Pathology of Renal Cell Carcinoma

4

Fang-Ming Deng, Jonathan Melamed, and Ming Zhou

Introduction

Many histological parameters obtained from routine pathological examination of renal tumor provide invaluable prognostic values. In the current WHO classification, the major histologic variants of RCC, namely, clear cell, papillary, chromophobe, and collecting duct renal cell carcinoma, account for 90–95 % of renal carcinoma. The classification also includes some less commonly encountered types and the "unclassified type." These tumor types represent the most common RCC subtypes encountered clinically. However, many other less common subtypes of RCC have been described with distinct clinical, pathological, and genetic features, and it is likely that additional ones will be identified in the future. As the molecular mechanisms of renal tumors have been increasingly elucidated, molecular classification may eventually replace morphological classification. The clinical, pathological, and genetic features in combination will eventually enable urologists to predict individual tumor behavior and stratify patients into more sophisticated risk groups, ultimately rendering individualized management and treatment options.

According to the World Health Organization (WHO), more than 270,000 new cases and 116,500 deaths from kidney cancer occurred worldwide in 2008 [1]. Arising from the renal tubular epithelial cells, renal cell carcinoma (RCC) accounts for more than 90 % of primary kidney tumors in adults. It encompasses a group of heterogeneous tumors with diverse clinical, pathological, and molecular characteristics as well as varied prognostic implications and distinct therapeutic options and responses. It is therefore of paramount importance to accurately classify renal tumors. In this chapter, we review the pathological and molecular characteristics of major histological subtypes of RCC that are recognized in the current WHO 2004 classification of renal tumors [2]. We also discuss several newly described subtypes of RCC and RCC associated with inherited cancer syndromes. The prognostic significance of various histological parameters will also be highlighted [3–5].

Pathological Classification of RCC

In addition to rendering an accurate diagnosis, pathological classification of RCC also provides relevant prognostic information and guidance to therapy.

F.-M. Deng, M.D., Ph.D. • J. Melamed, M.D.
Departments of Pathology and Urology,
New York University Langone Medical Center,
New York, NY, USA

M. Zhou, M.D., Ph.D. (✉)
Departments of Pathology and Urology,
New York University Langone Medical Center,
560 First Ave, New York, NY 10016, USA
e-mail: ming.zhou@nyumc.org

J.A. Libertino (ed.), *Renal Cancer: Contemporary Management*,
DOI 10.1007/978-1-4614-7236-0_4,

Table 4.1 2004 World Health Organization classification of renal cell carcinoma [2]

Renal cell carcinoma
Clear cell renal cell carcinoma
Multilocular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinomas
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Renal cell carcinoma, unclassified

The current 2004 WHO Classification of RCC [2] follows on earlier Heidelberg [6] and Rochester classifications, [7] which in turn represent expansions of the Mainz Classification [8]. The current classification emphasizes the heterogeneity of RCC and defines distinct types of RCC based on unique morphologic and genetic characteristics. This represents a major change from the earlier classifications of RCC where tumors were considered as a single relatively uniform group and, in a pioneering fashion, incorporates genetic characteristics into the classification.

In the current WHO classification, the major histologic RCC subtypes, namely, clear cell, papillary, and chromophobe RCC, account for 90–95 % of renal carcinoma (Table 4.1). This classification also includes some less commonly encountered types, which are multilocular cystic clear cell carcinoma, collecting duct carcinoma, renal medullary carcinoma, Xp11 translocation carcinoma, carcinoma associated with neuroblastoma, and mucinous tubular and spindle cell carcinoma. An important category retained in this classification is the "unclassified type" which is assigned when a tumor does not readily fit into any of the recognized subtypes. This unclassified group is useful to define a group of renal cancer whose clinicopathological and molecular characteristics are not well defined yet clearly different from other histological subtypes. These ten tumors represent the most common RCC subtypes encountered clinically. However, other renal cancers have been recently described with clinical, pathological, and genetic features distinct from these ten tumors, and it is likely that additional ones will be identified in the future. As the molecular mechanisms of renal tumors are increasingly elucidated, molecular classification will supplement and may eventually replace the morphological classification.

Pathologic and Molecular Characteristics of Subtypes of RCC

Renal Cell Carcinoma, Clear Cell Type (CCRCC)

Clinical Features

CCRCC is the most common histological subtype and accounts for 60–70 % of all RCCs. Although it may occur in all age groups, it most commonly affects patients in their sixth to seventh decades of life with a male to female ratio of approximately 2:1 [9]. Most CCRCCs arise sporadically; however, 2–4 % of the cases present as part of an inherited cancer syndrome, which include von Hippel-Lindau syndrome, Birt-Hogg-Dube syndrome, and constitutional chromosomal 3 translocation syndrome [10, 11]. As a general rule, familial CCRCC presents at a younger age and is much more likely to be multifocal and bilateral.

Pathology

Grossly, CCRCC usually presents as a unilateral and unicentric, round, and well-demarcated mass with a fibrous capsule. The mean diameter is 6.2 cm; however, smaller lesions are increasingly detected due to the wide use of radiologic imaging techniques. The cut surface often has a characteristic golden yellow color with a variable degree of hemorrhage, necrosis, cystic degeneration, and calcification (Fig. 4.1a). Bilaterality and/or multicentricity occur in <5 % of sporadic CCRCC cases but are more common in inherited cancer syndromes.

Microscopically, the tumor cells are arranged in compact nests, sheets, alveolar, or acinar structures separated by thin-walled blood vessels. Tumor cells have clear cytoplasm (Fig. 4.1b) due

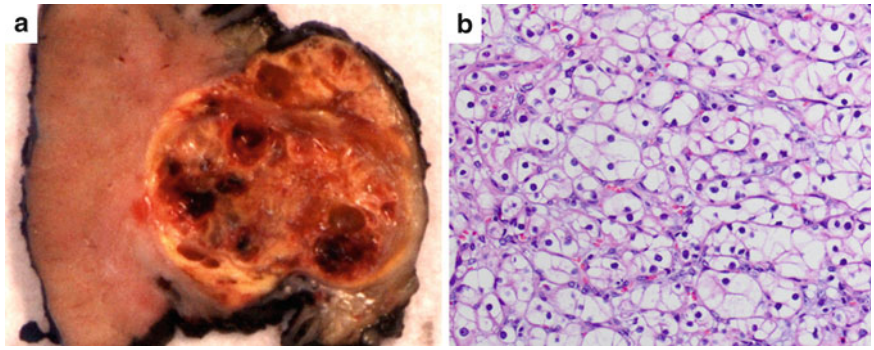

Fig. 4.1 Clear cell renal cell carcinoma. (**a**) Grossly the tumor is a well-circumscribed solid mass with characteristic *bright golden yellow color*. (**b**) Clear cell RCC is composed of compact nests of tumor cells with clear cytoplasm separated by delicate arborizing vasculature

to rich cytoplasmic lipid and glycogen content that is lost during tissue processing and slide preparation imparting an empty or clear appearance. In high-grade and poorly differentiated tumors, cells no longer show cytoplasmic clearing but instead acquire a granular eosinophilic cytoplasm. In high-grade areas, loss of typical alveolar or acinar growth pattern is quite common, and solid and sometimes sarcomatoid histology may be found. Sarcomatoid differentiation occurs in about 5 % cases and is regarded as high-grade tumor with ominous prognosis.

Molecular Genetics

Seventy to ninety percent of CCRCCs harbor chromosome 3p alterations which comprise deletion, mutation, or promoter methylation of several important genes, including *von Hippel-Lindau* (*VHL*) gene on chromosome 3p25-26, *RASSF1A* on 3p21, and *FHIT* on 3p14.2. Duplication of 5q22 is the second most common cytogenetic finding and may be associated with a better prognosis. Other cytogenetic alterations involve loss of chromosomes 6q, 8p12, 9p21, 9q22, 10q, 17p, and 14q [4, 12, 13].

Somatic mutations in *VHL* gene have been found in 18–82 % of sporadic CCRCC cases. Loss of heterozygosity at the *VHL* locus has been reported in up to 98 % of cases [14–16]. Hypermethylation of the *VHL* gene promoter resulting in gene inactivation has been detected in 5–20 % of patients without gene alteration. The vast majority of CCRCC showing somatic *VHL* mutations also exhibit allelic loss or LOH at the second *VHL* locus, consistent with Knudson's two-hit model of tumorigenesis.

