Image Interpretation
Practical Triage of Benign from Malignant Renal Masses

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KEYWORDS

• Kidney • Small enhancing renal mass • Clear cell renal cell carcinoma
• Papillary renal cell carcinoma • Chromophobe renal cell carcinoma • Oncocytoma
• Fat-poor angiomyolipoma

KEY POINTS

- Renal lesions not characterized as Bosniak I/II cysts or angiomyolipoma are indeterminate and require additional imaging characterization.
- Multiphase contrast-enhanced imaging has emerged as a means of characterizing indeterminate renal masses, with clear cell renal cell carcinoma (RCC), papillary RCC, chromophobe RCC, fat-poor angiomyolipoma, and oncocytoma as primary differential considerations.
- Relative corticomedullary enhancement greater than that of adjacent renal cortex of an indeterminate renal mass is a strong predictor for clear cell RCC.
- Multiphase contrast-enhanced imaging allows for quantitative analysis of renal lesions with many emerging applications, such as radiocytogenetics.

INTRODUCTION

Incidentally discovered renal masses that don't require immediate treatment and are not definitively characteristic of angiomyolipoma (AML) or Bosniak I/II cysts at initial imaging are indeterminate and require further imaging characterization.[1] For indeterminate renal masses, size is the leading determinant of renal mass triage. The larger an indeterminate renal mass, the greater the likelihood of high-grade/malignant disease.[2] Smaller indeterminate masses, conversely, are more likely benign.[2] Despite these observations, small (pT1a or <4 cm in size) indeterminate renal masses comprise 38% of surgically resected renal masses with 20% to 30% found benign on pathologic analysis.[3] Furthermore, given slow growth and low rate of progression/metastasis of small renal cell carcinoma (RCC) lesions, Jewett and colleagues[4] advocate for active surveillance with serial imaging for small RCC. Although these small indeterminate renal masses are traditionally presumed malignant with partial nephrectomy as preferred treatment,[5] accurate image characterization of these lesions will optimize triage to biopsy or ablative/surgical treatment and allow for better selection for active surveillance and to optimize follow-up based on risk of malignancy/benignity. This review focuses on current and evolving methods to triage indeterminate renal masses at multiphase imaging based on assessment of their enhancement characteristics.

NORMAL ANATOMY AND IMAGING TECHNIQUE

Current Society of Abdominal Radiology (SAR) computed tomographic (CT) protocol guidelines

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advocate for a minimum of unenhanced and nephrographic (120 sec) phases to assess for renal mass enhancement (**Fig. 1**; **Table 1**).[6] Unenhanced imaging provides a baseline to assess for lesion enhancement on subsequent phases and is also sufficient to assess for lesion homogeneity, macroscopic fat, and calcification.[7] Uniform enhancement of the renal cortex and medulla during the nephrographic phase optimizes detection of heterogeneously enhancing lesions.

Corticomedullary and excretory postcontrast CT phases are optional per the SAR, but can be very helpful in delineating renal vascular and collecting system anatomy before any intervention that may be pursued.[6] These additional phases also provide additional postcontrast time points to assess enhancement characteristics of renal masses.

Radiation exposure represents a significant risk for those undergoing CT surveillance, particularly given the prevalence of this modality in the medical community. Radiation dose of CT must be minimized, particularly in younger patients, because the equivalent of 8 lifetime CT scans theoretically increases lifetime cancer risk from 1/1000 to 1/82.[8] As more is understood about differentiation of small indeterminate masses, directed measures must be taken to minimize radiation dose.

Dynamic contrast-enhanced MRI is a robust alternative technique for indeterminate renal mass characterization with similar lesion enhancement characteristics demonstrated as compared with CT (see **Fig. 1**, **Table 1**).[9] In addition to assessment of enhancement characteristics, MRI has the added benefit of T2-weighted, opposed phase, and diffusion-weighted imaging (DWI). Although generally tolerated well, MRI has unique limitations, primarily related to patient factors, such as motion, body habitus, claustrophobia, metallic implanted devices, and foreign bodies. In addition, MRI acquisition times are generally significantly longer than for CT, and the examinations are more costly.

