# Principles and Practice of Genitourinary Oncology

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CHAPTER 77

# Pathology of Renal Cancers

## Lawrence D. True and David Grignon

Although this chapter focuses on malignancies, benign tumors are discussed when relevant to the differential pathologic diagnosis. Because an accurate pathologic diagnosis evolves from an accurate differential diagnosis, charts are provided that list the differential diagnostic considerations of tumors based on both gross and microscopic features. Furthermore, because accurate distinction of poorly differentiated tumors is best done by characterizing antigens expressed by the tumor cells, the immunohistochemical profiles of selected tumors is provided. Information is given concerning the genetic features of renal cell carcinomas.

## EPITHELIAL NEOPLASMS

### Principles of Pathologic Classification

The classification of renal epithelial tumors has traditionally been based on the cytologic and architectural patterns of growth. This approach is generally used in North America (see Table 77-1). Thoenes and colleagues[1] have proposed a system that is based on the cytoplasmic features of cells; this system has gained acceptance in Europe. Kovacs[2] presented a scheme based on cytogenetic features. These schemes are summarized in Table 77-2.

An assumption of these classifications is that cells in a given tumor have a common phenotype; however, many tumors belie this assumption. Some renal cell carcinomas are composed of mixtures of clear cells, granular cells, and spindle cells, and mixed collecting duct–transitional cell carcinomas have been reported.[3] The proportion of cells of different histologic type comprising tumors may be prognostically important.[4]

### Renal Cell Carcinoma, Usual Type

More than 90% of solid epithelial renal tumors are of the usual type. Although most cases occur sporadically, a small percentage of cases have a hereditary association (e.g., von Hippel-Lindau disease, tuberous sclerosis, adult polycystic kidney disease). Hereditary tumors tend to be multifocal and bilateral, in contrast with sporadic tumors, which tend to have a single focus and be unilateral. However, the histology of hereditary and sporadic tumors is identical. Both sporadic and familial tumors have similar cytogenetic changes, the most frequent of which are deletions within 3p. The von Hippel-Lindau locus has been mapped to 3p25. In addition, most renal carcinomas have deletions within 3p12-14.2.[5-9] Fluorescent in situ hybridization has demonstrated ploidy heterogeneity within tumors.[10]

Renal cell carcinomas have a highly variable gross appearance. Typically, they are large, lobulated masses that distort the kidney and bulge into perinephric fat (Fig. 77-1), which is not necessarily indicative of extracapsular invasion. A fibrous pseudocapsule gives these tumors a sharply circumscribed appearance. The cut surface is variegated yellow (indicating either necrosis or the high lipid content of clear tumor cells or macrophages) to red-brown (indicating a granular cell component). Necrosis, hemorrhage, cystic change, and fibrosis are frequent. Some cystic tumors resemble a multilocular cyst. Gross invasion of the renal vein or vena cava occurs in as many as 40% of cases.[11]

Histologically, the usual renal cell carcinoma is composed predominantly of clear, lipid-rich cells (Fig. 77-2). Variable numbers of eosinophilic (granular) and, rarely, spindle cells may be present. Tumors composed predominantly of spindle cells are classified as sarcomatoid carcinomas (discussed later). The ratios of cell types may be of prognostic value[4]; an increased proportion of spindle cells portends a poorer prognosis. Typically, tumor cells grow as sheets or confluent nests with a prominent sinusoidal vascular pattern. Other patterns (e.g., tubular, alveolar, papillary) may be present.

The most common grading scheme is a four-point system based on nuclear features.[12] Grade 1 nuclei are small, round, and hyperchromatic, without observable nucleoli. Grade 2 nuclei are large, with an open chromatin pattern and small nucleoli. Grade 3 nuclei have large, prominent nucleoli. Grade 4 nuclei are large and pleomorphic with marked atypia and hyperchromasia. Nuclear grade, which correlates with mitotic activity, has significant prognostic power, independent of tumor stage. The grade assigned is that of the highest grade within the tumor, even if it is only focal. Nuclear morphometry is potentially a more reliable way of grading renal carcinomas.[13]

Pathologic staging of resection specimens, using the TNM system of the Union Internationale Contre le Cancre, is based

**TABLE 77-1.** *Histologic classification of kidney tumors according to the modified WHO scheme*

Epithelial tumors of renal parenchyma
  Adenoma, including oncocytoma
  Carcinoma
    Usual renal cell carcinoma
    Other histologic types
Epithelial tumors of renal pelvis
  Transitional cell papilloma
  Transitional cell carcinoma
  Squamous cell carcinoma
  Adenocarcinoma
  Undifferentiated carcinoma
Nephroblastic tumors
  Nephroblastoma (Wilms' tumor)
  Mesoblastic nephroma
  Multilocular cystic nephroma (multilocular cyst)
Nonepithelial tumors
  Benign
    Angiomyolipoma
    Fibroma
    Hemangioma
    Others, including leiomyoma, lipoma, and neurilemmoma
  Malignant
    Sarcoma
Miscellaneous tumors
  Juxtaglomerular cell tumor
  Others, including neuroblastoma, carcinoid, and teratoma
Secondary (metastatic) tumors, including lymphoma
Unclassified tumors
Tumor-like lesions
  Renal blastema, persistent or massive
  Renal dysgenesis
  Cysts
  Xanthogranulomatous pyelonephritis
  Malakoplakia
  Others

Mostofi FK. Histological typing of kidney tumours. World Health Organization, Geneva, 1981.

