Subtypes of renal cell carcinoma: MRI and pathological features

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ABSTRACT
Renal cell carcinoma (RCC) is the most common malignant tumor involving the kidney. Determining the subtypes of renal cell carcinoma is among the major goals of preoperative radiological work-up. Among all modalities, magnetic resonance imaging (MRI) has several advantages, such as inherent soft tissue contrast, detection of lipid and blood products, and excellent sensitivity to detect small amounts of intravenous contrast, which facilitate the discrimination of subtypes of RCC. In this article, we review MRI and pathological features used for determining the main histologic subtypes of RCC, including clear cell, papillary, collecting duct, chromophobe, multilocular cystic, and unclassified RCC.

Renal cell carcinoma (RCC) is the most common malignant epithelial tumor of the kidney, accounting for 85%–90% of all solid renal tumors in adults and comprising 1%–3% of all malignant visceral neoplasms (1). Approximately 40% of patients with RCC eventually die from progression of this disease, making it the most lethal urologic malignancy (2). Today, most RCC instances are incidental masses identified on imaging studies performed for nonurological reasons.

Percutaneous biopsy is a minimally invasive method, and its accuracy for identifying renal tumors ranges from 70% to 90% (3, 4). However, widespread use of percutaneous biopsy remains controversial due to the potential complications of biopsy, the possibility of sampling errors, the dependence on an adequate biopsy sample for analysis, and concerns about how the biopsy information might alter the treatment plan (5). Therefore, histopathological characterization of renal masses with magnetic resonance imaging (MRI) compared with percutaneous biopsy becomes more advantageous.

Determining subtypes of RCC has significant prognostic and therapeutic implications for patients who are poor surgical candidates, for patients who have a metastatic disease, for surgical planning in patients who are surgical candidates, and for immunotherapy and use of the tyrosine kinase inhibitors “sunitinib” and “sorafenib” for clear cell RCC and “temsirolimus” for papillary RCC (6–9).

The need for a different approach to the management of RCC among classical surgical procedures has arisen. Nephron-preserving surgical methods, cryoablation, radiofrequency ablation, targeted molecular therapy or follow-up, and MRI are believed to surpass other modalities both in the diagnosis of RCC and determination of its subtypes (10, 11).

In this article, we review MRI findings and pathological features used for determining the main histologic subtypes of RCC, including clear cell carcinoma, papillary, collecting duct, chromophobe, multilocular cystic, and unclassified RCC.

The role of MRI in renal imaging
There are three indispensable components of renal MRI: breathhold imaging, three-dimensional (3D) gradient echo pulse sequence, and fat detection techniques.

Breathhold imaging is one of the essential techniques in renal mass MRI protocols. Suspended expiration eliminates respiratory motion artifacts and improves registration for subtraction postprocessing. MRI techniques with rapid acquisition times, such as the fast imaging technique and single-shot pulse sequences, are now widely available and very effective with suspended respiration (12). The speed of these se-
quences allows dynamic contrast-enhanced (DCE) MRI with or without fat suppression (13).

The 3D gradient echo sequence permits dynamic and volumetric imaging under breathhold (14). Image postprocessing with multiplanar reformattng, maximum intensity projection, and volume rendering is often used to assess the relationship between the tumor and vascular system. Subtraction is useful for maximum intensity projection, volume rendering, and determining the contrast enhancement of any mass high on T1 or tiny structures, such as the septa or mural components of a lesion. The 3D gradient echo sequence has decreased the total imaging time because it is no longer necessary to obtain postcontrast images in an additional plane. It also eliminates the need for magnetic resonance angiography sequences. For DCE imaging, interrogation of tumor signal intensity before, during, and after the intravenous administration of a bolus of contrast is possible. The accumulation of the contrast agent in the tumor over time can be used to extract both qualitative and quantitative information regarding the functional integrity of tumor microvasculature (15).