Contrast-enhanced ultrasound (CEUS) evaluation of indeterminate renal masses has been promising with less scan time than MRI, minimal risk of contrast morbidity, and no radiation exposure.[10] Unlike CT and MRI, CEUS contrast boluses can be given multiple times during imaging acquisition, although this modality can be significantly limited in patients with large body habitus. CEUS image acquisition can also be difficult to reproduce, with a high level of interoperator variability.

Effective and safe active imaging surveillance of indeterminate renal masses requires judicious use of CT to minimize radiation dose. Periodic use of MRI and CEUS can allow for longer intervals between CT scans during the surveillance period with resultant decrease in patient radiation exposure.

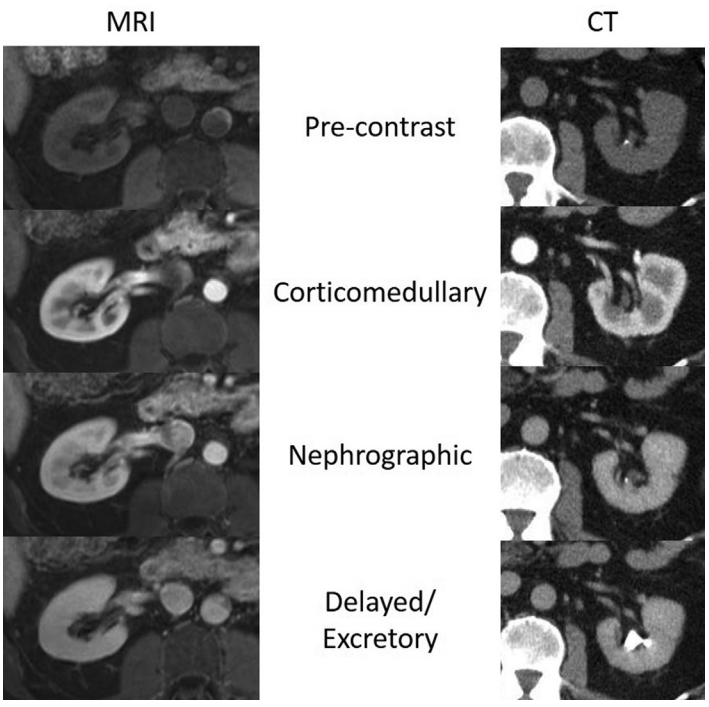

Fig. 1. Precontrast, corticomedullary, nephrographic, and delayed/excretory phases on both CT and MRI.

Table 1
Imaging protocols

CT[6]

Contrast: Low or isoosmolar, 35–52.5 g iodine (approximately 100–150 mL of 350 mg iodine/mL), rate: 2–5 mL/s

Phase	*Anatomic Coverage*	*Acquisition*	*Reconstructions*	*Additional reformats*
Precontrast	Kidneys only	Axial	3-mm slices, with or without 50% overlap	
Corticomedullary	Kidneys only	Axial, 40- to 70-s delay	3-mm slices, with or without 50% overlap	Coronal/sagittal, 3-mm slices without overlap
Nephrographic	Kidneys only	Axial, 100- to 120-s delay	3-mm slices, with or without 50% overlap	Coronal/sagittal, 3-mm slices without overlap
Excretory	Diaphragm to iliac crests	Axial, 7- to 10-min delay	3-mm slices, with or without 50% overlap	Coronal/sagittal, 3-mm slices without overlap

MRI[9]

Contrast: Extracellular gadolinium-based, 0.1 mL/kg, rate: 1–2 mL/s followed by 10–20 mL saline

Sequence	*Planes/Thickness/Gap*	*Details/Alternatives*
2D T2 SSFSE	Axial/4–5 mm/no gap Coronal/5–6 mm/no gap	2D T2 FSE/4- to 5-mm slice thickness/no gap
2D T1 GRE in/out of phase	Axial/5–6 mm/0.5–1 mm	3D Dixon/3 to 4-mm slice thickness/no gap
3D T1 SPGR fat saturation, precontrast	Axial/3–4 mm/no gap Coronal/3–4 mm/no gap	
3D T1 dynamic SPGR fat saturation, postcontrast	Axial/3–4 mm/no gap Coronal/3–4 mm/no gap	Postcontrast timing: 30, 90–100, 180–210 s, 5–7 min Obtain subtraction images as well
Diffusion-weighted imaging	Axial/5–6 mm/no gap	B values: 0–50, 400–500, 800–1000 s/mm^2

Abbreviations: GRE, gradient echo; SSFSE, single-shot fast spin echo; SPGR, spoiled gradient recalled.