VHL protein plays a critical role in the cellular response to hypoxia. Hypoxia-inducible factor (HIF) is a transcriptional factor whose cellular level is regulated by VHL. Under normoxic condition, HIF is hydroxylated, and the wild-type VHL protein binds to and targets this form of HIF for degradation in proteasomes. Consequently, HIF levels are kept low within normal cells under normoxic conditions. Under hypoxic condition, however, HIF is not hydroxylated and cannot be recognized by VHL and therefore accumulates. This in turn activates many downstream hypoxia-driven genes, including genes that promote angiogenesis (vascular endothelial growth factor [*VEGF*] and platelet-derived growth factor-β [*PDGF*-β]), cell growth or survival (transforming growth factor-α [*TGF*-α]), anaerobic metabolism (*Glut-1*), acid-base balance (*CA IX*), and red cell production (*erythropoietin*). Along the way, numerous intracellular signal transduction pathways are activated, including PI3 kinase-Akt-mTOR pathway and Ras-Raf-ERK-MEK pathway, which are involved in various cellular processes, including cell proliferation, survival, and differentiation [16, 17]. These signal transduction pathways serve a beneficial role to tumorigenesis by stimulating angiogenesis and compensatory metabolic changes in normal cells

coping with hypoxia. When *VHL* gene is inactivated by mutation or promoter hypermethylation, no functional VHL is produced. The end result is activation of the aforementioned cellular processes which are no longer controlled by normal physiological mechanisms and therefore contribute to the tumorigenesis and many of the clinical manifestations of CCRCC. The elucidation of these mechanisms has allowed development of several candidate targeted therapies that specifically act within these pathways. These agents that target the critical components of these pathways are under investigation in clinical trials for patients with advanced-stage CCRCC and target VEGF using neutralizing antibody bevacizumab; VEGFR and PDGFR using small-molecule inhibitors of tyrosine kinase, such as sorafenib and sunitinib; EGFR using erlotinib; and mTOR using temsirolimus [18, 19].

Prognosis

In CCRCC, about 50 % are stage I and II, 45 % are stage III, and less than 5 % stage IV. Prognosis of patients with CCRCC is most accurately determined by stage. Within stages, grade (nuclear grade) has strong predictive power. Sarcomatoid transformation, which was once considered a histologic type, is now recognized as a reflection of high-grade evolution and, when present, has a significant adverse impact on survival with few patients surviving to 5 years.

Renal Cell Carcinoma, Papillary Type (Papillary RCC, PRCC)

Clinical Features

PRCC is the second most common type of RCC and accounts for 10–15 % of RCCs. While the gender and age distribution are similar to those of CCRCC, the morphologic appearance and prognosis are quite different. Papillary RCC has a better prognosis with a 5-year survival approaching 90 % [9]. The vast majority of tumors occur sporadically, but some develop in members of families with hereditary papillary renal carcinoma (HPRCC) [20] or rarely in hereditary leiomyomatosis and renal cell cancer (HLRCC) [21].

Pathology

Grossly, PRCC typically presents as a well-circumscribed mass enclosed within a pseudocapsule. Some tumors appear entirely necrotic and friable (Fig. 4.2a). PRCC is more likely to be bilateral and multifocal than the other types of RCC.

Microscopically, PRCC is composed of varying proportions of papillae, tubulopapillae, and tubules (Fig. 4.2b). Occasionally, it has tightly packed tubules or papillae and imparts a solid appearance. The papillae characteristically contain delicate fibrovascular cores infiltrated by foamy histiocytes. Necrosis, hemorrhage, acute and chronic inflammation, hemosiderin deposition, and psammoma bodies are common.

PRCC is further divided into two morphological variants based on the histology [22]. Accounting for about two third of PRCC, type 1 tumor contains papillae that are delicate and short, lined with single layer of tumor cells with scant cytoplasm and low-grade nuclei (Fig. 4.2b). In contrast, papillae in type 2 PRCC are large and lined with cells having abundant eosinophilic cytoplasm and large pseudostratified nuclei with prominent nucleoli (Fig. 4.2c).

Molecular Genetics

Trisomy or tetrasomy 7, trisomy 17, and loss of Y chromosome (in men) are the most common cytogenetic changes in PRCC [23]. Type 1 and 2 PRCCs have distinct genetic features. For example, gain of 7p and 17p is more common in type 1 tumors [24]. Deletion of 9p is present in approximately 20 % of PRCC, and loss of heterozygosity at 9p13, limited to type 2 tumors in recent studies, has been linked to shorter survival [25].

Prognosis

Papillary RCC has an overall low risk of tumor recurrence and cancer death after nephrectomy. Patients with type 1 PRCC have a better prognosis than those with type 2 tumor. However, predictors of outcome appear to relate to stage and nuclear grade whereas morphological subdivision of papillary RCC itself does not appear to provide predictive potential. Nevertheless, recognition of the diversity, especially the genetic

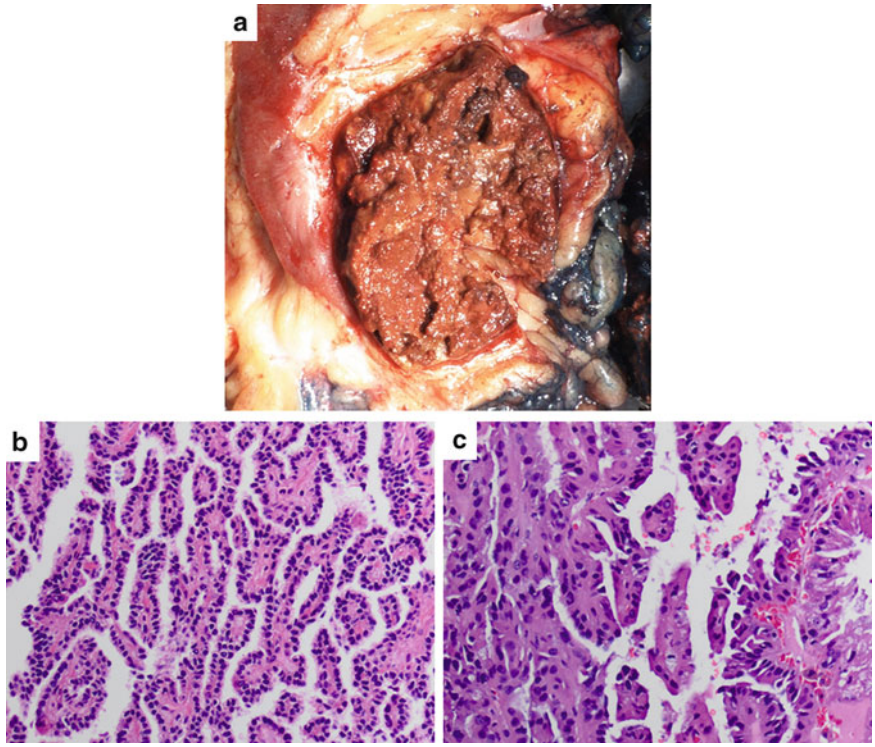

Fig. 4.2 Papillary renal cell carcinoma. (**a**) Grossly the tumor has a thick fibrous capsule with variegated dull color and is extensively necrotic. (**b**) Type 1 PRCC is composed of papillae covered by a single layer of tumor cells with scant cytoplasm and low-grade nuclei. (**c**) Type 2 tumor cells have abundant eosinophilic cytoplasm and large pseudostratified nuclei with prominent nucleoli

differences, within RCC with papillary architecture [15] may allow a better understanding of this subtype and lead to a better classification system.

Renal Cell Carcinoma, Chromophobe Type (Chromophobe RCC, ChRCC)

Clinical Features

ChRCC accounts for approximately 5 % of RCCs and is believed to arise from the intercalated cells of the collecting ducts [26]. ChRCC can occur in patients of wide age range. Males and females are affected almost equally. The prognosis is significantly better than that of CCRCC, with disease recurrence in <5 % of patients [9]. Most cases arise sporadically, while some familial cases are associated with Birt-Hogg-Dube syndrome [27, 28].

Pathology

ChRCC is typically a solitary, well-circumscribed, and non-encapsulated mass with homogenous light-brown solid cut surface. Hemorrhage and/or necrosis is uncommon. A central stellate scar can be seen in large tumors (Fig. 4.3a).

Microscopically, the tumor cells are usually arranged in solid sheets with tubulocystic architecture in some cases. The classic ChRCC tumor consists of large and polygonal cells with finely reticulated cytoplasm due to numerous cytoplasmic microvesicles and prominent "plant cell-like" cell membrane. The nuclei are typically irregular, hyperchromatic, and wrinkled with perinuclear haloes (Fig. 4.3b). Not infrequently, the tumor consists predominantly of cells with intensely eosinophilic cytoplasm, termed eosinophilic variant [29]. However, there is no substantial difference in the clinical characteristics between the two variants.

