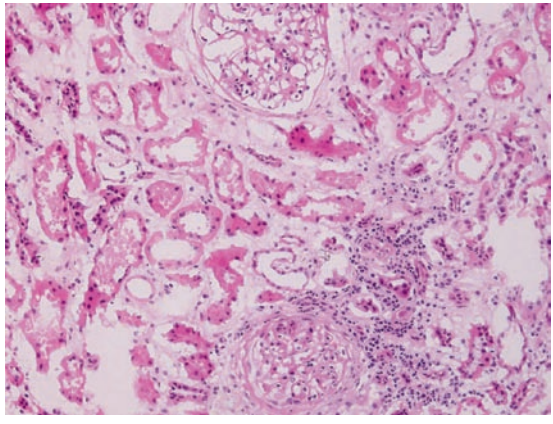


FIGURE 1.46 *Donor kidney*. Focal chronic tubulointerstitial injury (lower right) characterized by tubular trophy, thickened tubular basement membrane, interstitial fibrosis, and mild interstitial inflammation. A glomerulus in this area also shows features of chronic ischemic injury, including reduced size, mesangial sclerosis, and thickened glomerular capillaries. These changes contrast with the adjacent normal kidney tissue.

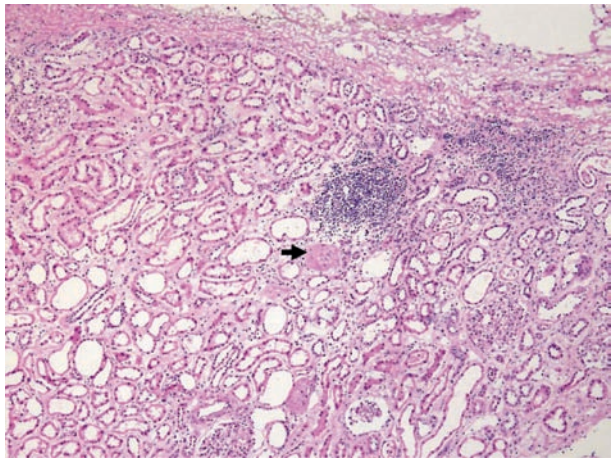


FIGURE 1.47 *Donor kidney*. A subcapsular scar characterized by a triangular area of chronic tubulointerstitial injury and sclerotic glomeruli (*arrow*) just below the renal capsule. The kidney tissue elsewhere is unremarkable. Area like this should be ignored in evaluating the extent of chronic tubulointerstitial injury.

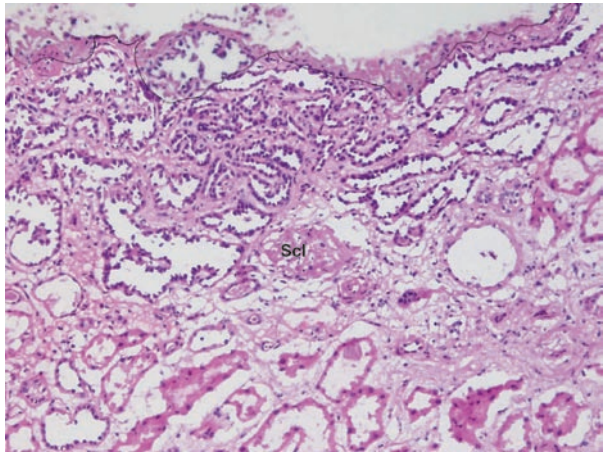


FIGURE 1.48 *Donor kidney*. A subcapsular microscopic papillary adenoma. Although this type of lesion is often associated with chronic ischemic renal injury, it should not by itself preclude donor acceptance. Adjacent to the adenoma is an area of chronic tubulointerstitial injury including a sclerotic glomerulus (*Scl*).

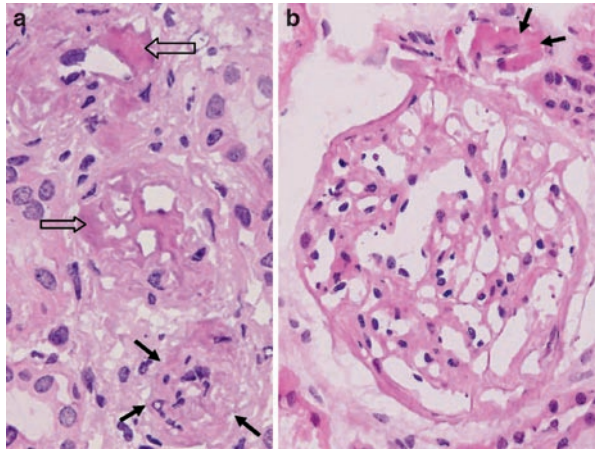


FIGURE 1.49 *Donor kidney*. (**a**) An arteriolar profile with marked intimal fibrous thickening and almost complete obliteration of the vascular lumen (*solid arrows*). Two arteriolar profiles with segmental hyalinosis (*open arrows*), intimal fibrous thickening, and almost complete obliteration of the vascular lumen. (**b**) Circumferential arteriolar hyalinosis with almost obliteration of the vascular lumen (*arrows*).