IMAGING FINDINGS/PATHOLOGY

Incidentally discovered renal masses with macroscopic fat and absence of calcification on any precontrast or postcontrast phase enables confident diagnosis of AML, especially if the lesion is exophytic and of soft contour conforming to the surrounding renal parenchyma and perirenal tissues.[1] Bosniak I/II cysts are characterized on unenhanced imaging based on homogeneity, CT attenuation values, or magnetic resonance (MR) T1 and T2 characteristics. Bosniak I/II cysts should also demonstrate absence of enhancement on all modalities. In lesions that enhance in the nephrographic phase and that lack macroscopic fat, the 5 primary differential considerations are clear cell, papillary or chromophobe RCC, oncocytoma, and fat-poor (FP) AML.

Under the current paradigm, these 5 subtypes of enhancing renal mass cannot be reliably differentiated based on enhancement characteristics derived only from unenhanced and nephrographic phases. If an enhancing small renal mass is detected, resection or ablation of the lesion with preservation of as many nephrons as possible represent the most definitive treatment options. Tissue diagnosis of the lesion is derived from the surgical specimen or a biopsy performed in conjunction with ablation. Accurate imaging-based subtyping of enhancing indeterminate renal masses will enable appropriate triage to biopsy, ablative or surgical treatment and will improve active surveillance.

Given the broad differential diagnosis of small enhancing renal masses, which includes both malignant and benign entities, additional postcontrast

phases are used to more specifically characterize indeterminate renal masses. Corticomedullary and excretory phases provide additional time points at which to assess lesion enhancement. Birnbaum and colleagues[11] recognized the need for both corticomedullary and nephrographic phases to best assess for indeterminate renal mass enhancement, particularly for lesions that demonstrate peak enhancement later than the corticomedullary phase. In a small pilot study in 2000, Jinzaki and colleagues[12] initially demonstrated differences between the most common renal mass subtypes based on their absolute peak enhancement and deenhancement in the corticomedullary and nephrographic phases, although these differences were not found to be statistically significant.

Generally, clear cell renal cell carcinomas (ccRCC) are round, oval, or lobular lesions that enhance heterogeneously and have a peak absolute HU greater than 160 on corticomedullary phase with unenhanced HU between 25 and 40, nephrographic HU at about 120, and excretory phase HU of approximately 100. Oncocytomas, the most common benign mimic of ccRCC, tend to be round or oval lesions that enhance more homogenously with peak corticomedullary HU 140 to 160 with deenhancement in the nephrographic phase near 120 HU and excretory phase HU values of about 100. Chromophobe RCC tend to be larger and more heterogenous compared with oncocytoma with peak enhancement in the nephrographic phase and excretory phase HU of 60 to 80. Patients with FP AML tend to be younger than patients with RCC. FP AML lesions tend to be ovoid- or mushroom-shaped space-occupying lesions that are typically 45 to 55 HU on unenhanced scans, with homogenous peak absolute enhancement of about 140 HU in the corticomedullary phase with deenhancement in the nephrographic and excretory phases at 100 to 120 and 80 to 100 HU, respectively. Finally, papillary RCCs tend to measure 40 to 50 HU on unenhanced scans and have absolute peak attenuation of 80 HU in the nephrographic phase with mild deenhancement to about 60 HU in the excretory phase.[13] Unfortunately, there is overlap between several of the above characteristics that make indeterminate renal mass characterization difficult under the current paradigm (**Fig. 2**).