The detection of fat is critical in characterizing renal masses (16, 17). Macroscopic fat is assessed using frequency-selective fat suppression techniques (18), while microscopic fat, i.e., intracytoplasmic vacuoles containing lipids, is assessed using chemical shift imaging, which is available only with gradient-echo imaging (19). The presence of intratumoral lipids results in a decrease in signal intensity on T1-weighted, opposed-phase images compared with the in-phase images in the non-necrotic “viable” tumor (20).

Diffusion-weighted imaging (DWI), an innovative technology for renal masses, is a vital component of renal imaging. DWI provides quantification of the Brownian motion of water molecules in tissues, which depends on tissue organization, cellularity, the integrity of cell membranes, and extracellular space tortuosity (21). Qualitative and quantitative information are obtained regarding tissue characterization without the need for gadolinium chelates and alternative imaging for renal lesion characterization in patients at risk for nephrogenic systemic fibrosis (21–24). Few studies have evaluated the correlation of apparent diffusion coefficient (ADC) values with nuclear grade, histological subtype, and cellularity of RCC. However, it is an evolving technology, and as recommended in the literature, it may improve tissue characterization when findings are interpreted along with the findings of conventional MRI sequences (25, 26).

**Pathological features of subtypes of RCC**

RCC is a group of malignancies arising from tubular epithelium. The classification of RCC has been revised due to advances in correlative, genetic, and histologic studies of both sporadic and familial tumors (27, 28). The World Health Organization working group on tumors of the urinary system and male genital organs proposed the classification in 2004 (29).

RCC is considered a clinicopathologically heterogeneous disease that can be classified into clear cell, papillary, chromophobe, collecting duct carcinoma, medullary carcinoma, multicellular cystic and unclassified (4%–5%) categories that can be histologically differentiated mostly with hematoxylin-eosin staining techniques (29). Some RCCs undergo sarcomatoid or rhabdoid dedifferentiation, a process thought to represent the high-grade end of all subtypes (29, 30).

**MRI findings of RCC subtypes**

**Clear cell carcinoma**

Clear cell carcinoma is the most common type of RCC, accounting for 70% of all RC. They are predominantly sporadic (95%) but can be familial or associated with Von Hippel Lindau disease. Up to 96% of clear cell RCCs are associated with 3p deletions, including somatic inactivating mutations of the von Hippel Lindau gene (31).

Clear cell RCC recapitulates the epithelium of the proximal convoluted tubules (32). At histologic analysis, clear cell RCC is composed of cells with optically clear cell cytoplasm due to accumulation of dissolved lipids and cholesterol. These tumors often contain cells with granular eosiophilic cytoplasm. Tumor cells are characteristically arranged in sheets, acini, or alveoli, and prominent thin-walled vasculature is characteristic (33). Hyalination, fibrosis, and coagulative tumor necrosis are common, while cystic degeneration occurs in 4%–15% of RCCs (34). They are predominantly hypervascular tumors and the microvessel density is higher than other subtypes of RCC (35).

Clear cell RCC has a relatively unfavorable prognosis, with a five-year survival of 50%–60%, which is less favorable than other RCC subtypes, with the exception of the collecting duct carcinoma subtype (33). Compared with papillary and chromophobe RCC, they tend to be symptomatic more commonly, present at an advanced stage and have a higher rate of metastasis (36). Sarcomatoid, and rhabdoid differentiations of clear cell RCC are also associated with a poorer prognosis.

Clear cell carcinoma displays common MRI characteristics of RCC. They originate from the renal cortex and typically exhibit an expansile growth pattern. Multicentricity and bilateral are rare (5%) in sporadic cases. They frequently have a signal intensity similar to that of the renal parenchyma on T1-weighted images and increased signal intensity on T2-weighted images. Necrosis, hemorrhage and cysts are the main causes of varying appearances on MRI. Central necrosis is common and typically considered a homogeneous hypointense area in the center of the mass on T1-weighted images. On T2-weighted images, necrosis tends to have a moderate to high signal intensity, although it may occasionally appear hypointense (Fig. 1a). In the presence of central necrosis, a solid rim of tumor is frequently observed at the periphery of the mass. Postcontrast images demonstrate a lack of enhancement in areas of necrosis and marked enhancement in the viable components of the tumor (Fig. 1b) (37).