**TABLE 77-2.** *Classification schemes of renal epithelial tumors*

| WHO (Mostofi, 1981) | Thoenes et al, 1986[1] | Kovacs, 1993[2] |
|---|---|---|
| Adenoma | Renal cell | Papillary tumor |
| Renal cell | carcinoma | Adenoma |
| carcinoma | Clear cell | Carcinoma |
|   Clear cell | Chromophil | Nonpapillary |
|   Granular cell |   Eosinophil | carcinoma |
|   Spindle cell |   Basophil | Chromophobe |
| Others | Chromophobe | carcinoma |
|   Collecting duct |   Typical | Oncocytoma |
|   Chromophobe cell |   Eosinophil | |
| | Collecting duct | |
| | Oncocytoma | |

on both gross and microscopic findings. Gross data include tumor size (the size threshold distinguishing T1 and T2 tumors is 2.5 cm in greatest dimension), invasion of perinephric tissues, involvement of extrarenal organs (e.g., lymph nodes, adrenal gland), and invasion of the renal vein, vena cava, or both. Microscopic invasion of vessels is irrelevant for staging. Invasion of perinephric fat requires histologic confirmation that tumor cells extend beyond the kidney parenchyma and the tumor pseudocapsule, if present.

Stage is the best predictor of tumor behavior.[11] Markers of cell proliferation, including mitotic activity, expression of proliferating cell nuclear antigen or the Ki-67 epitope, and S-phase fraction of cells, determined by flow cytometry, correlate with grade and survival but do not consistently provide prognostic information of value beyond that provided by stage and grade.[14–16]

### Adenoma

The distinction between adenoma and carcinoma is an unresolved but significant issue, because many small lesions are
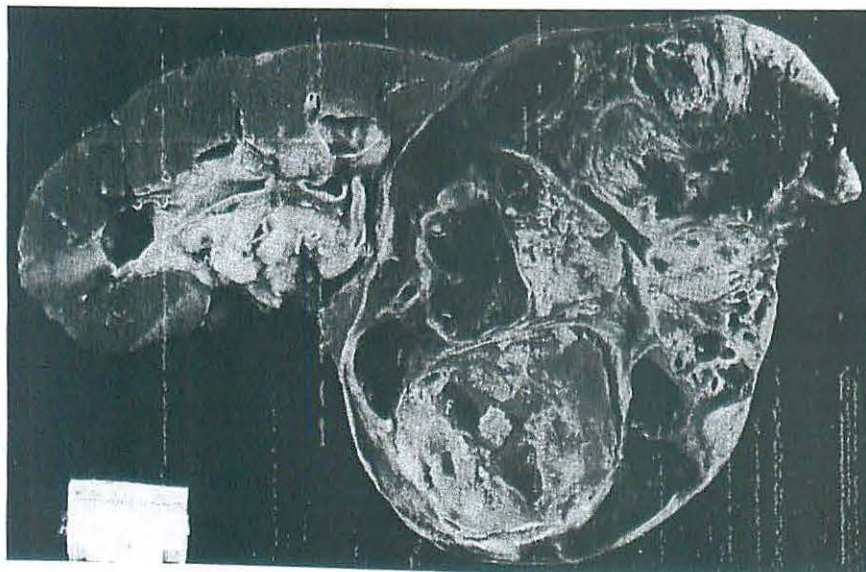


