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Renal Cell Carcinoma: The Evolving Role of Imaging in the 21st Century

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Kidney lesions are commonly an incidental finding on cross sectional studies carried out for a variety of reasons. The detection of renal cell carcinoma (RCC) has increased accordingly. There are a variety of different contrast-enhanced CT imaging protocols that have been developed to help diagnose and stage RCC. More recently, renal MRI and contrast-enhanced ultrasound have also been used as problem-solving tools. This paper describes the epidemiology of RCC and the role of imaging in diagnosis and follow-up.
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Introduction

The number of renal cell carcinomas (RCC) detected has increased over the last 20 years owing to incidental detection of lesions on routine imaging. Advanced CT protocols and MRI sequences allow better diagnosis, staging and potentially characterization of RCC and its subtypes. In the last 10 years interventional radiology techniques have developed to aid diagnosis and management of RCC including percutaneous biopsy and treatments such as percutaneous cryoablation.

RCC is the seventh most common cancer diagnosed worldwide, with incidence rates between 1 and 22 of 100,000.[1] It is 1.5 times more common in men with a peak incidence between 60 and 70 years.[2] The 2004 World Health Organization Classification describes the subtypes of RCC: the most common being clear cell (70%), papillary (10%-15%) and chromophobe tumors (5%).[3] Over 50% of all RCCs are detected incidentally on cross-sectional imaging carried out for other purposes.[4,5]

Risk factors for RCC include smoking, hypertension and diabetes however the potential for bias exists in this cohort who undergo more imaging than the general population.[6]

Other risk factors include genetic syndromes with strong associated predisposition to specific subtypes of RCC (Table 1). Although syndrome associated RCC only constitutes 2%-3% of RCC these conditions should be considered when RCC is detected in a young person. The most clinically relevant syndrome is Von-Hippel Lindau syndrome where patients can have multiple and bilateral simple renal cysts and cystic clear cell RCCs.

Imaging in RCC

US, CT, and MRI are used widely in clinical practice for the detection of RCC with CT and MRI being the main imaging modality used for surgical planning and disease monitoring.

Standard grey-scale (B mode) ultrasound has been used for a long time in RCC diagnosis as it is cost effective, easily repeatable and avoids ionizing radiation. Ultrasound provides greater spatial resolution than CT or MRI and is both sensitive and specific in the diagnosis of simple renal cysts, which appear as anechoic thin-walled structures with post acoustic enhancement. It should be noted that ultrasound can lead to false positives: for instance over calling internal complexity of renal cysts which otherwise demonstrate benign appearances on cross-sectional imaging; equally there can be false negatives such as dismissing a hyperechoic lesion as a benign angiomyolipoma (AML) as RCC can also appear hyperechoic due to presence of internal fat, blood and calcium.

Contrast-enhanced ultrasound (CEUS) using microbubbles injected into the systemic veins has a developing role in lesion characterization, particularly in patients who cannot

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Table 1 Common Renal Cell Carcinoma (RCC) Associated Syndromes

Syndrome	Tumor Subtype
Burt-Hogg-Dube	Oncocytoma, chromophobe
Hereditary leiomyomatosis and renal cell cancer	Papillary type 2
Hereditary papillary renal cell cancer	Papillary type 1
Tuberous sclerosis	Angiomyolipoma, epethelioid angiomyolipoma
Von Hippel Lindau disease	Clear cell

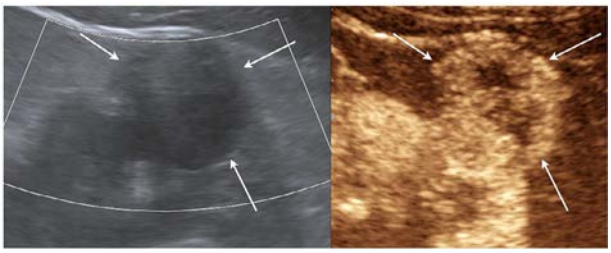

Figure 1 Contrast enhanced ultrasound. B mode ultrasound (left) demonstrates a hypoechoic lesion that demonstrates classical peripheral enhancement after injection of intravenous microbubbles with areas of central nonenhancement, typical for a clear cell RCC.