Intratumoral hemorrhage may occur and has a variable appearance depending at the stage of degradation of the component blood products. Subacute to chronic hemorrhage generally demonstrates a high signal intensity in both T1- and T2-weighted images. Long-standing hemorrhage, which predominantly contains hemosiderin,
is typically hypointense in both T1- and T2-weighted images (38).

Considerable loss of signal intensity within the solid portions of clear cell RCCs on opposed phase images compared with in-phase images is due to cytoplasmic fat and has been detected in up to 60% of clear cell RCC (Fig. 1c–e) (39).

Clear cell RCC is mostly hypervascular, which has been ascribed to inactivation of tumor suppressor genes (such as the von Hippel Lindau gene) and subsequent elaboration of vascular and other growth factors (40). In contrast-enhanced MRI with heterogeneous enhancement in the arterial phase continuing with or without washout (37), the degree of contrast enhancement may help distinguish clear cell RCC from non-clear cell subtypes. Sun et al. (41) reported the results of region-of-interest measurements within tumor and uninvolved renal cortex, which were used to calculate percentage signal intensity change and tumor-to-cortex enhancement index. On both the corticomedullary and nephrographic phase images, clear cell RCCs showed a greater signal intensity change (205.6% and 247.1%, respectively) than papillary RCCs (32.1% and 96.6%, respectively). The tumor-to-cortex enhancement indexes at the corticomedullary and nephrographic phases were largest for clear cell RCCs (1.4 and 1.2) compared with indexes of papillary and chromophobe RCC. Signal intensity changes on corticomedullary phase images are the most effective parameter for distinguishing clear cell and papillary RCC; a threshold value of 84% permitted distinction with 93% sensitivity and 96% specificity. Vargas et al. (42) examined the quantitative region of interest analysis of tumor enhancement patterns at multiphase MRI. They showed that in three postcontrast phases (corticomedullary, nephrographic, and excretory), the percentage change in signal intensity relative to the precontrast phase was significantly greater in clear cell carcinoma (230%, 250%, and 227% for corticomedullary, nephrographic, and excretory phases, respectively) compared with papillary and chromophobe RCC.

A hypointense rim or pseudocapsule might be observed on both T1- and T2-weighted images and is thought to be related to compression of the adjacent renal parenchyma by the expanding tumor, although a fibrous capsule can occasionally be observed at pathologic analysis. The interruption of this pseudocapsule correlates with advanced stage (invasion of perirenal fat) and higher nuclear grade (43).

In the case of DWI, Goyal et al. (26) showed that the mean ADC value of clear cell RCC was found to be significantly higher than that of non-clear cell RCC, with an optimal cut-off ADC value of 1.4904×10⁻³ mm²/s. Taouli et al. (25) and Wang et al. (24) reported similar results for clear cell RCC, while Sandrasegaran et al. (44) did not find any significant difference in the ADC values of clear cell RCCs and non-clear cell malignancies.

**Papillary cell carcinoma**

This subtype accounts for 10%–15% of all RCC (29). It may be sporadic or familial. Tumor epithelium is reminiscent of the epithelium of the proximal convoluted tubules (32). Histologically, it is characterized by a papillary growth pattern and occurs in both sporadic and familial forms. The cells covering the papillae range from small to large and have a variable cytoplasmic staining. Psammoma bodies and edema are common in the papillary cores. The most striking feature is the foamy histiocytic infiltration into the interstitium of the lesion, which is laden with fat and hemosiderin. Hemosiderin is also observed in the tumor cells (17). There are two histomorphologic subtypes of papillary RCC. Type 1 tumors are characterized by a monolayer
of small cells with scanty cytoplasm, while type 2 tumors contain high nuclear grade cells with abundant eosinophilic cytoplasm (29).

The most common cytogenetic abnormalities are trisomies of chromosomes 3, 7, 12, 16, 17, and 20 and loss of the Y chromosome and c-MET mutations of a subset of sporadic papillary RCC (45, 46). Cytogenetic features support the diagnosis of papillary RCC even when the papillary pattern is not prominent.