MRI can add more information, with T2 signal (tends to be low in FP AML and papillary RCC with higher signal noted in ccRCC; **Figs. 3** and **4**), opposed phase imaging (signal drop of 20% may be seen in 20%–40% of FP AML and ccRCC because of microscopic fat, whereas signal gain may be seen in papillary RCC because of hemosiderin), and DWI (papillary RCC has increased restriction and low ADC compared with ccRCC; **Fig. 5**) demonstrating additional utility in the characterization of indeterminate renal masses alongside qualitative and quantitative absolute and relative lesion enhancement.[14]

More recent CT and MR studies in the past 10 years with much larger cohorts have confirmed that the absolute peak enhancement of ccRCC is significantly greater than all other lesions in the corticomedullary phase with rapid deenhancement in the nephrographic and excretory phases,

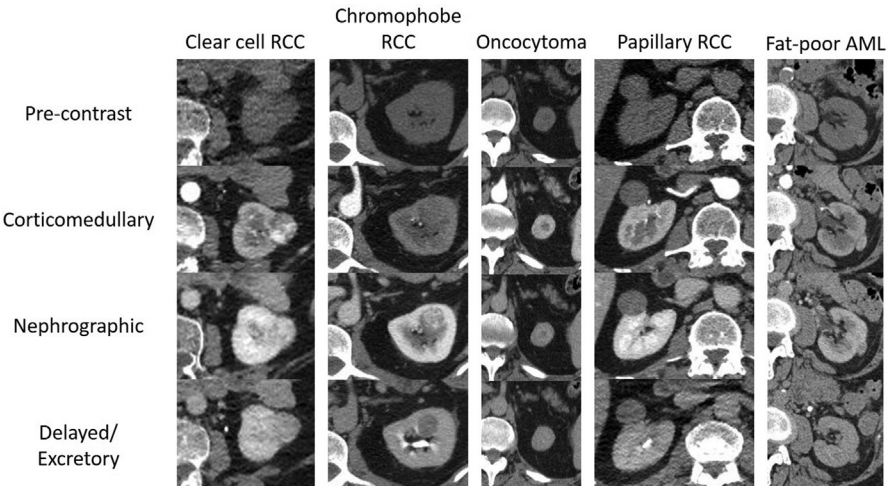

Fig. 2. Differential considerations for indeterminate renal masses shown at precontrast, corticomedullary, nephrographic, and excretory/delayed phases. Although there are some characteristics that allow for differentiation between these lesions, there is significant overlap in the subjective appearances of oncocytoma, FP AML, clear cell, papillary, and chromophobe RCC.

Fig. 3. A T2-weighted image shows characteristic hypointensity of a papillary RCC (*arrow*).

enabling quantitative and qualitative discriminative signatures and quantitative subtyping of enhancing indeterminate renal masses.[13–15] Lee-Felker and colleagues[13] also reported that the peak relative enhancement of ccRCC (enhancement above the renal cortical background) was significantly higher in comparison to the other common lesions. Similar absolute and relative enhancement features of ccRCC have also been demonstrated on contrast ultrasound (CEUS).[10] Refinement of methods and increasing sample sizes over the years have demonstrated more reliable and accurate differentiation of enhancing indeterminate renal masses at imaging. This review summarizes many of these methods.

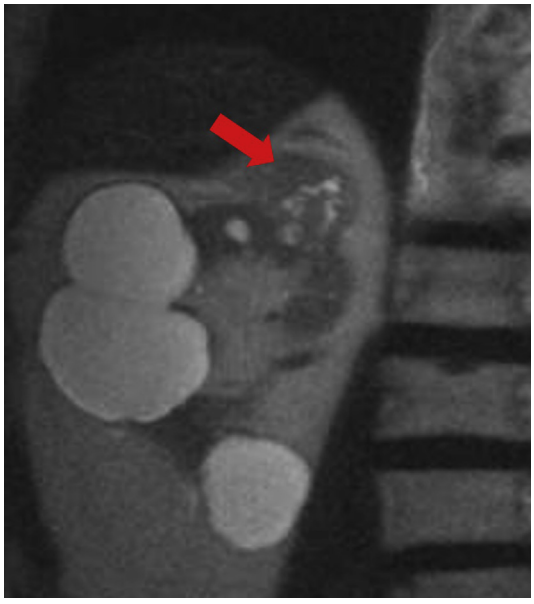

Fig. 4. A T2-weighted image depicts mild hyperintensity and heterogeneity within a ccRCC (*arrow*). Additional homogeneous T2 hyperintense simple cysts are also seen within the right kidney.