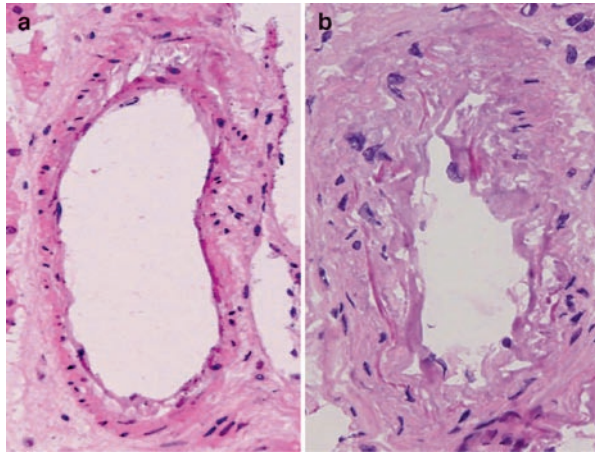


FIGURE 1.50 *Donor kidney*. (**a**) Normal small artery, with well-defined but thinned media and inconspicuous intima. (**b**) A small artery with thickened wall including intimal fibrosis, encroaching probably more than 50% of the original vascular luminal area.

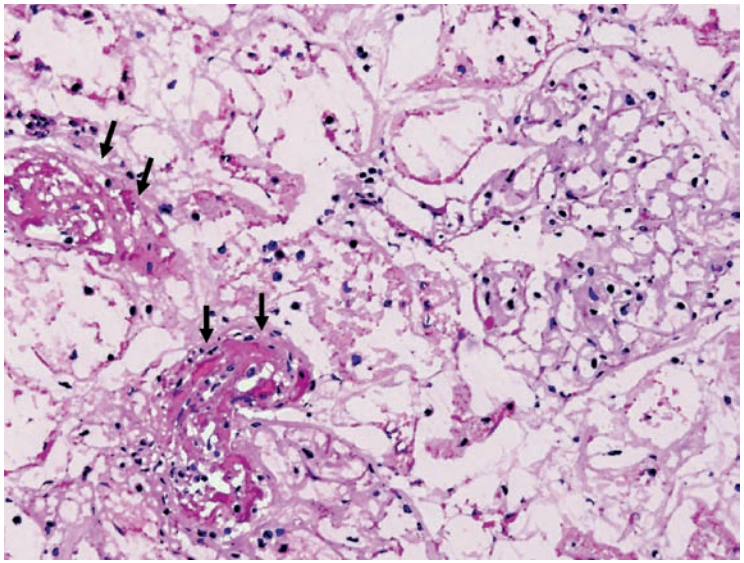


FIGURE 1.51 *Donor kidney*: Intravascular coagulation (*arrows*) with cortical necrosis characterized by necrosis of all tissue components including tubules and glomeruli.

release of brain thromboplastin, a potent procoagulant, into the circulation).[61] This is a frequent cause of petechial hemorrhage observed on the renal surface intraoperatively. It is characterized by the presence of fibrin thrombi in rare or many glomerular capillaries and in other blood vessels much less frequently. These thrombi, once being aware of, should be easily detectable in FS (Fig. 1.51). Intravascular coagulation, even when severe, should not, by itself, be a contraindication for transplantation, since the long-term outcome of the transplanted kidneys with this lesion is comparable with controls.[61] However, severe and prolonged intravascular coagulation may induce cortical necrosis which renders the kidney unacceptable.

Cortical necrosis is characterized by necrosis of all cortical elements including *tubules and glomeruli* and the injury is irreversible. Cortical necrosis in donor kidney is very rare and almost always due to massive intravascular coagulation.[61] Cortical necrosis must be differentiated from acute tubular cell injury, in which acute injury, including necrosis, is limited to the tubular cells and