Papillary RCC has a better prognosis than clear cell RCC, with a five-year survival rate of approximately 90% and often presenting at an early stage (33, 36). Type 1 papillary RCC is typically of a lower stage and grade than type 2 tumors and is thus associated with a better prognosis (29).

Papillary RCC tend to be solid, large, well-defined, and slow-growing tumors (46). They frequently exhibit bilaterality (4%) and/or multifocality (22.5%) more than other RCC subtypes and display distinct MRI features (36). Approximately 70% are intrarenal at presentation. They are small in size and hypointense compared with the cortex on T2-weighted images and have homogeneous signal intensity (Fig. 2a). Hypointensity on T2-weighted images has often been assigned to the hemorrhage or necrosis of the tumor. Hypointensity can still be present in the absence of these contents and provides an accurate distinction from clear cell RCC, which typically exhibits heterogeneously increased signal intensity on T2-weighted images (11). A fibrous capsule is typically present in papillary RCCs. Larger tumors show heterogeneity due to necrosis, hemorrhage, and calcification. The overall sensitivity and specificity of MRI in predicting the histologic subtype is reported to be 92% and 83% for clear cell RCC and 80% and 94% for papillary RCC, respectively (47). Sarcomatoid dedifferentiation may be observed in approximately 5% of cases.

Papillary carcinoma, either the primary tumor or its metastases, has been shown to contain microscopic fat that is detectable with chemical shift imaging (29). The major difference in fat content between clear and papillary cell carcinoma is the localization of fat, which can only be defined pathologically. Fat is present in the interstitial histiocytes of papillary cell carcinoma rather than tumor cells such as in clear cell carcinoma (29). Although extremely rare, the presence of macroscopic fat (corresponding histologically to cholesterol-laden macrophages) has also been reported (48).

Papillary RCC shows hypo- or avascularity on angiography. Due to hypovascularity, they tend to enhance minimally on cortical phase and seem hypointense compared with renal parenchyma on the nephrographic phase. On postcontrast series, they enhance homogenously, or small, curvilinear enhancing structures can be detected within the tumor (Fig. 2b, 2c) (11). Papillary RCC might also present as cystic neoplasms with hemorrhagic content and peripheral-enhancing solid papillary projections (Fig. 3a, 3b). Sun et al. (41) reported that the tumor-to-cortex enhancement indexes at corticomedullary and nephrographic phases were the smallest for papillary RCCs among clear cell and chromophobe RCC. Percentage signal intensity changes on corticomedullary phase images were found to be the most effective parameter for distinguishing clear cell and papillary RCC; a threshold value of 84% permitted distinction with 93% sensitivity and 96% specificity. Vargas et al. (42) reported similar results with region of interest measurements in all three postcontrast phases. In corticomedullary, nephrographic, and excretory phases, the percentage change in signal intensity relative to the pre contrast phase was significantly lower in papillary carcinoma (49%, 92%, and 88% for corticomedullary, nephrographic, and excretory phases) compared with clear cell and chromophobe RCC.

Figure 2. a–c. Axial T2-weighted STIR turbo spin echo (a) and oblique sagittal postcontrast 3D VIBE (b) images show papillary RCC. A left renal upper pole mass with well-defined margins is hypointense on T2-weighted image (a, arrow). On postcontrast image (b) there is minimal faint, irregular, spot-like enhancing foci (arrows) within the lesion with no considerable washout. Photomicrograph (hematoxylin-eosin, x200) of the surgically removed papillary RCC (c) shows papillae formation (arrow) with numerous pale stained histiocytes.

Figure 3. a, b. Axial T2-weighted STIR turbo spin echo (a) and axial postcontrast VIBE (b) images show a rhabdoid variant of papillary RCC. A huge hemorrhagic right renal lower pole mass with solid mural component is observed (a, b). There is heterogeneous signal intensity on T2-weighted image (a). On postcontrast images there is minimal heterogenous enhancement of the mural nodule (b, arrow).
Taouli et al. (25), Goyal et al. (26), and Wang et al. (24) reported low mean ADC values for papillary RCC compared with clear cell RCC, while no significant difference was detected compared with chromophobe RCC. However, Sandrasegaran et al. (44) did not find any significant difference in the ADC values of clear cell RCCs and non-clear cell malignancies. In papillary RCC, cells are organized into papillary projections. Its compact tissue architecture and higher nuclear cytoplasmic ratio (49) might be responsible for lower ADC values.