have intravenous contrast media and avoids radiation exposure particularly in younger patients. CEUS is very sensitive (>88%) and relatively specific (50%-80%) in the diagnosis of enhancing renal tumours[7-12] (Fig. 1). In addition, CEUS can also help characterize lesions that have indeterminate enhancement on CT, including hypovascular or complex cystic tumours.[13]

Routine abdominal CT commonly identifies renal lesions in adult patients (up to 14%) with only 1% of these needing further characterisation.[14] Multiphase contrast enhanced CT (Fig. 2) is still the gold-standard cross-sectional modality for diagnosing RCC.[15] Multiphase CT accurately identifies and quantifies enhancement within renal masses in 91%[16] of cases increasing to nearly 100% in lesions greater than 2 cm.[17] Contrast enhancement is defined as an increase of at least 20 Hounsfield units (HU) between pre and post contrast images.[18]

Unenhanced imaging is important to help determine the baseline attenuation of a lesion and to identify macroscopic intralesional fat and calcification. In addition, it can also reliably exclude simple cysts with internal attenuation of <20 HU, and hyperdense cysts which if demonstrate a uniform internal density of >70 HU are thought to be benign.[19]

The corticomedullary (arterial) phase is at 25-70 seconds after the start of the contrast injection. The renal cortex enhances brightly and can be differentiated from the hypoenhancing medulla. RCCs are hypervascular tumors and enhance strongly in the arterial phase. However, there are pitfalls of relying on just the corticomedullary phase as some cortical renal masses can enhance to the same degree as heathy surrounding tissue and therefore be disguised; equally poorly enhancing hypovascular lesions can enhance to the same degree as the medulla and can be missed particularly if they are endophytic central tumors. In addition, false positives can occur secondary to heterogeneous enhancement of the medulla mimicking a tumor. The corticomedullary phase helps to delineates arterial anatomy which aids surgical planning and can detect distant renal cancer metastases which are often hypervascular.

The nephrographic (venous) phase occurs 60-130 seconds after contrast injection and is arguably the most useful for identifying RCC. The renal parenchyma enhances more homogenously which allows better differentiation between normal renal medulla and a mass. Due to relative "washout" of renal masses, these lesions become more conspicuous in the nephrographic phase. When compared with arterial phase imaging, the sensitivity of detecting renal masses in the nephrographic phase increases from 84% to 100% with a specificity of 95%.[20] This phase also allows accurate assessment of spread of the tumor into the renal veins and vena cava, which has a bearing on staging and surgical treatment possibilities.

The excretory (delayed) phase occurs approximately 180 seconds after contrast injection and peaks at 5-8 minutes. Some institutions prefer to use an early excretory phase (240 seconds) as opposed to a nephrographic phase. This provides additional information about the relationship between the tumor and calyces.[21]

MRI (Fig. 3) is an increasingly used alternative cross sectional imaging modality to CT in renal imaging and is generally considered as a suitable comparable alternative to stage and follow up RCC.[22] It can be used in patients with

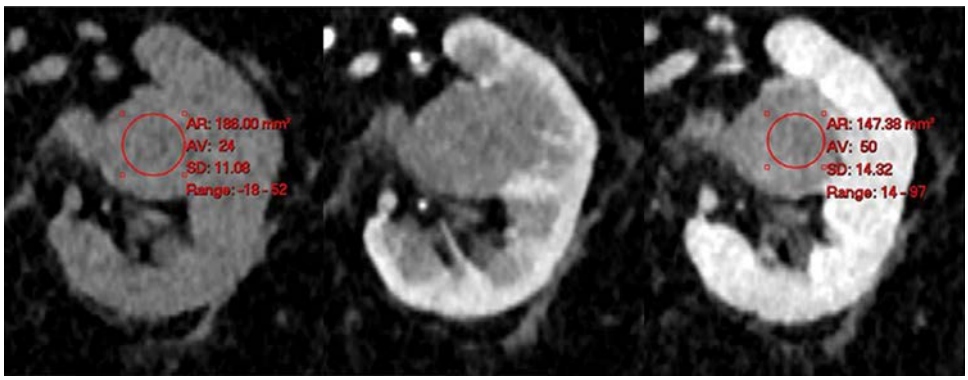

Figure 2 Papillary RCC. Three phase renal protocol CT demonstrating a parapelvic lesion that enhances slightly post-contrast (24-50 HU). On biopsy this proved to be a Type 2 papillary RCC.