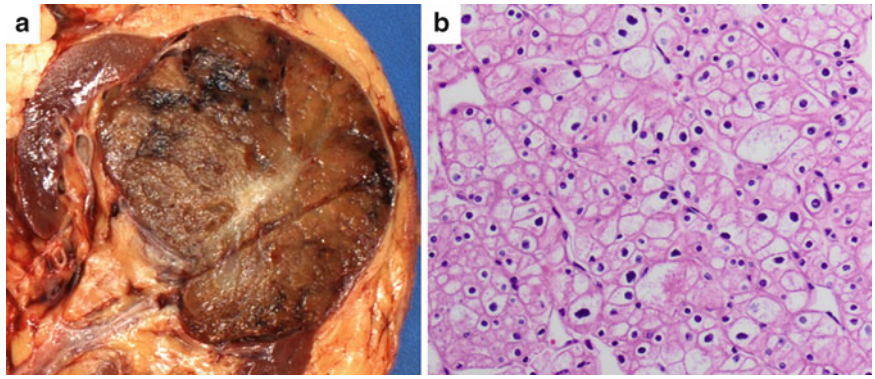

Fig. 4.3 Chromophobe renal cell carcinoma. (**a**) Grossly it is a circumscribed, non-encapsulated mass with a homogenous light-brown cut surface. (**b**) Large and polygonal tumor cells have finely reticulated cytoplasm, prominent cell border, and irregular nuclei with perinuclear clearing

Molecular Genetics

ChRCC harbors extensive chromosomal loss, most commonly involving chromosomes Y, 1, 2, 6, 10, 13, 17, and 21 [30]. Occasionally, ChRCC occurs in Birt-Hogg-Dube syndrome, characterized by mutations in *Birt-Hogg-Dube* (*BHD*) gene on 17p11.2, which encodes the protein folliculin [31]. However, *BHD* mutations are rarely found in sporadic ChRCC. It has been suggested that ChRCC may evolve from oncocytoma after acquiring additional cytogenetic abnormality [32].

Prognosis

The prognosis of these tumors is generally accepted as favorable except in the cases with sarcomatoid transformation which is associated with aggressive biological behavior and metastasis. The subset with an adverse outcome varies in series (in part related to case selection) with death of disease ranging from none to 15 %.

Other Uncommon Subtypes of Renal Cell Carcinoma

Other subtypes of RCC are uncommon and collectively account for <5 % of RCC cases in the kidney. However, they have clinical, pathological, and genetic characteristics distinct from the more common types discussed previously. The clinical, pathological, and genetic features of these uncommon RCC subtypes are summarized in Table 4.2. There are several other entities that have been identified only recently and therefore not included in the 2004 WHO classification. Several of these entities are reviewed in Table 4.3.

Renal Cell Carcinoma, Unclassified Type

RCC, unclassified type, is a term for the designation of RCC that does not fit into any of the accepted RCC categories. It is important to understand that this is a diagnostic category rather than a true biological entity. These tumors represent a heterogeneous group of malignancies with poorly defined clinical, morphological, or genetic features and therefore cannot be classified using the current criteria. Most unclassified tumors are poorly differentiated and are associated with a poor prognosis. As our understanding of RCC improves, this category is destined to diminish and perhaps eventually disappear.

Renal Cell Carcinomas in Inherited Cancer Syndromes

Less than 5 % of RCC occur in the setting of inherited cancer syndromes, including von Hippel-Lindau disease (VHLD), hereditary papillary renal cell carcinoma (HPRCC), hereditary leiomyomatosis and renal cell carcinoma

Table 4.2 Clinical, pathological, and genetic features of uncommon RCC subtypes included in the 2004 WHO classification [2]

RCC subtype	Clinical features	Pathology		Genetics	Prognosis	Reference
		Grossly	Microscopically			
Multilocular cystic RCC	Variant of CCRCC 5 % of CCRCC Mean age 51 years (range 20–76) Male/female = 2–3:1	Solitary, well-circumscribed, entirely cystic mass; no grossly visible nodules or necrosis	Variably sized cysts lined with one or several layers of flat or plump clear cells; no expansile cellular nodules; low-grade nuclei	3p deletion as observed in CCRCC	Favorable No local or distant metastasis after complete surgical removal	[33, 34]
Carcinoma of the collecting ducts of Bellini (Fig. 4.5a)	<1 % of all renal tumors; arising in the collecting ducts of Bellini Often seen in fourth to seventh decade with mean age 55 years Male/female = 2:1	Poorly circumscribed usually centrally located Cut surface gray, white, and firm	High-grade tumor cells form complex tubulocystic structures; prominent desmoplastic stroma	Variable results Allelic loss on chromosomes 1q, 6p, 8p,9p, 13q, 19q32, and 21q; 1q32.1–32.2 deletion; *c-erB2* amplification	Poor; 1/3 presenting with metastasis 2/3 of patients died of disease within 2 years of diagnosis	[35–38]
Medullary carcinoma	Exceedingly rare; almost exclusively in patients with sickle cell hemoglobinopathies or traits; majority are African-Americans Mean age 19 years (5–69) Male/female = 2:1	More common in right kidney; poorly circumscribed, centrally located; tan to gray, with varying degrees of hemorrhage and necrosis	High-grade tumor cells with reticular, microcystic, or solid patterns Desmoplastic stroma; may have abundant neutrophils	Not well defined	Highly aggressive 95 % presenting with metastasis; often died of disease within 6 months of diagnosis	[39, 40]
Xp11.2 translocation carcinoma (Fig. 4.5b)	Mainly affecting children and young adults; accounts for 40 % of RCCs in this age group; occurs post-chemotherapy in some cases Male/female = 1:1; affects adult patients with a striking female predominance	Usually circumscribed; not distinct from other RCCs	Most distinctive features: papillary structures lined with clear cells, psammomatous calcification, and hyalinized fibrovascular cores	Chromosomal translocation involving *TFE3* gene on Xp11.2 resulting in overexpression of the TFE3 protein; has several translocation partner genes	Usually resent at advanced stage but indolent clinical course in children Adult tumors may pursue more aggressive course	[41–47]
Mucinous tubular spindle cell carcinoma (Fig. 4.5c)	Mean age 53 years (range 13–82) Male/female = 1:4 Incidental finding in most cases	Sharply circumscribed; gray-white with myxoid appearance; many have minimal hemorrhage and/or necrosis	Elongated compressed tubules and bland spindle cells with low-grade nuclei embedded in a myxoid stroma	Not well defined Losses on chromosomes 1, 4, 6, 8, 9, 11, 13, 14, 15, 18, 22 reported; 3p alterations and gain of chromosome 7, 17 not present	Favorable; majority of patients remain disease-free after surgical resection; rare reports of metastasis and death of tumor	[48–51]
Post- neuroblastoma renal cell carcinoma	In long-term survivors of neuroblastoma Male/female = 1 Neuroblastoma diagnosis in the first 2 years of life; mean age of RCC diagnosis 13.5 years (range 2–35)	Same as CCRCC	Limited data; many tumors are typical CCRCC; some tumors have cells with abundant granular cytoplasm and arranged in solid, nests, or in papillae	Not well defined Loss of multiple chromosomal loci observed	Similar to other common RCC subtypes	[52]

Table 4.3 Uncommon subtypes of renal cell carcinoma not included in 2004 WHO classification [5]

RCC subtype	Clinical features	Pathology		Genetics	Prognosis	Reference
		Grossly	Microscopically			
Tubulocystic carcinoma (Fig. 4.5d)	Occurs in fifth and sixth decade (range 30–94 years) Male/female = 7:1	Usually solitary; circumscribed and unencapsulated; spongy cut surface resembling "bubble wrap"	Circumscribed collection of tubules and cysts with varied sizes; separated by fibrous stroma; no desmoplastic reaction; the lining cells usually exhibit high-grade nuclei and eosinophilic cytoplasm	Gain in chromosome 7 and 17 in some cases; may be related to PRCC	Not fully established; majority of cases have indolent clinical course; recurrence or metastasis in a few cases	[53–55]
Clear cell tubulopapillary carcinoma	Mean age 60 years Male/female = 1:1	Small tumor with mean size of 2.4 cm; cystic mass having prominent fibrous capsule or stroma	Branching tubules, acini, and/or clear cell ribbons with low-grade nuclei; positive for CK7 and negative for CD10	Limited data; do not exhibit the genetic changes characteristic of CCRCC or PRCC	Low-grade and low-stage tumor Mostly biological indolent tumors	[56]
Thyroid-like follicular carcinoma	Very rare; mean age 45 years	Wide size range; tan colored	Prominent Pseudocapsule; micro- and macro-follicles lined with low-grade cells; colloid-like material present in >50 % of follicles	Limited data	Not well defined; available cases are free of disease after surgical resection	[57]
Acquired cystic kidney disease (ACKD)-associated RCC	2–7 % incidence in ACKD patients; occur in relatively young patients Male/female = 7:1	Frequently multicentric and bilateral; generally well circumscribed	About 40 % are classic CCRCC, PRCC, or ChRCC; 60 % so-called ACKD-associated RCC with various architectures; 80 % of tumor cells show abundant intratumoral calcium oxalate crystals	Limited data; gains in chromosomes 1, 2, 6, and 10	Less aggressive than sporadic RCC	[58]