Mean Enhancement

Bird and colleagues[16] demonstrated a statistically significant difference in mean enhancement between oncocytoma and all types of RCC. This study used the entire lesion as a region of interest (ROI), including areas of hypoenhancing scar and necrosis. Because RCC has a much higher propensity for necrosis than oncocytoma, using the entire lesion likely underestimated the peak enhancement of these lesions and may have precluded differentiation between the subtypes of RCC in this study.

Absolute Enhancement

Absolute enhancement is based on the peak Hounsfield unit attenuation (HU) of small ROIs placed on the most enhancing portions of the lesion in the corticomedullary phase and in the same location across other phases (unenhanced, nephrographic, and excretory). Overall, there is statistically significant increased absolute enhancement of ccRCC compared with papillary RCC, chromophobe RCC, FP AML, and oncocytoma in the corticomedullary phase with narrow confidence intervals[13,15] (see **Fig. 2**).

Peak enhancement in the nephrographic phase has been shown to be suboptimal for lesion characterization because the mean peak HU for almost all lesions except papillary RCC tends to cluster in a narrow range between 70 and 90 HU. Papillary RCC tends to have peak absolute enhancement during the nephrographic phase near 70 to 80 HU, which is significantly less than the peak enhancement of ccRCC during the corticomedullary phase. Chromophobe RCC lesions can show peak enhancement in either the corticomedullary or the nephrographic phase[15] (**Fig. 6**). Absolute nephrographic phase enhancement of high Fuhrman grade ccRCC lesions was statistically significantly decreased compared with low-grade lesions.[17] These results were further corroborated by Coy and colleagues,[18] more specifically showing that nephrographic phase enhancement less than 52.1 HU is a statistically significant predictor of high-grade ccRCC lesions.

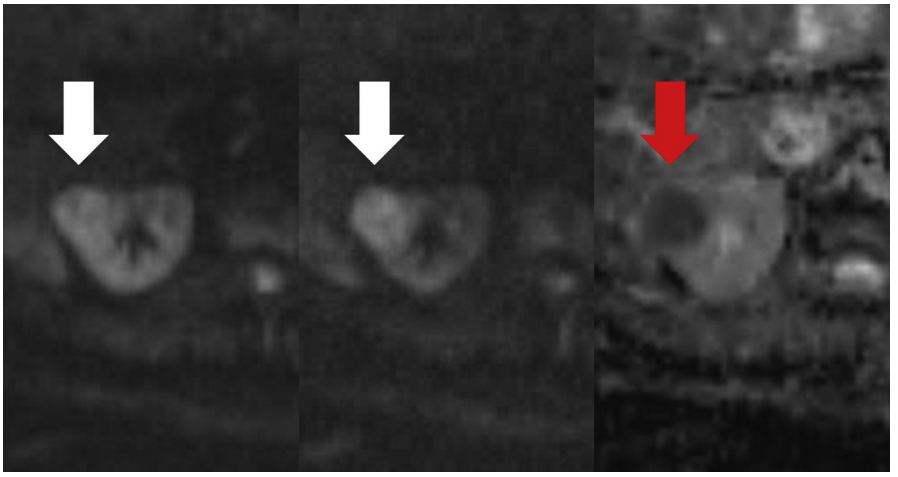

Fig. 5. A papillary RCC depicts increasing signal on DWI as the b value increases from 400 to 800 (*white arrows*) compatible with restriction of diffusion with diminished signal on ADC (*red arrow*).