Chromophobe RCC

Among all RCC subtypes, chromophobe RCC is the third most common subtype and accounts for approximately 4%–11% of RCCs (29). Chromophobe RCC shows a mean age of incidence in the 6th decade. Men and women are equally affected. Incidence in the 6th decade. Men and women are equally affected. Median age at diagnosis was 60 years (29). Interestingly, in male patients, the median age at diagnosis was 66 years, whereas in female patients, the median age was 57 years (29).

Chromophobe RCC is postulated to arise from the intercalated cells of the renal cortex. Histologically, tumor cells are round to polygonal and have well-defined cytoplasm borders, pale eosinophilic cytoplasm with a fine reticular pattern, and perinuclear haloes (33). Tumor cells usually demonstrate a pattern of solid growth. Cytogenetically multiple monosomy (1, 2) and hypodiploidy is associated with chromophobe RCC (29, 32, 45).

This tumor type has the best prognosis among the RCC categories. Metastasis occurred in approximately 7.1% of patients, and 3%–6% died of chromophobe RCC. The reported five-year survival is approximately 78%–92% (33, 36).

MRI features of chromophobe RCC can be identical to those of clear cell RCC. They might appear hypointense on T2-weighted images compared with renal parenchyma (Fig. 4a). Cystic changes can be observed within a solid tumor, and central necrosis might be absent, even in very large chromophobe carcinomas (50). Signal loss on out of phase images due to microscopic fat has been reported (51). It is interesting that oncocytomas and chromophobe RCC share similar ontogenic and histologic features (on hematoxylin-eosin-stained slides) and some imaging findings. Oncocytomas develop from type B intercalated cells of the cortical collecting duct and are indistinguishable from chromophobe RCC on imaging studies, sharing features such as central scar and spoke wheel pattern of enhancement (51).

Chromophobe RCC is the second most common hypovascular tumor after papillary RCC. Despite its large size, chromophobe RCC demonstrates relatively homogeneous enhancement compared with papillary RCC (Fig. 4b–d). Sun et al. (41) reported that chromophobe RCC showed an intermediate change in both percentage signal intensity (109.9% and 192.5%) and tumor-to-cortex enhancement indexes at corticomedullary and nephrographic phases (0.6 and 0.8, respectively), which is lower than clear cell RCC and higher than papillary RCC. Vargas et al. (42) reported similar results, showing that chromophobe RCC displayed significantly less enhancement than clear cell carcinoma at all three postcontrast phases.

In chromophobe RCC, cells are arranged in solid sheets. Its compact tissue architecture and dense cytoplasm may cause lower ADC values. Wang et al. (24) showed a significantly higher mean ADC of clear cell RCC (1.849×10⁻³ mm²/s) than papillary (1.087×10⁻³ mm²/s) and chromophobe (1.307×10⁻³ mm²/s) RCC. However, there was no significant difference in the ADC values of papillary and chromophobe RCC. Goyal et al. (26) also reported similar results.

Collecting duct carcinoma

Collecting duct carcinoma is rare, accounting for less than 1% of cases, and an aggressive RCC subtype. The mean age of patients with collecting duct carcinoma is mid-50s, and the male-to-female ratio is approximately 2:1. This carcinoma has a very unfavorable prognosis because one-third of the patients have distant metastasis at diagnosis, and two-thirds of patients die within two years (39).