(HLRCC), and Birt-Hogg-Dube (BHD) syndrome [10]. Each inherited cancer syndrome predisposes patients to distinct subtypes of RCC which often occur at a younger age and have a higher incidence of bilaterality and multifocality than sporadic cases [59].

von Hippel-Lindau Disease (VHLD)

VHLD is an autosomal dominant hereditary condition with stigmata including CCRCCs, central nervous system hemangioblastomas, pheochromocytomas, pancreatic cysts, and endolymphatic sac tumors of the inner ear [17]. It is caused by germline mutations in *VHL* gene. VHLD patients are born with a germline defect in one of the alleles, and the second allele is inactivated by somatic mutations. Renal lesions in VHLD are always CCRCC and tend to be bilateral and multifocal. Dozens or even hundreds of microscopic tumor foci can be identified in resected kidney specimens. VHLD-related RCC develops early with a mean age of onset of 37 years as compared with 61 years for sporadic CCRCC. Although metastasis typically only occurs when tumors are greater than 3 cm, RCC is nevertheless the leading cause of death in this syndrome. However, VHLD patients with renal involvement fare better in 10-year survival than their sporadic counterparts [10].

Hereditary Papillary Renal Cell Carcinoma (HPRCC)

HPRCC is an inherited renal cancer characterized by a predisposition to multiple bilateral papillary renal tumors of type 1 histology. To date, kidney is the only organ to be affected in these patients [20]. HPRCC is associated with a germline mutation in the tyrosine kinase domain of the *c-met* proto-oncogene on chromosome 7q31. *c-met* gene encodes a cell surface receptor protein for hepatocyte growth factor (HGF) and has tyrosine kinase activity [60]. Gain-of-function mutations result in activated cellular processes that contribute to carcinogenesis, including angiogenesis, cell motility, proliferation, and morphogenic differentiation. The tyrosine kinase domain of MET is a promising therapeutic target [61].

Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC)

HLRCC is an autosomal dominant disease and predisposes patients to cutaneous leiomyomas, uterine leiomyomas in women, and PRCC of type 2 histology. The renal tumors are often solitary, unilateral, and aggressive and lethal. Only 20–35 % of patients develop RCC. Germline mutations are identified in the fumarate hydratase (FH) gene on chromosome 1 (1q42.3-43) [62], an essential regulator of the Krebs cycle. Inactivation of *FH* impairs the Krebs cycle, thereby activating anaerobic metabolism and upregulation of HIF and hypoxia-inducible genes.

Birt-Hogg-Dube Syndrome (BHD)

RCC is also part of the Birt-Hogg-Dube syndrome, an autosomal dominant disorder characterized by benign skin tumors (fibrofolliculomas, trichodiscomas of hair follicles, and skin tag), renal epithelial neoplasms, lung cysts, and spontaneous pneumothorax [28]. Renal neoplasms are often multifocal and bilateral, the most common being hybrid oncocytic tumors (50 %) with features of both ChRCC and oncocytoma [63]. Renal tumors can also include ChRCC (33 %), oncocytomas (5 %), and occasionally CCRCC or PRCC. *BHD*, the gene implicated in the syndrome on 17p11.2, is a potential tumor suppressor gene and encodes the protein folliculin.

Common Benign Renal Tumors

Papillary Adenoma

By WHO definition, papillary adenoma constitutes epithelial neoplasms <5 mm in size with papillary and/or tubular architecture lined with tumor cells with low-grade nuclei.

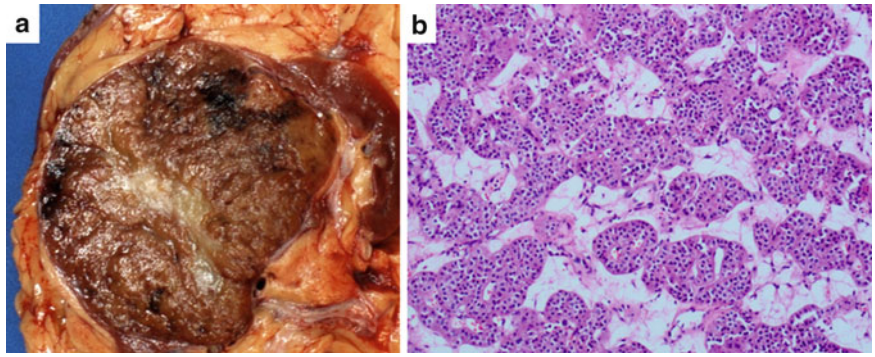

Fig. 4.4 Renal oncocytoma. (**a**) Grossly it is a solitary, well-circumscribed, non-encapsulated mass with homogeneous dark-brown cut surface. (**b**) It consists of bright eosinophilic cells nested in a loose stroma. The tumor cells are uniform, round to polygonal with granular eosinophilic cytoplasm and regular round nuclei

Clinical Features

Adenoma is the most common renal cell neoplasm, frequently as incidental findings in nephrectomy specimens or at autopsy. In one autopsy study, papillary adenomas were found in up to 40 % of patients older than 70 years of age. Its incidence increases with age and also in patients on long-term dialysis.

Pathology

Papillary adenomas appear as small (<5 mm), well-circumscribed, yellow or white nodules in the renal cortex. They have papillary, tubular, or tubulopapillary architecture similar to papillary RCC [64]. The tumor cells have uniform small nuclei and inconspicuous nucleoli equivalent to Fuhrman grade 1 or 2 nuclei.

Molecular Genetics

Papillary adenomas share many genetic alterations with PRCC. Both have combined gains of chromosomes 7 and 17 and loss of the Y chromosome in men. PRCCs acquire additional genetic alterations, including trisomy 12, 16, or 20. The cytogenetic findings support the hypothesis that papillary adenoma is a precursor of PRCC [65].

Renal Oncocytoma

Clinical Features

Renal oncocytoma accounts for 5 % of surgically resected non-urothelial renal neoplasms. Patients vary greatly in age with a peak incidence in the seventh decade of life. The male to female ratio is 1.7:1. Most cases are sporadic, although familial cases have been reported in association with Birt-Hogg-Dube syndrome and familial renal oncocytoma syndrome.

Pathology

Oncocytoma is typically solitary and well-circumscribed and has varying degrees of encapsulation. The cut surface exhibits a characteristic homogeneous mahogany-brown color (Fig. 4.4a). A central stellate scar can be seen in one third of the cases, more commonly in larger tumors. More than 10 % of cases are multifocal or bilateral.

Microscopically, oncocytoma is characterized by bright eosinophilic cells, termed oncocytes, arranged in nested, acinar, or microcystic pattern associated with a loose hypocellular and hyalinized stroma (Fig. 4.4b). Extension of oncocytoma into the perinephric fat, or rarely into vascular space, can be found sometimes and does not adversely affect the benign prognosis of the lesion.