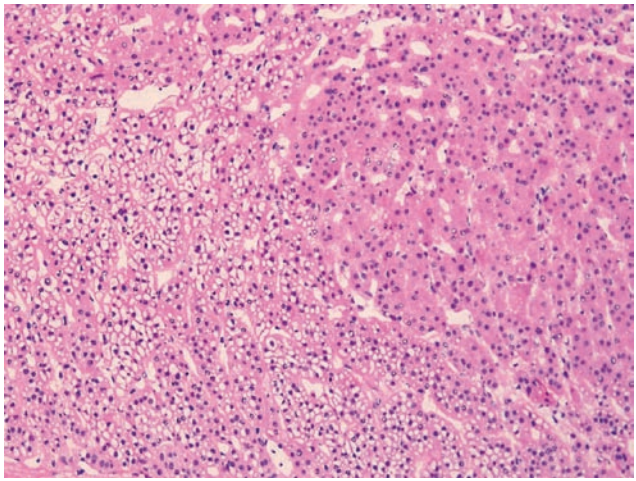


FIGURE 1.52 *Adrenal cortical heterotopia* can be seen within the donor kidney and must be differentiated from renal cell carcinoma. The presence of both clear and granular cell types and a uniform trabecular pattern are diagnostic clues.

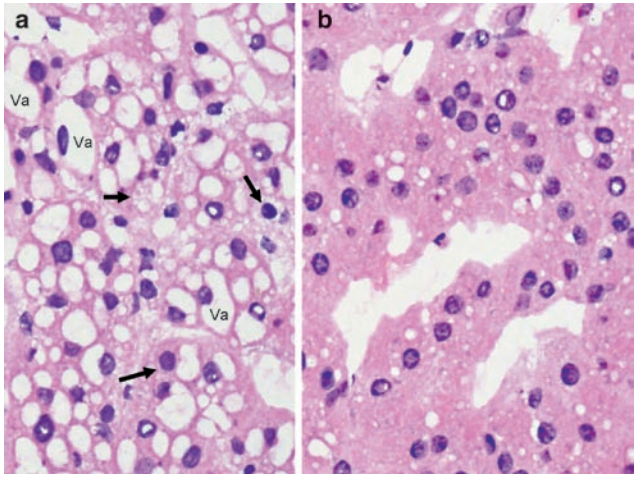


FIGURE 1.53 *Adrenal cortical heterotopia*. (**a**) At higher magnification, the cells in the clear area may show a single cytoplasmic vacuole (*Va*), an artifact; but may display finely vacuolated cytoplasm (*arrows*), typical for the adrenal cortical cells in the zona fasciculata or zona glomerulosa. (**b**) The cells with granular cytoplasm display uniform round nuclei and a trabecular growth pattern typical for the cells in the zona reticularis.

the injury is potentially reversible. Recognizing cortical necrosis in FS may not be difficult, especially in case of frank coagulative necrosis or infarct (Fig. 1.51), but acute tubular injury may be very difficult to diagnose since many changes characteristic for acute tubular injury are either masked by FS or confused with FS artifacts (Fig. 1.45). Fortunately, acute tubular injury is not a reason for rejecting a kidney since, when transplanted, such kidney may have delayed graft function but enjoys a normal long-term outcome.[58]

Donors with a significant *glomerulonephritis* are often recognized and eliminated by clinical criteria. Mild glomerulonephritis, which is often asymptomatic, may escape FS detection only to be diagnosed on permanent studies. This sequence is probably most frequent for IgA nephropathy, a disease with very high prevalence in some ethnic groups. Other diseases have been rarely reported including lupus nephritis, membranous glomerulonephritis, and membranoproliferative glomerulonephritis.[62] Fortunately, these mild forms of donor-transmitted glomerulonephritis have not shown to adversely affect the long-term graft and may even regress.[58]

Grossly visible *subcapsular nodules* may be identified during renal harvesting. They are usually excised and submitted for FS for both diagnosis and surgical margin. An accurate diagnosis is important in this context. If a benign tumor such as cyst, leiomyoma, AML, papillary adenoma (papillary growth, low nuclear grade, less than 0.5 cm), or adrenal cortical heterotopia is identified, it should not be a cause for rejecting the kidney.[58] True RCC that escapes clinical screening are, however, identified in up to 0.3% of donated kidneys.[63] Whether it precludes transplantation has not been determined but probably depends on many features including tumor size, histological type, and nuclear grade. FS should be helpful in this context. A misdiagnosis of RCC for adrenal cortical heterotopia may result in the discard of not only the kidney with the lesion but also the contralateral kidney. This happens in 3 of the 12 renal cortical nodules reported by Ditonno et al.[64] Conversely, transplantation of a kidney in which RCC is incorrectly diagnosed as adrenal cortical heterotopia by FS may result in subsequent graft nephrectomy.[64] A surgical margin negative for tumor is also important since a positive margin may be associated with subsequent metastasis.[65] Among the RCC types, adrenal cortical heterotopia may closely simulate a low-grade clear cell RCC. Features that facilitate their differential diagnoses are illustrated in Figs. 1.52 and 1.53.

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