The Mainz Classification of Renal Cell Tumors

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Background: Tumors arising from the renal tubular epithelium have variable characteristics and have been subject to a variety of histologic classifications.

Methods: The authors describe the distinct clinical, pathologic, phenotypic, and genotypic features of different types of renal tumors.

Results: The Mainz classification is now widely accepted because characteristic genetic alterations have been demonstrated in each tumor type.

Conclusions: The increasing emphasis on utilizing genetic characteristics of specific tumors is reflected by the more widespread use of the Mainz classification for renal cell tumors.

Introduction

A wide variety of benign and malignant neoplasms have been described in the kidney. The tumors typically encountered in adults are rare in children. Conversely, the tumors seen in children are rare in adults. In this article, we review the pathobiology of the most common renal tumors in adults. These are the tumors derived from the renal tubular epithelium, all of which are included in the Mainz classification of renal cell tumors.

Etiology and Epidemiology of Renal Cell Tumors

Renal cell carcinoma (RCC) is extremely rare in the first two decades of life, rare in patients below 40 years of age, and most prevalent in patients over age 60. The number of new cases of renal cell carcinoma in the United States in 1996 was projected to be 30,600 with an estimated 12,000 deaths.¹

Most of the carcinogens that cause renal cancer are unknown. Smoking, obesity, long-term use of phenacetin and acetaminophen, presence of kidney stones, and exposure to cadmium, thorotrast, petroleum products, and other industrial chemicals are important risk factors for developing renal cancer. Von Hippel-Lindau disease is associated with RCC in one third to one half of patients.² RCC occurs earlier in patients with von Hippel-Lindau disease. In addition, it is multiple or bilateral and metastasizes more frequently.
Whether polycystic kidney disease is associated with RCC remains controversial; however, acquired renal cystic disease, which typically occurs in patients with chronic renal failure on hemodialysis, is strongly associated with RCC. There have been a few reports of RCC clustering in families without von Hippel-Lindau disease.2 The relationship between benign renal adenomas and RCC is controversial and will be discussed later.

The Mainz Classification

RCC was originally named hypernephroma because it was believed that the tumors originated from adrenal rests due to the histologic resemblance to the adrenal. In 1960, Oberling et al3 demonstrated its origin from the proximal renal tubule based on the ultrastructural features. The tumor was renamed renal cell adenocarcinoma or renal cell carcinoma. For many years, RCC was considered a single pathologic entity and was subdivided into clear, granular, and mixed cell variants based on the cytoplasmic features of the tumor cells. The term papillary renal cell carcinoma was used to designate a subset of granular cell type RCC with exclusive or predominant papillary architecture. While significant variability in clinical behavior was observed in RCC, the old classification failed to provide good clinicopathologic correlation.

In 1976, Klein and Valensi4 reported a subtype of renal neoplasms with granular cell features, the so-called renal oncocytoma, which appeared to have an excellent prognosis. Nine years later, Thoenes and colleagues5 described another subtype of RCC with clear cell features, which closely resembled the renal tumors experimentally induced in rats.6 This tumor was named chromophobe renal cell carcinoma. Shortly after, a new renal tumor was described that appeared to originate from the collecting ducts.7 This also had granular cell features and was named collecting duct carcinoma. Overlapping of granular and clear cell features among tumors with marked clinical, pathologic, and phenotypic differences promoted the need for a new classification. In 1986, Thoenes and colleagues8 from the Gutenberg University in Germany proposed a new classification for renal tumors of tubular epithelial origin known as the Mainz classification. This classification was still based on conventional histopathologic criteria and included all the new entities described earlier.