Molecular Genetics

Most oncocytomas are composed of a mixed population of cells with normal and abnormal karyotypes [66]. Combined loss of chromosomes 1 and X/Y is the most frequent chromosome abnormality. Translocations involving chromosome 11, with a breakpoint at 11q12-13, have also been reported. Other rare chromosome

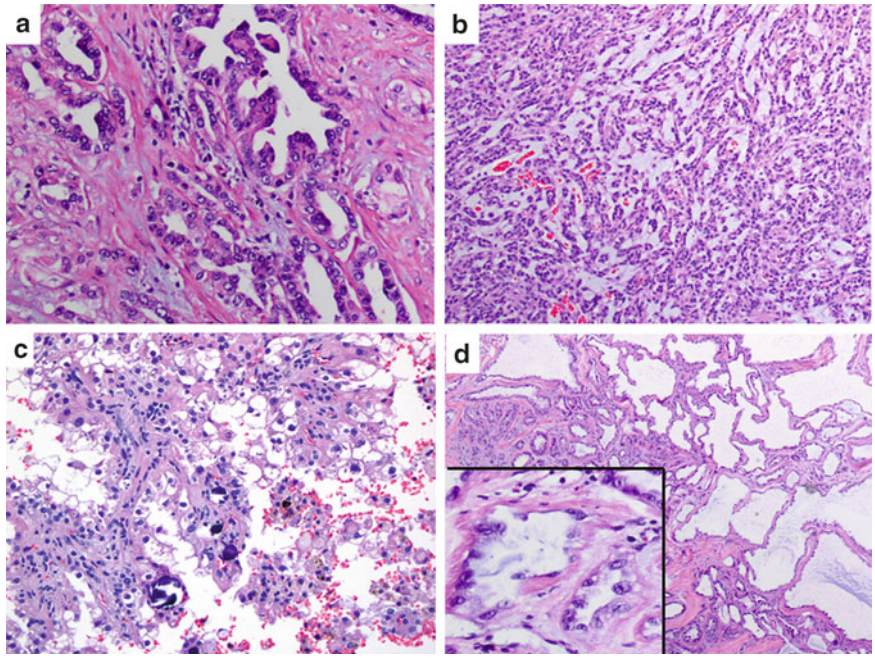

Fig. 4.5 (**a**) Collecting duct carcinoma consists of high-grade tumor cells forming complex tubules or tubulopapillary structures embedded in a remarkably desmoplastic stroma. (**b**) Mucinous tubular and spindle cell carcinoma is composed of elongated cords and collapsed tubules with slit-like spaces embedded in a lightly basophilic myxoid background. The tumor cells have low-grade nuclear features. (**c**) Xp11.2/TFE3 translocation renal cell carcinoma with characteristic papillary structure lined with tumor cells with abundant partly clear, partly eosinophilic cytoplasm and high-grade nuclei. Psammomatous calcification is also present. (**d**) Tubulocystic renal cell carcinoma is composed of closely packed tubules and cysts separated by thin, fibrous septae. The lining tumor cells have a hobnail appearance and prominent nucleoli (Insert, high magnification)

rearrangements have been reported, such as t(1;12)(p36;q13), loss of chromosome 14, and gain of chromosome 12 [67]. Oncocytoma can be a manifestation of Birt-Hogg-Dube syndrome.

Whether oncocytoma and ChRCC are related is still controversial. They not only have overlapping morphological features but also share some cytogenetic changes, such as the loss of heterozygosity at chromosome 1 [68]. However, monosomy of chromosomes 2, 10, 13, 17, and 21 occurred exclusively in ChRCC [69].

Angiomyolipoma

Clinical Features

Angiomyolipoma (AML) is a renal mesenchymal tumor comprising variable proportions of adipose tissue, smooth muscle bundles, and blood vessels. The prevalence in autopsies is 0.3 % and 0.1 % in ultrasound screened patients. It accounts for 0.3–3 % of all renal tumors in surgically resected renal neoplasms. AMLs are strongly associated with tuberous sclerosis (TS), in which most individuals will have multiple angiomyolipomas affecting both kidneys. Patients with TS develop AML earlier (mean age at diagnosis at 25–35 years with TS vs. 40–45 years without TS). The male to female ratio is 4:1. AMLs, particular those associated with TS, are usually asymptomatic and detected by imaging studies. Intra-abdominal bleeding owing to rupture may be an uncommon presentation initially or during follow-up.

Pathology

AML is typically well-circumscribed non-capsulated mass with or without lobulation and

sometimes with subtle infiltrative edges. The cut surface depends on the relative amount of three tissue components.

As its name implies, AML consists of thick-walled blood vessels, spindle cells with smooth muscle features, and mature adipose tissue in variable proportions. Blood vessels typically have an eccentrically thickened wall with spindle cells spun off the wall. Spindle cells range from mature-appearing smooth muscle cells to immature spindle cells, epithelioid cells, and even bizarre cells with atypical nuclear features. Mature adipose tissue may have cytologic atypia. Classical AMLs are benign; however, one fourth to one third of epithelioid AML are malignant with local and distant metastasis. Pathological features that correlate with adverse outcomes include large size, tumor necrosis, atypical mitosis, and diffuse atypical nuclei. Melanocytic markers, including Melan-A and HBM-45, are positive in AMLs and are often used to confirm the diagnosis.

Molecular Genetics

The origin and genetic basis of AMLs is uncertain. AMLs in TSC show evidence of bi-allelic inactivation of the TSC1 or TSC2 gene, corresponding to the germline mutation present in such individuals. Loss of heterozygosity for the TSC2 region, TSC2 inactivation by mutation, is likely a necessary genetic event in the pathogenesis of most sporadic AMLs [70–72].

Pathological Prognosis Parameters for Renal Cell Carcinoma

Stage

The role of staging as defined in the AJCC/UICC tumor-lymph node and metastasis (TNM) classification has been well validated and is widely accepted as a key prognostic parameter in RCC. With higher stage, lymph node invasion and metastasis to other organs, there is a progressively worse prognosis and shorter survival. A key to the TNM classification is the tumor size. Recent studies found that risk of malignancy increases with the size of mass lesions. In an analysis of over 2,700 patients undergoing nephrectomy for renal tumors, Frank et al. found that whereas nearly half of all tumors <1 cm were benign, only 6 % of those >7 cm were benign. For each 1 cm increase in size, the likelihood of malignancy in renal tumors increased by 17 % [73]. More recently, size was shown to correspond with higher grade such that each 1 cm increase in size increased the likelihood of having a tumor of high grade by 25 %. This translated into a 0 % incidence of high-grade features in tumors <1 cm to 59 % in tumors >7 cm [74].

The 2010_ENREF_6 (Table 4.4) [75] TNM staging differs from the earlier 2002 version in reexamining size thresholds in T stage, specifically by dividing T2 based on a size cutoff of less than or greater than 10 cm, reclassifying renal vein invasion as T3a instead of T3b, and classifying adrenal involvement as T4 when contiguous invasion and M1when not contiguous. It also has simplified N classification into N0 and N1. The newly adopted 2010 TNM classification has also been validated as a robust predictor of cancer-specific survival and shown to provide modest improvement in predictive ability compared with the 2002 version.

Fuhrman Nuclear Grading

Currently, the four-tiered Fuhrman scheme, first described in 1982, remains the most commonly used grading system for RCC [76]. Fuhrman grade, based on the nuclear size and shape, chromatin, and nucleolar prominence, is categorized into G1-4 (Table 4.5). Most studies have confirmed that Fuhrman nuclear grade is an independent prognostic predictor for CCRCC [77]. Simplified two-tiered (G1–2 vs. G3–4) or three-tiered (G1–2 vs. G3 vs. G4) Fuhrman systems have been proposed to improve interobserver agreement and still preserve its prognostic significance [78]. Grade 1 and 2 may be grouped together as low grade since the two are not prognostically different in multivariate analysis. However, studies have shown that grade 3 and grade 4 tumors should not be grouped together as grade 3 tumors have

Table 4.4 Pathology stage of primary renal cell carcinoma (AJCC 2010) [75]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest admission, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2 b	Tumor more than 10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral and renal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia including contiguous extension into the ipsilateral adrenal gland
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
M0	No distinct metastasis
M1	Distant metastases

Table 4.5 Fuhrman nuclear grading system [76]

Grade	Nuclear size (μm)	Nuclear shape	Chromatin	Nucleoli
1	<10	Round	Dense	Inconspicuous
2	15	Round	Finely granular	Small, not visible at 10× magnification
3	20	Round/oval	Coarsely granular	Prominent, visible at 10× magnification
4	>20	Pleomorphic, multilobated	Open, hyperchromatic	Macronucleoli

better 5-year cancer-specific survival than grade 4 tumors (45–65 % in grade 3 cancers vs. 25–40 % in grade 4 cancers). A recent study showed that the three-tiered Fuhrman grading system is an appropriate option for the prognostication of CCRCC in both univariate analysis and multivariate model setting [79]. The use of a simplified Fuhrman nuclear grading system in clinical practice requires further clarification and preferably a consensus between pathologists and urologists.

The prognostic value of Fuhrman grading for non-clear cell RCC, however, remains controversial. For papillary RCC, it is significantly associated with survival in univariate analysis, but this significance is lost in multivariate models. One recent study demonstrated that only nucleolar prominence is significantly associated with survival in both univariate and multivariate analyses [80]. Another study showed that Fuhrman grade, not the nucleolar grade, is an independent prognostic factor and should be used as the standard grading system for PRCC [81]. Only a few studies addressed the prognostic significance of Fuhrman grading system for ChRCC using univariate analysis. A recent study found that Fuhrman grading does not correlate with survival, therefore is not appropriate for ChRCC [82]. A new grading system was recently proposed for ChRCC based on the assessment of geographic nuclear crowding and anaplasia.

This grading scheme was shown to be an independent predictor of clinical outcomes for ChRCC [83].