Collecting duct carcinoma is thought to originate in the distal segment of the collecting duct in the renal medullary pyramids and is histologically characterized by tubular or tubulopapillary growth patterns, the presence of inflammatory or desmoplastic stroma, and mucin production (52). Cytogenetically, the loss of multiple chromosomes (1, 6, 14, 15, 22) and gain of chromosome 3 have been detected (45).
On MRI, collecting duct carcinoma have variable signal intensity on T1-weighted and frequent hypointensity on T2-weighted images (Fig. 5a, 5b) (53). They may appear heterogeneous, with areas of necrosis, hemorrhage, and calcification and a cystic component can be observed in 50% of patients. They are hypovascular tumors angiographically and display heterogeneous or predominantly peripheral contrast enhancement (Fig. 5c–e). The epicenter of these tumors is typically located in the medullary portion of the kidney near the region of the pelvis. However, almost all tumors exhibit focal cortical extension, and some even exhibit perirenal extension (54). They have a tendency to display infiltrative patterns, preserving renal contour rather than an expansile growth. This infiltrative appearance may be difficult to detect when the lesion is large or has an expansile component and differentiation from clear cell RCC is not possible (54).

Although it could be classified as a non-clear cell type and be expected to have lower ADC compared with clear cell RCC, there is a lack of data specific for collecting duct type RCC in both DCE MRI and DWI.

Unclassified RCC

This is a diagnostic category for RCC that does not fit readily into any other category and is a diagnosis of exclusion. It accounts for 4%–5% of RCC subtypes.

Tumors in this category are histologically heterogeneous and most often of high grade. There are some features that may help identify a tumor as unclassified: sarcomatoid cells without recognizable epithelial elements, mucin production, mixtures of epithelial and stromal elements, and unrecognizable cell types (33). This category has the worst prognosis among RCC subtypes (29, 36).

There is little information about MRI findings of this subtype. When heterogeneous histological features are taken into consideration, MRI findings likely display a wide spectrum. They may be solid with a cystic component, hyperintense on T1- and isointense on T2-weighted images, show heterogeneous enhancement and contain hemorrhage (Fig. 6a–d) (55). Unclassified RCCs display significantly smaller mean signal intensity changes than clear cell carcinoma at three postcontrast phases (42). Although it is classified as non-clear cell type and expected to have lower ADC than clear cell RCC, there is a lack of data specific for unclassified RCC in DWI.

Multilocular cystic RCC

This is a rare entity with an incidence varying between 1%–4% of all RCC (56). Multilocular cystic RCC is found in adults aged 20–76 years, with a mean age of 51 years, and observed predominantly in males (male:female, 3:1) (57). Multilocular cystic RCC is characterized by septated, variable-sized cysts separated from the kidney by a fibrous capsule (58). If treated early, multilocular cystic RCC has an excellent prognosis and may be permanently cured. Recurrence and metastasis have not yet been reported (58).

Histopathologic analysis demonstrates serous, gelatinous, or hemorrhagic cysts lined by a monolayer of epithelial cells with clear cytoplasm (1). These cells, consisting of clear cytoplasm, form small collections but do not form expansile collections, which is an important differential criterion to distinguish multilocular cystic RCC from clear cell RCC with extensive cystic change (57). Calcification can be found in the septa or pseudocapsule of more than 20% of multilocular cystic RCC.

On MRI, multilocular cystic RCCs typically manifest as multilocular cystic tumors. They have a variable imaging pattern, with a Bosniak category ranging from IIF to IV. As multilocular cystic RCC lesions increase in complexity on images (higher Bosniak category), there is a corresponding increase in the volume of malignant cells lining the tumor and an increase in the presence of vascularized fibrous tissue (59). On
T1- and T2-weighted images, they frequently show hyperintensity, likely due to proteinaceous fluid or hemorrhage, or may display heterogenous signal intensity on both pulse sequences (Fig. 7a, 7b) (59). Blood products of different ages may create various signal intensities. On post contrast series, there is minimal internal, asymmetric septal, or wall enhancement (Fig. 7c, 7d).

There are not sufficient specific data regarding multilocular cystic RCC in DCE MRI and DWI.

Conclusion
Determining the subtypes of RCC is essential for predicting prognosis and managing therapeutic strategies. In the preoperative radiological work-up, MRI is the best modality for providing important information to diagnose RCC subtypes.

Conflict of interest disclosure
The authors declared no conflicts of interest.

References