Absolute enhancement at the excretory phase is derived from HU values taken from ROIs, including the same portion of the indeterminate renal mass on both unenhanced and excretory phases. The difference between these 2 values results in the absolute excretory phase enhancement of the mass.

There was statistically significant increased absolute enhancement of ccRCC compared with

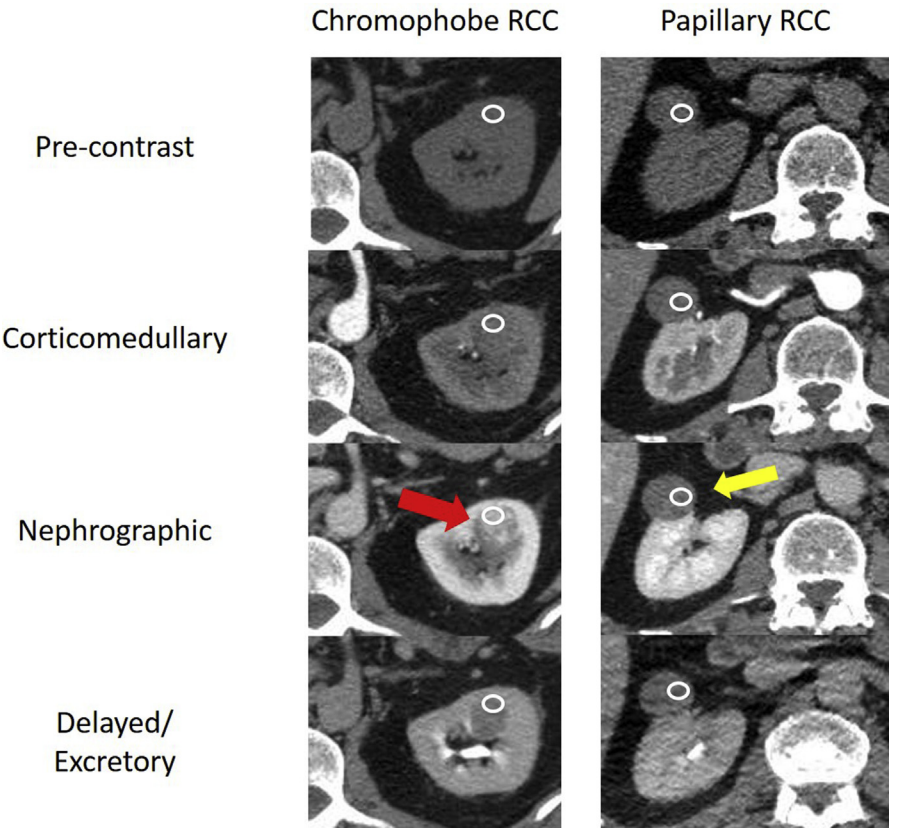

Fig. 6. Precontrast and postcontrast phases of chromophobe and papillary RCC depicting subtle absolute peak enhancement in the nephrographic phase (*red* and *yellow arrows*, respectively). ROIs placed on these lesions demonstrate precontrast, corticomedullary, nephrographic, and excretory phase HU of 13, 39, 144, and 50 for the chromophobe lesion and 29, 35, 42, and 25 for the papillary lesion, respectively.

papillary RCC, chromophobe RCC, and oncocytoma at the excretory phase with nonoverlapping confidence intervals.[15] Absolute excretory phase enhancement of high Fuhrman grade ccRCC lesions was statistically significantly decreased compared with low-grade ccRCC lesions on excretory phase.[17]

Although most research focused on absolute enhancement characteristics of indeterminate renal masses have been derived from CT, both Sun and colleagues[14] and Young and colleagues[19] have shown similar results on dynamic contrast-enhanced multiphasic MRI, with ccRCC showing the greatest magnitude of peak absolute enhancement and deenhancement, followed by FP AML, oncocytoma, and chromophobe with papillary RCC demonstrating the least absolute enhancement.