Sarcomatoid and Rhabdoid Differentiation

Sarcomatoid differentiation is present in about 5 % of RCCs and can be observed in any RCC subtype [84]. Therefore, sarcomatoid RCC is not considered a distinct subtype of RCC by 2004 WHO classification; rather, it is thought to represent a high-grade and poorly differentiated component.

RCC with sarcomatoid differentiation typically has other adverse pathological features, including large tumor size, extension into perinephric fat and vessels, and presence of hemorrhage and necrosis. It is also significantly associated with an increased likelihood of distant metastasis and cancer-specific death. It is an adverse independent prognostic indicator in both univariate and multivariate analyses [85]. Any RCC with sarcomatoid differentiation is assigned a Fuhrman grade 4.

Sarcomatoid components usually appear as bulging, lobulated areas with white to gray, firm and fibrous cut surface within a tumor. Histologically, the sarcomatoid component ranges from malignant spindle cells to those resembling leiomyosarcoma, fibrosarcoma, angiosarcoma, rhabdomyosarcoma, and other sarcomas. The coexisting RCC component, including clear cell, papillary, chromophobe RCC, and sometimes collecting duct RCC, can often be identified and is used to subtype the RCC with sarcomatoid differentiation. Rarely, such subtyping may not be possible when the sarcomatoid component overruns RCC epithelial components.

Rhabdoid differentiation can be identified in approximately 5 % of RCCs with tumor cells having large eccentric nuclei, macronucleoli, and prominent acidophilic globular cytoplasm. The presence of rhabdoid component is also associated with high grade and high stage with frequent extrarenal extension. The rhabdoid foci may account for 5–90 % of the tumor area. It is a marker of high risk for metastasis and poor prognosis even when the rhabdoid component is limited [86].

Tumor Necrosis

For CCRCC, tumor necrosis, identified either macroscopically or microscopically, is an adverse pathological factor and is associated with worse clinical outcomes in both univariate and multivariate analyses. Studies from Mayo Clinic clearly showed that histological necrosis is associated with twice the cancer-specific death rate compared to those without necrosis [9]. The presence and extent of histological necrosis in CCRCC are independent predictors of survival in localized but not metastatic cases, although one recent study showed limited prognostic value [87]. Two outcome prediction models, SSIGN (stage, size, grade, and necrosis) from Mayo Clinic and the postoperative outcome nomogram from Memorial Sloan Kettering Cancer Center, both incorporate tumor necrosis in their models [88, 89]. A few recent studies also report that the proportional extent of necrosis correlates with a worse outcome and cancer-specific death in clear cell RCC [90, 91]. The data on the prognostic role of tumor necrosis in non-clear cell RCC is limited.

Microvascular Invasion

Microvascular invasion (MVI), defined as neoplastic cells invading the vessel wall or neoplastic emboli in the intratumoral vessel detected microscopically, is present in 13.6–44.6 % of RCC. It is more common in RCC of high stage and grade and large size. As an important prognostic factor in other malignancies including liver, testis, bladder, and upper tract urothelial carcinoma, its prognostic role in RCC is however controversial. Several studies have demonstrated that MVI may have an independent predictive role for either disease recurrence or cancer-specific mortality after adjusting for other clinical and pathologic covariates [92, 93]. Further studies are needed to better define its prognostic significance.

Histologic Subtyping in Localized and Metastatic RCC

The issue on prognostic utility of histologic subtypes remains debated with some convinced of the independent prognostic acceptance of subtype, while others are not. However, over the last decades, based on series and cumulative reports on RCC subtypes, the prognostic value of histologic typing of RCC has been widely accepted. In general, chromophobe RCC is considered an indolent, low-stage tumor with low risk of recurrence. Papillary RCC is presented as having a slightly higher risk of recurrence but less than in clear cell type. Additionally, collecting duct renal cell carcinoma is recognized as a highly aggressive tumor with an expectation for a more adverse outcome than CCRCC. It should be mentioned that, while distinct biologic differences between histologic types are accepted, proof of prognostic importance is required from evaluation of large cohort studies where other associated clinical data are concurrently examined [94].

The biologic and genetic differences in RCC types suggest that histologic subtyping has prognostic and therapeutic potential in metastatic RCC. In most studies, metastatic papillary and chromophobe RCC appear to have a worse prognosis as compared to clear cell RCC. In a series of metastatic RCC [95], 64 patients (less than 10 %) were non-clear cell type. These were found to be resistant to systemic cytokine and conventional therapy (particularly immunotherapy) and poor survival (overall survival of 9.4 months with 29 months for those with chromophobe, 11 months for those with collecting duct, 5.5 months for those with papillary RCC). In a study on IL-2 evaluating the influence of histologic types on response to treatment, non-clear cell type showed a poor response to therapy [96].

As the treatment of metastatic RCC moves from cytokines to targeted agents that inhibit angiogenic growth factors, the evaluation of histologic type is expected to play an increasingly important role in determination of therapy. Earlier trials restricted treatment with targeted agents to clear cell type; however, subsequent studies have shown response of metastatic papillary or chromophobe RCC to sorafenib or sunitinib [97]. Further studies are awaited to determine most appropriate therapeutic strategy related to histologic types. Prospective controlled studies may enable data for predictive models to incorporate histologic type in nomograms for treatment of metastatic disease.

Each histologic type of RCC shows differences in pathologic and clinical parameters including prognostic relevance; however, the extent of type in outcome prediction remains controversial. Most studies show relevance for outcome of each histologic type when correlated with survival by univariate analysis; however, only few studies are able to show differences in outcome once other key prognostic attributes such as stage and grade are taken into account (using multivariate analysis). These studies with disparate results highlight the challenges to prove outcome relevance, such as the requirement for large cohort size to allow sufficient statistical strength and the importance of standardized pathology review, often missing in pooled multi-institution datasets. Evidence of this is seen in single institution large cohort series which have shown independent value of subtype, while pooled studies have not. As greater knowledge is gleaned on RCC, newer entities are emerging which may shift distribution of cases, such as from papillary RCC and unclassified RCC to other subtypes, potentially strengthening the prognostic value in separation of entities. Despite the contested independent value of subtype for outcome prediction, separation of RCC into types is well accepted and substantiated on clinical, biologic, and molecular differences [94].

Summary

Renal cell carcinoma encompasses a group of heterogeneous tumors with diverse clinical, pathological, and molecular characteristics as well as distinct prognosis and therapeutic responses. The current classification is based primarily on morphology, but genetic features of renal tumors have been increasingly incorporated into the classification scheme. Many histological