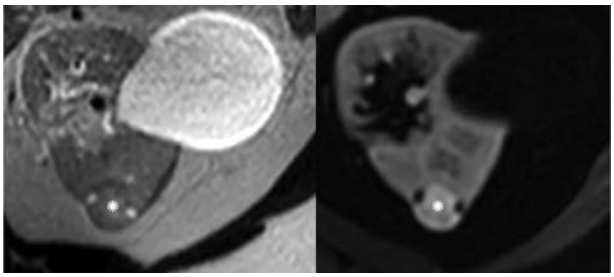

Figure 3 MRI in RCC. (A) Axial slices from renal protocol MR: (a) T2w and (b) postcontrast T1w in a young patient with Birt-Hogg-Dubé syndrome and previous bilateral chromophobe RCCs. Asterisks indicate an enhancing solid-cystic lesion in the posterior cortex of the left kidney. A simple cyst is seen anterior to this.

contraindications to iodinated CT contrast and in avoiding radiation exposure particularly in young patients undergoing frequent follow up screening scans.[23]

Multiparametric renal MRI protocols typically include a combination of anatomical sequences (T2 in different orthogonal planes), in- and out-of-phase imaging for assessing fat content, diffusion weighted imaging (DWI) and dynamic contrast-enhanced sequences (DCE). Images are acquired in end inspiration to maintain consistent position of the kidneys.

Chemical shift imaging uses in-phase and opposed-phase gradient-recalled echo in order to demonstrate the presence of intratumoral fat. It is important to note that although AML typically contain fat, other RCC subtypes can also demonstrate intratumoral fat (both intracellular and less commonly macroscopic fat) including approximately 60% of clear cell RCCs[24] and 15% of papillary RCCs.[25]

DWI forms part of many MRI protocols and gives functional data on the tissues within the kidney. Gradient echo planar imaging with imaging at different b-values including b 0-100 s/m^2 and b $\geq$600 s/m^2 most commonly employed.[24] Some studies have suggested DWI can be used to characterize the subtype of RCC: for instance increased restricted diffusion may be able to predict more aggressive tumours.[26] Wang et al found DWI and/or ADC imaging with b values of $>$500 s/m^2 in 85 tumors allowed sensitive and specific differentiation of clear cell from papillary and chromophobe RCC subtypes. DWI/ADC must not be relied upon in isolation as it is not uncommon to observe very marked restricted diffusion within some benign lesions such as fat poor AMLs and within interstitial pyelonephritis (lobar nephronia) and renal abscess.[27]

DCE can aid in differentiating indeterminate lesions, particularly partial cystic lesions with an equivocally enhancing solid component on post contrast CT.[28] Enhancement is assessed qualitatively in MRI compared to CT where HU can be objectively measured with region of interest tools. It has been shown that in the hands of an experienced radiologist, DCE-MRI is extremely sensitive in identifying true enhancement, particularly when using semiquantitative techniques. Hecht et al analyzed 93 renal masses with DCE as part of MRI assessment and compared this to post resection histology. This group found the use of semiquantitative techniques such as image subtraction, where percentage enhancement of greater than 15% was considered significant enhancement, aided the assessment of true enhancement in those lesions that returned high signal on precontrast T1 images.[29] Al Salmi et al verified a similar technique, with a threshold of 20% for true enhancement, for characterizing 104 renal lesions as malignant or benign compared to the final pathological diagnosis.[30]

Imaging Features of Common Subtypes of RCC

RCCs are classically hyperarterialized, heterogeneous lesions with characteristic exophytic appearance. It is important to appreciate there is a broad spectrum of imaging appearances of RCC and to be aware of atypical imaging features of certain subtypes:

Clear cell RCC (Fig. 4) is the most common subtype and these tumors often demonstrate internal heterogeneity including cystic elements due to internal necrosis and hemorrhage. Presence of a fibromuscular pseudocapsule, which is the result of compression and fibrosis of surrounding perirenal tissue as the tumor expands, is more commonly seen in clear cell RCC compared with other subtypes and is a predictor of lower grade tumours.[31-33] Sarcomatoid differentiation is a predictor of aggressive malignancy in RCC and imaging features include large heterogeneous tumors with peritumoral neovascularity and cystic necrosis.[34-36]

Papillary RCC is the second most common subtype and has 2 distinct genetic and clinical subtypes with a range of phenotypes that range from indolent multifocal lesions to solitary aggressive tumors. Type 1 tumors are seen in patients with hereditary papillary renal cell cancer syndrome and are often multifocal and bilateral. Nonhereditary type 1 papillary tumors are associated with the same proto-oncogene somatic mutations (MET) as in hereditary papillary RCC syndrome.[37] Type 2 tumors are more likely to be solitary heterogeneous lesions. A more aggressive phenotype of type 2 papillary RCC is seen in patients with hereditary leiomyomatosis and RCC syndromes.[38] Papillary tumors in general are less histologically vascular than clear cell RCC[39] which results in papillary tumors only having subtle enhancement that may be dismissed as a benign cyst if due care and attention are not paid. Particular care should be taken when assessing a patient with multiple inconsistent renal cysts on a single phase CT for instance.

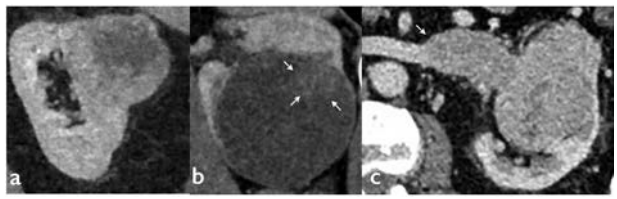

Figure 4 Clear cell renal carcinoma examples. (A) Postcontrast CT showing a peripherally enhancing, heterogeneous exophytic mass in the upper pole of the left kidney in keeping with a classical clear cell RCC T1b. (B) Postcontrast CT with a predominantly cystic lesion containing a solid enhancing nodule; this was also a clear cell RCC histologically. (C) Postcontrast CT with a large left sided solid tumor with tumor thrombus extending into the left renal vein in keeping with T3a RCC.

Chromophobe RCCs are fairly rare lesions representing up to 6% of RCCs. They can demonstrate a central stellate scar with a spoke-wheel enhancement pattern which is similar to that in the classical description of oncocytomas.[40]

The Role of Radiology in Diagnosis

The British Urology Association dataset for nephron sparing surgery reported between 18%-44% of resected renal lesions had benign histology, yet these lesions (including complex cysts and oncocytomas) exhibited malignant characteristics on prior imaging.[41] Renal mass biopsy prior to any therapeutic treatment including surgery and ablation is therefore being increasingly recommended by renal cancer multi-disciplinary meetings and can clearly help avoid unnecessary interventions.[15]

Renal masses can be biopsied using US, CT, and even now in-bore MRI guidance. The majority of published series use an 18-20 gauge biopsy needle and carry out a median number of 2 passes.[42] The role of biopsy is indicated before ablation therapy by the European Association of Urology.[15] Prior histological diagnosis can be useful to help risk stratify patients before commencing active surveillance, and deciding between radical nephrectomy and nephron sparing surgery.[43-45]

Percutaneous renal biopsy has high sensitivities of 97% and specificity above 96% for diagnosis of RCC[42,46] but can be inconclusive in necrotic or fibrotic tumors. Rebiopsy in these cases will be sufficient for diagnosis in more than 80% of cases.[47] Image guided biopsy is relatively safe with a theoretical risk of tumor seeding along the biopsy tract (less than