The Mainz classification is now widely accepted because several cytogenetic studies9-12 have confirmed

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Relative Frequency</th>
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<tbody>
<tr>
<td>Renal Cell Carcinoma:</td>
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<tr>
<td>Clear Cell</td>
<td>70%</td>
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<tr>
<td>Chromophil (eosinophil, basophil)</td>
<td>15%</td>
</tr>
<tr>
<td>Chromophobe (typical, eosinophil)</td>
<td>5%</td>
</tr>
<tr>
<td>Collecting Duct Carcinoma</td>
<td>2%</td>
</tr>
<tr>
<td>Renal Oncocytoma</td>
<td>5%</td>
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Table 1. — The Mainz Classification of Renal Cell Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Histopathology</th>
<th>Cytogenetics</th>
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<tbody>
<tr>
<td>Clear Cell RCC</td>
<td>- Compact alveolar, tubular, and cystic architecture</td>
<td>- 3p losses</td>
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<td></td>
<td>- Clear cytoplasm, low N:C ratio</td>
<td>- 3:8 reciprocal translocation</td>
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<td></td>
<td>- Vascular stroma</td>
<td>- 5q gains</td>
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<td>Chromophil RCC</td>
<td>- Papillary architecture with aggregates of foamy histiocytes</td>
<td>- Trisomy and tetrasomy 7 &amp; 17</td>
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<tr>
<td></td>
<td>- Basophilic cytoplasm and low N:C ratio or eosinophilic cytoplasm and high N:C ratio</td>
<td>- Loss of Y chromosome</td>
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<tr>
<td>Chromophobe RCC</td>
<td>- Compact solid architecture</td>
<td>- Losses of chromosomes 1, 2, 6, 10, 13, 17, &amp; 21</td>
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<tr>
<td></td>
<td>- Clear or eosinophilic cytoplasm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Prominent cell membranes</td>
<td></td>
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<tr>
<td></td>
<td>- Great variability in cell size</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Positive colloidal iron stain</td>
<td></td>
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<tr>
<td></td>
<td>- 150-300 nm cytoplasmic microvesicles</td>
<td></td>
</tr>
<tr>
<td>Collecting Duct Carcinoma</td>
<td>- Medullary location</td>
<td>- Losses of chromosomes 1, 6, 14, 15, &amp; 22</td>
</tr>
<tr>
<td></td>
<td>- Tubular and glandular architecture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Hobnail cells</td>
<td></td>
</tr>
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<td></td>
<td>- Desmoplastic stroma</td>
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characteristic genetic alterations on each tumor type. Today, RCC is no longer considered a single pathologic entity. The term RCC embraces a group of renal cancers, all of which are derived from the renal tubular epithelium but each with distinct clinical, pathologic, phenotypic, and genotypic features. The Mainz classification of renal cell neoplasms is presented in Table 1 with the relative frequency of each tumor. The most characteristic histopathologic and cytogenic features are presented in Table 2.

Renal Adenoma

Small renal epithelial neoplasms are commonly and incidentally found during autopsies. Many investigators believe that these lesions lack the ability to progress to RCC and are benign. However, since the same lesions are not uncommonly associated with concomitant RCC, other investigators claim that some of these neoplasms might progress to RCC. Methods to distinguish the benign adenomas from the potentially malignant tumors remain controversial.13

In 1950, Bell14 conducted an autopsy study and reported that metastases were exceptional when renal tumors were less than 3 cm in size. He suggested that these lesions should be considered benign adenomas. With the advent of computed tomography scans, an increasing number of small tumors (1 cm or even less) that had already metastasized were reported.13 Therefore, tumor size is no longer considered a reliable criterion. At the present time, most urologic pathologists agree that there are no reliable criteria to distinguish benign renal adenomas from RCC. Microscopically, histopathologic features of both greatly overlap, and almost any histologic pattern described in RCC can be encountered in benign adenomas. Although it is acknowledged that many of these small renal neoplasms are probably benign, they should be considered potentially malignant, regardless of their size, until reliable diagnostic criteria become available. Tumors with clear cells should never be accepted as benign adenomas. The ideal candidate for a benign renal adenoma is a small and superficial tumor with tubular, papillary, or mixed architecture and without clear cells or nuclear anaplasia.