parameters obtained from routine pathological examination of renal tumor provide invaluable prognostic values. The clinical, pathological, and genetic features in combination will eventually enable urologists to predict individual tumor behavior and stratify patients into more sophisticated risk groups, ultimately rendering individualized management and treatment options.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127: 2893–917.
2. Eble JN, Sauter G, Epstein JI, Sesterhenn IA. Pathology and genetics, tumors of the urinary system and male genital organs, vols 9–88. Lyon: IAPC Press; 2004.
3. Murphy WM, Grignon DG, Perlman EJ. Tumors of the kidney, bladder, and related urinary structures. Washington DC: American Registry of Pathology; 2004.
4. Cheng L, Zhang S, MacLennan GT, Lopez-Beltran A, Montironi R. Molecular and cytogenetic insights into the pathogenesis, classification, differential diagnosis, and prognosis of renal epithelial neoplasms. Hum Pathol. 2009;40:10–29.
5. Srigley JR, Delahunt B. Uncommon and recently described renal carcinomas. Mod Pathol. 2009;22(Suppl 2):S2–23.
6. Kovacs G, Akhtar M, Beckwith BJ, Bugert P, Cooper CS, Delahunt B, et al. The Heidelberg classification of renal cell tumours. J Pathol. 1997;183:131–3.
7. Storkel S, Eble JN, Adlakha K, Amin M, Blute ML, Bostwick DG, et al. Classification of renal cell carcinoma: Workgroup No. 1. Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC). Cancer. 1997;80:987–9.
8. Thoenes W, Storkel S, Rumpelt HJ. Histopathology and classification of renal cell tumors (adenomas, oncocytomas and carcinomas). The basic cytological and histopathological elements and their use for diagnostics. Pathol Res Pract. 1986;181:125–43.
9. Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol. 2003;27:612–24.
10. Cohen D, Zhou M. Molecular genetics of familial renal cell carcinoma syndromes. Clin Lab Med. 2005;25:259–77.
11. Rosner I, Bratslavsky G, Pinto PA, Linehan WM. The clinical implications of the genetics of renal cell carcinoma. Urol Oncol. 2009;27:131–6.
12. Strefford JC, Stasevich I, Lane TM, Lu YJ, Oliver T, Young BD. A combination of molecular cytogenetic analyses reveals complex genetic alterations in conventional renal cell carcinoma. Cancer Genet Cytogenet. 2005;159:1–9.
13. Hoglund M, Gisselsson D, Soller M, Hansen GB, Elfving P, Mitelman F. Dissecting karyotypic patterns in renal cell carcinoma: an analysis of the accumulated cytogenetic data. Cancer Genet Cytogenet. 2004;153:1–9.
14. Banks RE, Tirukonda P, Taylor C, et al. Genetic and epigenetic analysis of von Hippel-Lindau (VHL) gene alterations and relationship with clinical variables in sporadic renal cancer. Cancer Res. 2006;66:2000–11.
15. Gimenez-Bachs JM, Salinas-Sanchez AS, Sanchez-Sanchez F, et al. Determination of vhl gene mutations in sporadic renal cell carcinoma. Eur Urol. 2006; 49:1051–7.
16. Gossage L, Eisen T. Alterations in VHL as potential biomarkers in renal-cell carcinoma. Nat Rev Clin Oncol. 2010;7:277–88.
17. Kaelin Jr WG. The von Hippel-Lindau tumor suppressor protein and clear cell renal carcinoma. Clin Cancer Res. 2007;13:680s–4.
18. Lane BR, Rini BI, Novick AC, Campbell SC. Targeted molecular therapy for renal cell carcinoma. Urology. 2007;69:3–10.
19. Linehan WM, Bratslavsky G, Pinto PA, et al. Molecular diagnosis and therapy of kidney cancer. Annu Rev Med. 2010;61:329–43.
20. Zbar B, Tory K, Merino M, et al. Hereditary papillary renal cell carcinoma. J Urol. 1994;151:561–6.
21. Launonen V, Vierimaa O, Kiuru M, et al. Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proc Natl Acad Sci USA. 2001;98:3387–92.
22. Delahunt B, Eble JN, McCredie MR, Bethwaite PB, Stewart JH, Bilous AM. Morphologic typing of papillary renal cell carcinoma: comparison of growth kinetics and patient survival in 66 cases. Hum Pathol. 2001;32:590–5.
23. Brunelli M, Eble JN, Zhang S, Martignoni G, Cheng L. Gains of chromosomes 7, 17, 12, 16, and 20 and loss of Y occur early in the evolution of papillary renal cell neoplasia: a fluorescent in situ hybridization study. Mod Pathol. 2003;16:1053–9.
24. Jiang F, Richter J, Schraml P, et al. Chromosomal imbalances in papillary renal cell carcinoma: genetic differences between histological subtypes. Am J Pathol. 1998;153:1467–73.
25. Schraml P, Muller D, Bednar R, et al. Allelic loss at the D9S171 locus on chromosome 9p13 is associated with progression of papillary renal cell carcinoma. J Pathol. 2000;190:457–61.
26. Storkel S, Steart PV, Drenckhahn D, Thoenes W. The human chromophobe cell renal carcinoma: its probable relation to intercalated cells of the collecting duct. Virchows Arch B Cell Pathol Incl Mol Pathol. 1989;56:237–45.

27. Zbar B, Alvord WG, Glenn G, et al. Risk of renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg-Dube syndrome. Cancer Epidemiol Biomarkers Prev. 2002;11:393–400.
28. Adley BP, Smith ND, Nayar R, Yang XJ. Birt-Hogg-Dube syndrome: clinicopathologic findings and genetic alterations. Arch Pathol Lab Med. 2006;130:1865–70.
29. Thoenes W, Storkel S, Rumpelt HJ, Moll R, Baum HP, Werner S. Chromophobe cell renal carcinoma and its variants – a report on 32 cases. J Pathol. 1988;155:277–87.
30. Brunelli M, Eble JN, Zhang S, Martignoni G, Delahunt B, Cheng L. Eosinophilic and classic chromophobe renal cell carcinomas have similar frequent losses of multiple chromosomes from among chromosomes 1, 2, 6, 10, and 17, and this pattern of genetic abnormality is not present in renal oncocytoma. Mod Pathol. 2005;18:161–9.
31. Vira M, Linehan WM. Expanding the morphological and molecular genetic phenotype of kidney cancer. J Urol. 2007;177:10–1.
32. Al-Saleem T, Cairns P, Dulaimi EA, Feder M, Testa JR, Uzzo RG. The genetics of renal oncocytosis: a possible model for neoplastic progression. Cancer Genet Cytogenet. 2004;152:23–8.
33. Suzigan S, Lopez-Beltran A, Montironi R, et al. Multilocular cystic renal cell carcinoma: a report of 45 cases of a kidney tumor of low malignant potential. Am J Clin Pathol. 2006;125:217–22.
34. Halat S, Eble JN, Grignon DJ, et al. Multilocular cystic renal cell carcinoma is a subtype of clear cell renal cell carcinoma. Mod Pathol. 2010;23:931–6.
35. Antonelli A, Portesi E, Cozzoli A, et al. The collecting duct carcinoma of the kidney: a cytogenetical study. Eur Urol. 2003;43:680–5.
36. Karakiewicz PI, Trinh QD, Rioux-Leclercq N, et al. Collecting duct renal cell carcinoma: a matched analysis of 41 cases. Eur Urol. 2007;52:1140–5.
37. Tokuda N, Naito S, Matsuzaki O, et al. Collecting duct (bellini duct) renal cell carcinoma: a nation wide survey in Japan. J Urol. 2006;176:40–3. Discussion 43.
38. Selli C, Amorosi A, Vona G, et al. Retrospective evaluation of c-erbB-2 oncogene amplification using competitive PCR in collecting duct carcinoma of the kidney. J Urol. 1997;158:245–7.
39. Leitao VA, da Silva Jr W, Ferreira U, Denardi F, Billis A, Rodrigues Netto Jr N. Renal medullary carcinoma. Case report and review of the literature. Urol Int. 2006;77:184–6.
40. Watanabe IC, Billis A, Guimaraes MS, et al. Renal medullary carcinoma: report of seven cases from Brazil. Mod Pathol. 2007;20:914–20.
41. Argani P, Ladanyi M. Renal carcinomas associated with Xp11.2 translocations/TFE3 gene fusions. In: Eble J, Sauter G, Epstein J, et al., editors. World Health Organization classification of tumours: pathology and genetics of tumors of the urinary system & male genital organs. Lyon: IARC; 2004. p. 37–8.
42. Argani P, Olgac S, Tickoo SK, et al. Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. Am J Surg Pathol. 2007;31:1149–60.
43. Armah HB, Parwani AV. Xp11.2 translocation renal cell carcinoma. Arch Pathol Lab Med. 2010;134:124–9.
44. Argani P, Lal P, Hutchinson B, Lui MY, Reuter VE, Ladanyi M. Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. Am J Surg Pathol. 2003;27:750–61.
45. Ross H, Argani P. Xp11 translocation renal cell carcinoma. Pathology. 2010;42:369–73.
46. Argani P, Antonescu CR, Illei PB, et al. Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. Am J Pathol. 2001;159:179–92.
47. Argani P, Antonescu CR, Couturier J, et al. PRCC-TFE3 renal carcinomas: morphologic, immunohistochemical, ultrastructural, and molecular analysis of an entity associated with the t(X;1)(p11.2;q21). Am J Surg Pathol. 2002;26:1553–66.
48. Fine SW, Argani P, DeMarzo AM, et al. Expanding the histologic spectrum of mucinous tubular and spindle cell carcinoma of the kidney. Am J Surg Pathol. 2006;30:1554–60.
49. Yang G, Breyer BN, Weiss DA, MacLennan GT. Mucinous tubular and spindle cell carcinoma of the kidney. J Urol. 2010;183:738–9.
50. Cossu-Rocca P, Eble JN, Delahunt B, et al. Renal mucinous tubular and spindle carcinoma lacks the gains of chromosomes 7 and 17 and losses of chromosome Y that are prevalent in papillary renal cell carcinoma. Mod Pathol. 2006;19:488–93.
51. Brandal P, Lie AK, Bassarova A, et al. Genomic aberrations in mucinous tubular and spindle cell renal cell carcinomas. Mod Pathol. 2006;19:186–94.
52. Eble JN. Mucinous tubular and spindle cell carcinoma and post-neuroblastoma carcinoma: newly recognised entities in the renal cell carcinoma family. Pathology. 2003;35:499–504.
53. Zhou M, Yang XJ, Lopez JI, et al. Renal tubulocystic carcinoma is closely related to papillary renal cell carcinoma: implications for pathologic classification. Am J Surg Pathol. 2009;33:1840–9.
54. Amin MB, MacLennan GT, Gupta R, et al. Tubulocystic carcinoma of the kidney: clinicopathologic analysis of 31 cases of a distinctive rare subtype of renal cell carcinoma. Am J Surg Pathol. 2009;33:384–92.
55. Osunkoya AO, Young AN, Wang W, Netto GJ, Epstein JI. Comparison of gene expression profiles in tubulocystic carcinoma and collecting duct carcinoma of the kidney. Am J Surg Pathol. 2009;33:1103–6.
56. Aydin H, Chen L, Cheng L, et al. Clear cell tubulopapillary renal cell carcinoma: a study of 36 distinctive low-grade epithelial tumors of the kidney. Am J Surg Pathol. 2010;34:1608–21.