**FIG. 77-1.** The typical gross appearance of renal cell carcinoma is a large tumor mass with cystic areas admixed with bridging bands of fibrous tissue, and more solid areas of renal cell carcinoma, which are multifocally yellow as a result of the clear cell component of this tumor.
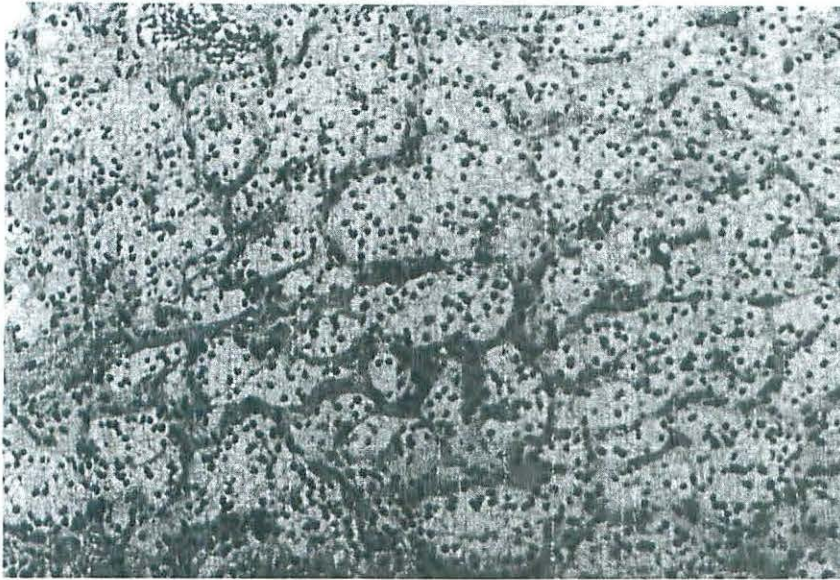
**FIG. 77-2.** The most common histologic pattern of clear cell—type renal cell carcinoma consists of cells with a clear cytoplasm as a result of the high content of lipid, which is extracted during tissue processing. Note the fine network of capillaries between the nests of tumor cells. This tumor is classified as Fuhrman's grade 2 because of the small nuclei and infrequent nucleoli.

being detected with increasingly sensitive techniques. In a large autopsy series, small cortical epithelial lesions were found in 21% of patients; frequency increased with age, from 10% in 21- to 40-year-old patients to 40% in 70- to 90-year-old patients.[17] Adenomas have other clinical associations. Those with a papillary histology are often multiple and are associated with papillary carcinoma.[18] Many patients with acquired cystic disease develop adenomas. Papillary adenomas have characteristic cytogenetic changes: trisomy 7 and 17 and loss of the Y chromosome.[18]

Grossly, the adenoma is sharply circumscribed and yellowtan to gray; it protrudes from the cortical surface. Histologically, the tumor has a tubulopapillary architecture and lacks a capsule, merging with adjacent renal parenchyma. Cells have an eosinophilic to basophilic cytoplasm and small, uniform nuclei (Fig. 77-3). When clear tumor cells are present, the tumor should be regarded as a carcinoma, regardless of size.
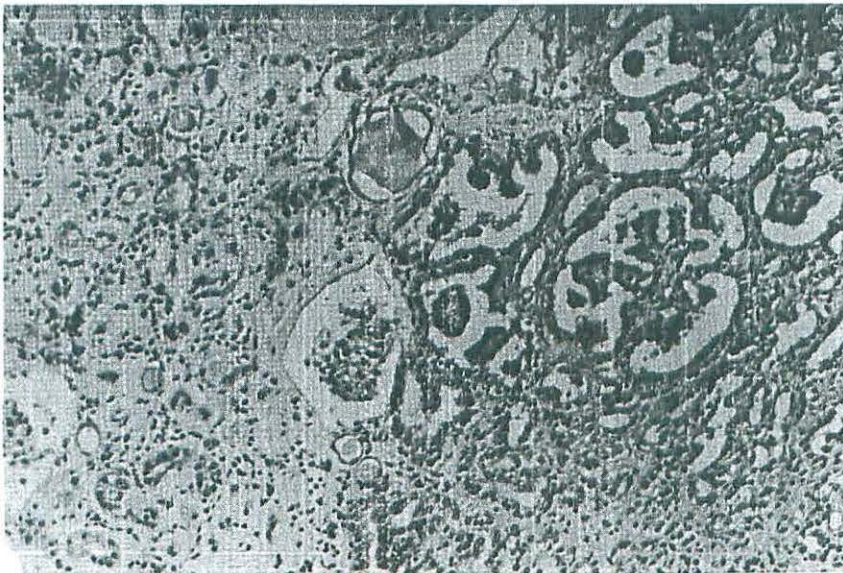
Investigators have used different pathologic criteria to distinguish adenoma from carcinoma. Size is not a sufficiently specific criterion, because small tumors (as small as 0.5 cm in diameter) have metastasized.[19] Some authors restrict the diagnosis of adenoma to small lesions composed of closely packed tubules and papillae with small, uniform cuboidal cells having nuclei of uniform size and shape and virtually absent mitoses.[20] Others recommend diagnosing such tumors as "small renal epithelial neoplasms of low malignant potential."[21] Adenoma should not be diagnosed by fine needle aspiration biopsy, because sampling may not be representative.

**Papillary Renal Cell Carcinoma**

As many as 10% of renal cell carcinomas are papillary variants; according to Kovacs and Kovacs'[18] criteria, more than



**FIG. 77-3.** A typical adenoma is not encapsulated and has a complex papillary tubular architecture of cells with scanty basophilic cytoplasm and a high nuclear—cytoplasmic ratio but minimal nuclear atypia. No mitoses are seen.

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