Renal Oncocytoma

Renal oncocytoma is uncommon but not rare (5% of the tumors derived from tubular epithelium). While most tumors are incidentally found, they can present as a palpable mass or with hematuria. Oncocytomas may resemble RCC clinically and pathologically, and this resemblance may lead to radical nephrectomy. However, conservative surgery is considered an adequate treatment since true oncocytomas are always benign.16

Fig 1. — Renal oncocytoma. The mahogany appearance of the tumor contrast with the white fibrous scar in the center of the mass.

Fig 2. — Renal oncocytoma. Eosinophilic tumor cells with large granular cytoplasm form small aggregates and tubules. Note the lack of mitotic activity and cytologic atypia (hematoxylin-eosin, × 600).
Renal oncocytoma has a characteristic mahogany appearance and often has a central white fibrous scar (Fig 1). Although rare, necrosis may occur, resembling RCC. Hemorrhage is common. Bilaterally or multicentricity are common. Occasionally, oncocytomas are predominantly cystic.

The histologic features are very characteristic. Strongly eosinophilic tumor cells forming islands and tubules dominate throughout the tumor. Tumor cells exhibit large and finely granular cytoplasm, uniform round nuclei, clumped chromatin and small nucleoli (Fig 2). Bizarre, enlarged nuclei may be scattered throughout the tumor, but mitoses are rare. Oncocytomas sometimes extend into the perinephric fat or into venous sinuses without affecting the prognosis. These two features are never observed grossly. The differential diagnosis with eosinophilic chromophobe RCC would be difficult without Hale's colloidal iron stain, which is negative in oncocytomas, or without electron microscopy (EM), which in oncocytomas shows numerous mitochondria filling the cytoplasm of the tumors cells (Fig 3).

Few cases of metastatic oncocytomas have been reported. Retrospectively, these tumors were most probably eosinophilic chromophobe RCC and were easily mistaken with oncocytomas because Hale's colloidal iron stain and EM were not applied. When fulfilling all the diagnostic criteria described earlier, oncocytomas are always benign and do not recur or metastasize.

Clear Cell Renal Cell Carcinoma

Clinically, this is the most common renal neoplasm seen in adults (70% of tumors derived from tubular epithelium). This tumor can be as small as 1 cm or less and discovered incidentally, or it can be as bulky as several kilograms. Most often it presents with pain, as a palpable mass or with hematuria, but a wide variety of paraneoplastic syndromes have been described. Clear cell RCC might be clinically silent for years and may present with symptoms of metastasis.

The gross appearance is characteristic. The tumor is solid, lobulated, and yellow, with variegation due to necrosis and hemorrhage (Fig 4). The tumor might be well circumscribed, or it might invade the perirenal fat or the renal vein. Cystic degeneration is common, but some tumors are predominantly cystic (15%). The so-called cystic RCC is more often multilocular and with clear cells, but it can be unilocular and with chromophil cells. RCC may arise also in benign renal cysts as mentioned earlier. Obtaining extensive histologic sampling of all cystic renal masses is an important precaution to assure the correct diagnosis. Multicentricity occurs in 13% of cases, but bilaterality is rare, occurring in approximately 1% of cases.

Many tumors demonstrate a predominant compact alveolar architecture (Fig 5). Tubular or cystic areas are...
commonly associated with the alveolar pattern. Focal papillarity is not rare, but a predominantly papillary architecture is almost never associated with clear cell RCC; such tumors are most likely chromophil RCC. Most clear cell RCC contains numerous capillaries and thin-walled blood vessels in the supporting stroma — a helpful diagnostic feature that is usually retained when the tumor metastasizes. The cytoplasm of many tumor cells is rich in lipids and glycogen, which dissolve during processing and provide the characteristic clear cytoplasm. The cytoplasm of adrenal cortical cells from the zona fasciculata, although similar, is foamy. Scattered tumor cells with eosinophilic granular cytoplasm are not uncommon. They can be the predominant constituent in focal areas, especially near necrosis. Tumor cell nuclei are round and centrally placed. Nuclear pleomorphism is variable depending on tumor grade. The Fuhrman nuclear grading system is widely used. Several studies with large numbers of patients have shown an excellent correlation with staging and survival.13