57. Amin MB, Gupta R, Ondrej H, et al. Primary thyroid-like follicular carcinoma of the kidney: report of 6 cases of a histologically distinctive adult renal epithelial neoplasm. Am J Surg Pathol. 2009;33:393–400.
58. Pan CC, Chen YJ, Chang LC, Chang YH, Ho DM. Immunohistochemical and molecular genetic profiling of acquired cystic disease-associated renal cell carcinoma. Histopathology. 2009;55:145–53.
59. Coleman JA, Russo P. Hereditary and familial kidney cancer. Curr Opin Urol. 2009;19:478–85.
60. Lubensky IA, Schmidt L, Zhuang Z, et al. Hereditary and sporadic papillary renal carcinomas with c-met mutations share a distinct morphological phenotype. Am J Pathol. 1999;155:517–26.
61. Giubellino A, Linehan WM, Bottaro DP. Targeting the met signaling pathway in renal cancer. Expert Rev Anticancer Ther. 2009;9:785–93.
62. Sudarshan S, Pinto PA, Neckers L, Linehan WM. Mechanisms of disease: hereditary leiomyomatosis and renal cell cancer – a distinct form of hereditary kidney cancer. Nat Clin Pract Urol. 2007;4:104–10.
63. Murakami T, Sano F, Huang Y, et al. Identification and characterization of Birt-Hogg-Dube associated renal carcinoma. J Pathol. 2007;211:524–31.
64. Grignon DJ, Eble JN. Papillary and metanephric adenomas of the kidney. Semin Diagn Pathol. 1998;15:41–53.
65. Wang KL, Weinrach DM, Luan C, et al. Renal papillary adenoma – a putative precursor of papillary renal cell carcinoma. Hum Pathol. 2007;38:239–46.
66. Brown JA, Takahashi S, Alcaraz A, et al. Fluorescence in situ hybridization analysis of renal oncocytoma reveals frequent loss of chromosomes Y and 1. J Urol. 1996;156:31–5.
67. Yusenko MV. Molecular pathology of renal oncocytoma: a review. Int J Urol. 2010;17:602–12.
68. Cochand-Priollet B, Molinie V, Bougaran J, et al. Renal chromophobe cell carcinoma and oncocytoma. A comparative morphologic, histochemical, and immunohistochemical study of 124 cases. Arch Pathol Lab Med. 1997;121:1081–6.
69. Yusenko MV, Kuiper RP, Boethe T, Ljungberg B, van Kessel AG, Kovacs G. High-resolution DNA copy number and gene expression analyses distinguish chromophobe renal cell carcinomas and renal oncocytomas. BMC Cancer. 2009;9:152.
70. Henske EP, Neumann HP, Scheithauer BW, Herbst EW, Short MP, et al. Loss of heterozygosity in the tuberous sclerosis (TSC2) region of chromosome band 16p13 occurs in sporadic as well as TSC-associated renal angiomyolipomas. Genes Chromosomes Cancer. 1995;13:295–8.
71. Smolarek TA, Wessner LL, McCormack FX, Mylet JC, Menon AG, et al. Evidence that lymphangiomyomatosis is caused by TSC2 mutations: chromosome 16p13 loss of heterozygosity in angiomyolipomas and lymph nodes from women with lymphangiomyomatosis. Am J Hum Genet. 1998;62:810–5.
72. Qin W, Bajaj V, Malinowska I, Lu X, MacConaill L, et al. Angiomyolipoma have common mutations in TSC2 but no other common genetic events. PLoS One. 2011;6:e24919. doi:10.1371/journal.pone.0024919.
73. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. J Urol. 2003;170:2217–20.
74. Thompson RH, Kurta JM, Kaag M, Tickoo SK, Kundu S, Katz D, et al. Tumor size is associated with malignant potential in renal cell carcinoma cases. J Urol. 2009;181:2033–6.
75. Edge SBB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
76. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982;6:655–63.
77. Novara G, Martignoni G, Artibani W, Ficarra V. Grading systems in renal cell carcinoma. J Urol. 2007;177:430–6.
78. Rioux-Leclercq N, Karakiewicz PI, Trinh QD, et al. Prognostic ability of simplified nuclear grading of renal cell carcinoma. Cancer. 2007;109:868–74.
79. Hong SK, Jeong CW, Park JH, et al. Application of simplified Fuhrman grading system in clear-cell renal cell carcinoma. BJU Int. 2011;107:409–15.
80. Sika-Paotonu D, Bethwaite PB, McCredie MR, William Jordan T, Delahunt B. Nucleolar grade but not fuhrman grade is applicable to papillary renal cell carcinoma. Am J Surg Pathol. 2006;30:1091–6.
81. Klatte T, Anterasian C, Said JW, et al. Fuhrman grade provides higher prognostic accuracy than nucleolar grade for papillary renal cell carcinoma. J Urol. 2010;183:2143–7.
82. Delahunt B, Sika-Paotonu D, Bethwaite PB, et al. Fuhrman grading is not appropriate for chromophobe renal cell carcinoma. Am J Surg Pathol. 2007;31:957–60.
83. Paner GP, Amin MB, Alvarado-Cabrero I, et al. A novel tumor grading scheme for chromophobe renal cell carcinoma: prognostic utility and comparison with Fuhrman nuclear grade. Am J Surg Pathol. 2010;34:1233–40.
84. de Peralta-Venturina M, Moch H, Amin M, et al. Sarcomatoid differentiation in renal cell carcinoma: a study of 101 cases. Am J Surg Pathol. 2001;25:275–84.
85. Cheville JC, Lohse CM, Zincke H, et al. Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome. Am J Surg Pathol. 2004;28:435–41.
86. Gokden N, Nappi O, Swanson PE, et al. Renal cell carcinoma with rhabdoid features. Am J Surg Pathol. 2000;24:1329–38.
87. Isbarn H, Patard JJ, Lughezzani G, et al. Limited prognostic value of tumor necrosis in patients with renal cell carcinoma. Urology. 2010;75:1378–84.
88. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An outcome prediction model for patients with clear cell renal cell carcinoma treated

with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. J Urol. 2002;168:2395–400.
89. Sorbellini M, Kattan MW, Snyder ME, et al. A postoperative prognostic nomogram predicting recurrence for patients with conventional clear cell renal cell carcinoma. J Urol. 2005;173:48–51.
90. Klatte T, Said JW, de Martino M, et al. Presence of tumor necrosis is not a significant predictor of survival in clear cell renal cell carcinoma: higher prognostic accuracy of extent based rather than presence/absence classification. J Urol. 2009;181:1558–64. Discussion 1563–4.
91. Katz MD, Serrano MF, Grubb 3rd RL, et al. Percent microscopic tumor necrosis and survival after curative surgery for renal cell carcinoma. J Urol. 2010;183:909–14.
92. Antunes AA, Srougi M, Dall'Oglio MF, et al. Microvascular invasion is an independent prognostic factor in patients with prostate cancer treated with radical prostatectomy. Int Braz J Urol. 2006;32:668–75. Discussion 675–7.
93. Madbouly K, Al-Qahtani SM, Ghazwani Y, Al-Shaibani S, Mansi MK. Microvascular tumor invasion: prognostic significance in low-stage renal cell carcinoma. Urology. 2007;69:670–4.
94. Deng FM, Melamed J. Histologic variants of renal cell carcinoma: does tumor type influence outcome? Urol Clin North Am. 2012;39:119–32.
95. Motzer RJ, Bacik J, Mariani T, Russo P, Mazumdar M, Reuter V. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. J Clin Oncol. 2002;20:2376–81.
96. Upton MP, Parker RA, Youmans A, McDermott DF, Atkins MB. Histologic predictors of renal cell carcinoma response to interleukin-2-based therapy. J Immunother. 2005;28:488–95.
97. Sun M, Lughezzani G, Perrotte P, Karakiewicz PI. Treatment of metastatic renal cell carcinoma. Nat Rev Urol. 2010;7:327–38.