The magnitude of absolute enhancement has also been correlated with radiocytogenetics. The gain of chromosome 12 in ccRCC is associated with higher tumor grade and worse prognosis. Absolute enhancement of ccRCC with gain of chromosome 12 has been shown to be significantly higher on nephrographic and excretory phases compared with ccRCC with no gain of chromosome 12.[20]

Relative Enhancement

Relative enhancement is a novel variant quantitative concept that has been used to successfully differentiate subtypes of indeterminate renal masses. Relative enhancement is calculated as peak absolute enhancement of the mass subtracted from the peak enhancement of background uninvolved renal cortex with a comparably sized ROI on each phase, thus controlling for patients who may have intrinsic renal dysfunction or variable enhancement owing to diminished cardiac output or renal artery stenosis. The formula is as follows, with all values taken from the same postcontrast phase: [(Mass ROI – Uninvolved cortex ROI)/Uninvolved cortex ROI] $\times$ 100%.[13] Relative corticomedullary attenuation greater than 0% supports a positive predictive value of 90% in favor of ccRCC[13] (**Fig. 7**). Lesions greater than 45 HU on unenhanced phases that have less than 10% relative corticomedullary attenuation can be differentiated from ccRCC with 97% negative predictive value.[13]

Analysis of relative enhancement characteristics has been applied to differentiate between type 1 and type 2 papillary RCC, with significantly greater relative attenuation of type 2 papillary RCC compared with type 1 on excretory phase.[21]

Similar to absolute enhancement, most studies on relative enhancement have focused on CT. In their 2007 study, Sun and colleagues[14] initially showed that ccRCC had the greatest relative enhancement compared with chromophobe and papillary RCC. Young and colleagues[19] reproduced their multidetector CT results on MRI and showed that ccRCC is the only lesion to routinely enhance above background cortex compared with both chromophobe RCC and papillary RCC. Oncocytoma and FP AML showed a similar relationship, but with narrower confidence intervals. A similar relationship between lesion enhancement and that of adjacent cortex has been demonstrated on CEUS as well.[10]

In correlating markers of aggressive ccRCC, such as those lacking phosphatase and tension homolog (PTEN) expression, relative corticomedullary CT enhancement was found to be

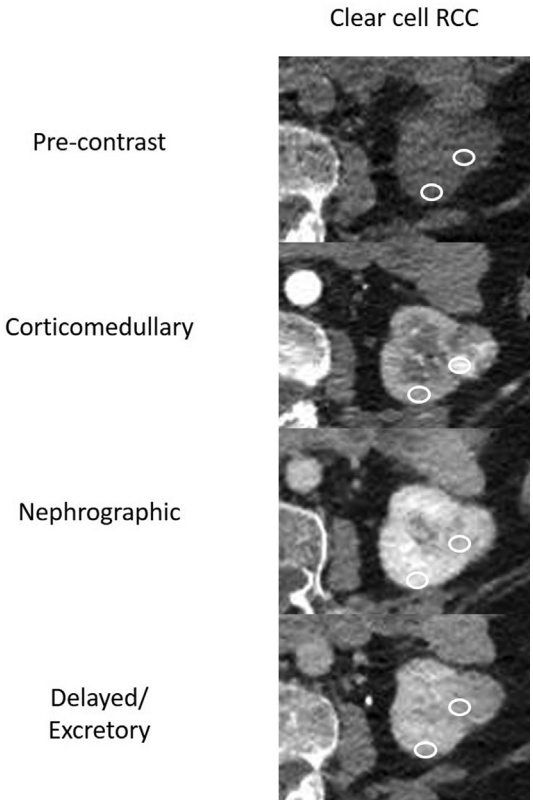

Fig. 7. Precontrast and postcontrast CTs depict relative enhancement assessment of a ccRCC with ROIs placed over the area with peak corticomedullary enhancement as well as an area of uninvolved cortex on all phases. The relative enhancement of this lesion, as calculated with the formula described in the text, is 77% in the corticomedullary phase, −24% in the nephrographic phase, and −29% in the excretory phase.

significantly less in PTEN-negative ccRCC compared with PTEN expressing RCC. PTEN is implicated in tumor cell growth, metabolism, and tumorigenesis, and lack of its expression is associated with worse survival, poor response to anti-VEGF and anti-EGF therapies, higher Fuhrman grade, and higher likelihood of lymph node metastasis.[22]