Four grades are recognized based on nuclear size, nuclear contour, and the presence of nucleoli. Mitotic activity is not considered because it varies among tumors and does not correlate well with prognosis. Grade I tumors (10%) demonstrate small, uniform nuclei without nucleoli. Grade II tumors (35%) demonstrate larger nuclei with greater nuclear size variability and without nucleoli. Grade III tumors (35%) demonstrate larger and more pleomorphic nuclei with prominent nucleoli. Multinucleated giant tumor cells are seen only in grade IV tumors (20%), which occasionally may demonstrate spindling and severe nuclear anaplasia resembling a sarcoma, the so-called sarcomatoid variant of clear cell RCC. When tumor heterogeneity is present, the highest grade is always assigned. The survival rates at five and 10 years are 67% and 51% for grade I tumors, 56% and 42% for grade II tumors, 33% and 15% for grade III tumors, and 8% and 0% for grade IV tumors, respectively.

In the rare cystic-multilocular variant, the wall of each cystic space is made of thick fibrous septa containing very few tumor cells. Cystic RCC has very good prognosis, and metastases are rare.

Staging is the most important prognostic factor in clear cell RCC. Several staging systems are available, but the TNM system is widely used. At the time of the diagnosis, metastases to regional lymph nodes are seen in 10% to 15% of cases, and direct invasion or metastasis to ipsilateral adrenal is seen in 5% of cases. Occult renal cell carcinoma may present with distant metastases to lungs, bone, brain, and many other locations. Although rare, spontaneous regression of metastases has been described.20

Clear cell RCC must be differentiated from other malignant tumors and nonneoplastic conditions. Xanthogranulomatous pyelonephritis, which is usually associated with calculus, is the most important benign condition that can be grossly and microscopically mistaken as clear cell RCC. The inflammatory cell infiltrate contains numerous histiocytes that may be misinterpreted as tumor cells. In this inflammatory process, the vascular stroma characteristic of clear cell RCC is missing. The cytoplasm of the histiocytes can be clear but is also foamy. The histiocytes are typically admixed with other inflammatory cells such as lymphocytes and plasma cells. Malacoplakia is another inflammatory process usually associated with immunosuppression, which may resemble clear cell RCC. Its gross appearance, characterized by tan-brown masses infiltrating the perinephric fat, might be highly suggestive of RCC. Histologically, the inflammatory cell infiltrate is predominantly composed of eosinophilic histiocytes, resembling the granular cells of clear cell RCC. However, extensive histologic sampling fails to identify the characteristic histologic features of clear cell RCC. Also, in malacoplakia, Michaelis-Gutmann laminated bodies are seen in the cytoplasm of some histiocytes, assuring the correct diagnosis.

Among the malignant tumors, the differential diagnosis includes urothelial carcinoma originating in the
renal pelvis or renal calyces, which is occasionally composed of tumor cells with clear or pale cytoplasm but lacks the prominent vascular stroma observed in clear cell RCC. The differential diagnosis between the sarcomatoid variants of urothelial carcinoma and RCC can be extremely difficult and is possible only if focal areas with classic urothelial carcinoma or clear cell RCC are found. When immunohistochemistry is applied, the expression of high-molecular-weight cytokeratins and carcinoembryonic antigen supports the diagnosis of urothelial carcinoma. The differential diagnosis with classic chromophobe RCC can be very difficult; this is discussed later. The sarcomatoid variant of clear cell RCC may closely mimic a true sarcoma, which is extremely rare in the kidney. After extensive sampling, foci with typical clear cell histology are usually found. EM may reveal epithelial ultrastructural features in areas that appear sarcomatous under the light microscope.