Table 2 TNM 8 Staging RCC

Tumor (T)		
TX	The primary tumor cannot be assessed.	
T0	No evidence of a primary tumor.	
T1	The tumor is limited to the kidney and is no larger than 7 cm across.	
	A	The tumor is 4 cm across or smaller and is limited to the kidney.
	B	The tumor is larger than 4 cm but not larger than 7 cm across and is limited to the kidney.
T2	The tumor is larger than 7 cm across but is still limited to the kidney.	
	A	The tumor is more than 7 cm but not more than 10 cm across and is limited to the kidney.
	B	The tumor is more than 10 cm across and is limited to the kidney.
T3	The tumor is growing into a major vein or perinephric tissues, but it is not growing into the ipsilateral adrenal gland or beyond Gerota's fascia	
	A	The tumor is growing into the renal vein/branches, perirenal fat, renal sinus fat or pelvicalyceal system.
	B	The tumor extends into the infradiaphragmatic inferior vena cava.
	C	The tumor extends into the supradiaphragmatic inferior vena cava or into the wall of the vena cava.
T4	The tumor has spread beyond Gerota's fascia. The tumor may have contiguous growth into the ipsilateral adrenal (NB: a focus of tumor within the adrenal but not in continuity with the primary tumor is defined as M1 disease).	
Nodal Categories (N)		
NX	Regional lymph nodes cannot be assessed	
N0	No spread to nearby lymph nodes	
N1	Tumor has spread to nearby lymph nodes (ie, hilar, caval, aortic)	
Metastases (M)		
M0	No metastases.	
M1	Distant metastases are present; includes spread to distant lymph nodes and/or to other organs.	

1:10,000, but there may be under-reporting). Coaxial needle use in renal mass biopsy is recommended to reduce this risk.[15,48] Other complications include bleeding in approximately 5% of cases, with transfusion and embolization required in <1% of cases.[42,46]

Staging and Assessing Response

The Tumour, Node, Metastasis staging still remains the most robust predictor of RCC prognosis.[49] The eighth edition has been updated (Table 2). The recent edition includes redefinition of T3 disease, which now includes tumor invading the pelvicalyceal system and involvement of segmental and main renal vein by tumor thrombus in addition to local extension into perirenal or renal sinus fat >90% of clear cell RCCs ≥7 cm invade the renal sinus[50] yet cross sectional imaging is relatively insensitive to sinus fat invasion.[51] Under reporting of potential renal sinus invasion is the most frequent cause for surgical upstaging to T3 disease.[52] Therefore any abutment of the renal sinus by a cortically based tumor (even without overt invasion) should be considered as suspicious for T3 disease.[53]

Patients with metastatic RCC are now surviving longer due to the introduction of novel antiangiogenic immune therapies including suppressors of vascular endothelial growth factor such as Sunitanib and Sorafenib.[54] Several trials have shown that anti-vascular endothelial growth factor therapies confer improved disease progression-free survival although this is not necessarily reflected by standard current treatment response criteria such as response evaluation criteria in solid tumors (RECIST).[55,56]

RECIST is useful to assess tumor size regression, but underestimate the effects of anti-angiogenic therapies that induce a cytostatic rather than a cytotoxic response; in addition, RECIST can overestimate progression secondary to tumor pseudogrowth with infiltration of tumors by induced immune cells.[57] Further more refined criteria have been proposed including; the "−10% criteria" that defines partial response as a reduction ≥10% in the sum length of target lesions;[58] the modified Choi criteria that defines partial response as a ≥10% decrease in size and a ≥15% decrease in attenuation on CT and progressive disease as a ≥10% increase in tumor size.[59] Further more complicated criteria that assess changes in tumor morphology, development of central necrosis as well as size and enhancement have been suggested including: Size and Attenuation CT[60] and Morphology, Attenuation, Size, and Structure criteria[61] with neither of these being commonly adopted in clinical practice partly due to practicality and inconsistency in assessment.[62] Currently the −10% criteria applied to metastatic target lesions has proved to be the most effective method of predicting progression-free survival.[63,64]

Conclusion

The rate of RCC detection has increased secondary to routine imaging becoming common practice. Radiologists have met this challenge with the development and validation of contrast-enhanced ultrasound, multiphase CT and MRI techniques to characterize renal lesions and facilitate image guided biopsy. Immune therapies that have led to an increased survival in metastatic RCC and have required a paradigm shift in the way radiologists assess response to these novel treatments.

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