Cytogenetic correlations with CT-based relative enhancement have also been significant. Relative nephrographic phase enhancement was significantly lower in ccRCC with loss of Y chromosome compared with those without loss of Y. ccRCC lesions with loss of Y chromosome have been associated with higher T stage, higher Fuhrman grade, and greater risk of metastatic disease.[23] ccRCC with gain of chromosome 20 had significantly less relative nephrographic and excretory enhancement compared with lesions without gain of 20. Gain of chromosome 20 is associated with a higher rate of tumor recurrence.[24]

Absolute Deenhancement

Absolute deenhancement is derived from subtracting the peak ROI of a lesion in the nephrographic phase from peak ROI in the corticomedullary phase. This parameter is significantly increased in ccRCC compared with oncocytoma. Lee-Felker and colleagues[13] also showed a 90% positive predictive value favoring ccRCC in lesions that demonstrate less than 50 HU of absolute deenhancement.

Relative Washout

Relative washout is another quantitative tool and is calculated as follows: [(Mass attenuation, corticomedullary phase – Mass attenuation, nephrographic, OR excretory phase)/(Mass attenuation, corticomedullary phase)] × 100%. This equation can be used to calculate relative washout for either the nephrographic or excretory phase, as shown above.

Levels of carbonic anhydrase-IX (CA-IX) in ccRCC have been assessed using relative nephrographic washout. CA-IX is a transmembrane protein involved in maintaining cellular pH. Low levels are associated with poor prognosis, and high levels are associated with good response to interleukin-2 immunotherapy. ccRCC lesions with high levels of CA-IX showed significantly higher relative nephrographic washout and a trend toward significantly higher relative excretory washout compared with lesions with low levels of CA-IX.[25]

SUMMARY

Quantitative parameters derived from multiphase imaging of small indeterminate masses have proven useful for differentiation of ccRCC from chromophobe/papillary RCC, FP AML, and oncocytoma. More investigation is needed to more reliably differentiate between chromophobe/papillary RCC, FP AML, and oncocytoma by multiphase imaging, although early results show promise. Accurate differentiation of these lesions by multiphase imaging at initial characterization will allow for better triage of patients for renal mass biopsy, ablation, and resection and also will strengthen the role of multiphase imaging in active surveillance.

DISCLOSURE

Nothing to disclose.

Diagnostic Features Useful for Characterization

Clear cell renal cell carcinoma

- Heterogeneous, even at small size
- Peak enhancement in corticomedullary phase
- Relative enhancement in corticomedullary phase greater than 0
- Mild T2 hyperintensity
- Can have signal drop out on out-of-phase imaging, owing to microscopic fat

Papillary renal cell carcinoma

- More likely to be homogeneous than clear cell renal cell carcinoma at small size
- Peak enhancement in nephrographic phase
- Relative enhancement less than 0 in all phases
- Restricted diffusion
- T2 hypointense

Chromophobe renal cell carcinoma

- Peak enhancement in corticomedullary or nephrographic phase
- Relative enhancement less than 0 in all phases

Oncocytoma

- Mimic of clear cell renal cell carcinoma
- Peak enhancement in corticomedullary phase
- Relative enhancement less than 0 in all phases

Fat-poor angiomyolipoma

- Peak enhancement in corticomedullary phase
- Relative enhancement less than 0 in all phases
- Tends to be >45 HU on unenhanced CT
- T2 hypointense

Summary Points

- Clear cell RCC is the only lesion with relative enhancement reliably greater than 0
- FP AML tends to be >45 HU on unenhanced CT
- Despite the findings above, RCC cannot and should not be excluded in lesions that do not fulfill diagnostic criteria of lipid rich AML or Bosniak I/II cysts
- T2 hypointensity is most strongly associated with FP AML and papillary RCC

What the Referring Physician Needs to Know

- RCC cannot be excluded based on imaging alone, but if an indeterminate renal mass also has characteristics of a benign lesion, this should be clearly stated as an additional differential consideration.

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