The combination of microvilli and abundant cytoplasmic glycogen is suggestive of clear cell RCC. Like sarcomas, clear cell RCC is usually positive for vimentin but also positive for epithelial membrane antigen and low-molecular-weight cytokeratins. Clear cell RCC must be distinguished from the adult variant of nephroblastoma or Wilms’ tumor, when the latter is predominantly epithelial. Metastatic clear cell RCC to the adrenal glands must be differentiated from adrenal cortical adenomas and the rare adrenal carcinomas, both of which express vimentin but not epithelial membrane antigen and express cytokeratins only focally and weakly. Metastatic clear cell RCC must be differentiated from a variety of tumors with clear cell features, especially when the renal primary is unknown, which is a common situation. Coexpression of vimentin and cytokeratins is uncommon in many carcinomas and is highly suggestive of metastatic RCC.

The most common and consistent genetic finding in clear cell RCC is 3p loss. Complete loss of chromosome 3 is rare but losses of the terminal bands (13 to 14) are common. Partial losses in the proximal region of 3p are also known to occur in individuals with von Hippel-Lindau disease. A reciprocal 3:8 chromosomal translocation has been described in a report of a familial form of clear cell RCC not associated with von Hippel-Lindau disease. All family members who developed RCC showed this translocation, while the other members did not. These data support the concept that the deletion of unknown suppressor genes located on 3p are most likely involved in the pathogenesis of clear cell RCC. Less consistent genetic alterations such as 5q gains are also common in clear cell RCC.

Chromophil Renal Cell Carcinoma

Chromophil RCC is the second most common renal tumor (10% to 15% of tumors derived from the renal tubular epithelium). This tumor is also known as papillary RCC. It is unclear if the prognosis of chromophil RCC is better than the prognosis of clear cell RCC, but these tumors are clearly malignant with a 10-year mortality rate of at least 16%. Chromophil RCC is often a well-circumscribed tan-brown tumor that contains hemorrhagic and necrotic areas and a granular cut surface due to its papillary architecture.

Many tumors are predominantly papillary, but some also contain tubular areas (90%). Tight papillary compression may lead to a predominantly solid appearance (10%). Occasionally, tubular architecture is so prominent that this tumor has also been called tubulopapillary carcinoma. The term chromophil RCC proposed in the Mainz classification, which refers to its cytologic characteristic, is preferred. The papillae are made of a thin fibrovascular core covered by cuboidal tumor cells, which may demonstrate complex branching and very often contain aggregates of foamy macrophages (Fig 6). In tubular areas, the small tubules are lined by a monolayer of tumor cells with the same cytologic features. Tumor cells vary from small size with scanty cytoplasm and large nuclei...
resulting in high N:C ratio (the basophilic variant) to large tumor cells with abundant eosinophilic and granular cytoplasm (the eosinophilic variant). The nuclei of tumor cells are usually round and uniform and without nucleoli. Occasionally, tumor cell nuclei may be pleomorphic and with prominent nucleoli, depending on the grade of the tumor. The same grading and staging systems proposed for clear cell RCC are recommended for chromophil RCC. A sarcomatoid variant corresponding to a nuclear grade IV is also recognized, which has the same diagnostic and prognostic implications already observed for clear cell RCC.

Chromophil RCC has characteristic cytogenetic alterations that differ from those observed in clear cell RCC. Chromosomal gains, particularly trisomy or tetrasomy 7 and 17, are common. In contrast, 3p losses or 5q gains are never found. Also, complete loss of chromosome Y is seen in many chromophil RCC in men.

Chromophobe Renal Cell Carcinoma

Chromophobe RCC was discovered by Bannasch et al while conducting experiments of renal cancer induction in the rat. Thoenes et al described the human counterpart later. Chromophobe RCC is infrequent but not rare (5% of tumors derived from tubular epithelium). In contrast with clear cell and chromophil RCC, which affect men more often than women, chromophobe RCC is seen in men and women with the same frequency. It has been suggested that the prognosis of chromophobe RCC is better than the prognosis of clear cell RCC. The same grading and staging systems used for clear cell and chromophil RCC are recommended for chromophobe RCC.

Chromophobe RCC is a well-circumscribed, light brown tumor that only rarely demonstrates hemorrhage or necrosis.

Fig 7. — Chromophobe RCC, typical type. Polyhedral tumor cells with abundant pale cytoplasm and a solid pattern of growth. Note the marked variation in cell size and the prominent cytoplasmic membranes, which resemble vegetable cells (hematoxylin-eosin, × 600).

Fig 8. — Chromophobe RCC, typical type. The ultrastructural micrograph shows numerous cytoplasmic microvesicles (arrows) of paranuclear location and peripheral mitochondria.
strong blue cytoplasmic staining in chromophobe RCC, which is negative in clear cell RCC. EM reveals numerous oval cytoplasmic microvesicles measuring from 150 to 300 nm in diameter (Fig 8) that are not found in any other renal tumor and that are considered diagnostic. It is quite likely that Hale’s colloidal iron reacts with a substance present in the microvesicles.

The eosinophilic variant of chromophobe RCC was recognized later.27 Tumor cells are large and with strongly eosinophilic and granular cytoplasm. EM reveals numerous mitochondria but also the same cytoplasmic microvesicles described earlier. Hale’s colloidal iron stain is also strongly positive. This variant closely resembles renal oncocytoma. While oncocytomas are clearly benign neoplasms, the eosinophilic variant of chromophobe RCC behaves in a similar fashion as other RCC. As mentioned earlier, some oncocytomas have been mistaken with this tumor in the past. EM and Hale’s colloidal iron stain must be performed whenever the possibility of oncocytoma or chromophobe RCC is considered in the differential diagnosis. Chromophobe RCC demonstrates characteristic cytogenetic abnormalities. Complete and multiple losses involving chromosomes 1, 2, 6, 10, 13, 17, and 21 are seen in more than 90% of tumors.28 Loss of 3p and trisomy or tetrasomy of chromosomes 7 and 17 have never been observed.

Collecting Duct Carcinoma

Collecting duct carcinoma is a neoplasm derived from the collecting ducts. However, recent studies show that other renal neoplasms such as oncocytomas and chromophobe RCC most likely originate also in the collecting ducts.29,30

Collecting duct carcinoma is usually a poorly circumscribed and centrally necrotic tumor. Its most characteristic gross feature is its medullary location. This might not be well appreciated when tumors are large.

Histologically, the tumor cells form glands, tubules, solid nests, or cords embedded in a loose, desmoplastic stroma. The solid areas can be easily mistaken with urothelial carcinoma. An extremely helpful diagnostic feature is the hobnail appearance of the tumor cells lining the glandular and tubular spaces. Atypical cells with a similar appearance are occasionally found in the normal tubules surrounding the tumor. Papillary areas resembling chromophil RCC are occasionally seen. Also, a sarcomatoid variant has been described but is very rare. The main differential diagnosis is with RCC and urothelial carcinoma. Immunohistochemistry can help to establish the correct diagnosis. Collecting duct carcinomas stain positively for cytokeratin 19, ulex europaeus lectin, and vimentin, while urothelial carcinomas stain negatively for vimentin, and RCCs stain negatively for ulex europaeus lectin.

Collecting duct carcinoma is a rare tumor (2% of tumors derived from tubular epithelium). Davis and colleagues23 reported collecting duct carcinomas in young black patients with sickle cell trait. These may represent an aggressive variant of collecting duct carcinoma. Other investigators52-34 have described other tumors of possible collecting duct origin. However, until more knowledge is accumulated, it is better to define collecting duct carcinomas as renal tumors that appear to arise in the medullary region of the kidney and that demonstrate tubular and glandular structures lined with hobnail cells in a desmoplastic background. Tumors with suggestive features of collecting duct carcinoma, that do not fulfill these criteria should be considered unclassified carcinomas, which represent 3% of renal cell tumors. Cytogenetic information is still very limited in these tumors, but losses of chromosomes 1, 6, 14, 15, and 22 have been reported.34

References