

Imaging Advances in the Management of Kidney Cancer

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ABSTRACT

New developments in cross-sectional imaging, including contrast-enhanced ultrasound, dual-energy computed tomography, multiparametric magnetic resonance imaging, single-photon emission computed tomography, and positron emission tomography, together with novel application of existing and novel radiotracers, have changed the landscape of renal mass characterization (ie, virtual biopsy) as well as the detection of metastatic disease, prognostication, and response assessment in patients with advanced kidney cancer. A host of imaging response criteria have been developed to characterize the response to targeted and immune therapies and correlate with patient outcomes, each with strengths and limitations. Recent efforts to advance the field are aimed at increasing objectivity with quantitative techniques and the use of banks of imaging data to match the vast genomic data that are becoming available. The emerging field of radiogenomics has the potential to transform further the role of imaging in kidney cancer management through eventual noninvasive characterization of the tumor histology and genetic microenvironment in single renal masses and/or metastatic disease. We review of the effect of currently available imaging techniques in the management of patients with kidney cancer, including localized, locally advanced, and metastatic disease.

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INTRODUCTION

The revolution in medical imaging during the past decades has had an enormous effect on the management of kidney cancer. Routine use of imaging has led to increased detection of small renal tumors that pose diagnostic and management dilemmas. Conversely, active surveillance protocols with serial imaging and systematic evaluation of radiopathologic correlations in renal masses have enhanced our understanding of the natural history of renal cancer and potential implications of the imaging phenotype. Advances in cross-sectional imaging techniques have improved staging. However, novel treatments demand implementation of new imaging strategies to assess response beyond traditional morphologic changes. We present a comprehensive review of the current role of imaging in the management of kidney cancer, including challenges and opportunities for further development.

Widespread use of cross-sectional imaging has resulted in a steady increase in the prevalence of kidney cancer.¹ Approximately 70% of renal cell carcinomas (RCCs) are diagnosed incidentally on cross-sectional imaging.² Increased prevalence has been greatest for lower-stage tumors, which suggests an effect of early detection.¹ However, despite an increase in surgical resections, a clear effect on cancer-specific mortality has not been seen.³ Moreover, the likelihood of benign histology increases inversely with tumor size, with a prevalence approaching 20% for small renal masses (SRMs; T1a < 4 cm).⁴ Consequently, better presurgical characterization of SRMs may optimize patient selection for active surveillance and avoid unnecessary biopsies and/or surgery.

Renal angiomyolipoma (AML) and oncocytoma represent the most common benign histologies in surgical series of SRMs (44% and 35%, respectively).⁵ Classic AMLs that contain fatty tissue (ie, adipocytes) are easily recognized on computed tomography (CT) and magnetic resonance imaging (MRI). However, AMLs with minimal or no visible fat on imaging (also called fat poor AMLs) can be mistaken for RCC, and the patient can undergo unnecessary resection. Although a central scar may be visible in up to one third of oncocytomas,⁶ it is also frequently present in RCC or confused with tumor necrosis.

THE INCIDENTAL SOLID RENAL MASS: AN IMAGING DILEMMA

Kidney cancer, once considered a clinical diagnosis, is now primarily a radiologic diagnosis.

ASSOCIATED CONTENT



Appendix
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Various CT and MRI features can assist in differentiating AML and oncocytoma from RCC (Appendix Table A1, online only). Intense uptake on [^{99m}Tc]-sestamibi single-photon emission tomography (SPECT)/CT is sensitive (87.5%) and specific (95.2%) for differentiating oncocytoma and hybrid oncocytic/chromophobe tumors from other renal masses, which demonstrate minimal or no uptake.⁷

CT/MRI differentiation of RCC subtypes relies primarily on analyses of postcontrast time-attenuation curves and lesion homogeneity, whereas other signal-based MRI features are also helpful. Contrast enhancement and heterogeneity of clear cell RCC (ccRCC) is significantly higher than in papillary RCC (pRCC) and chromophobe RCC.⁸ The relative enhancement ratio between the renal mass and the aorta on contrast-enhanced CT (CECT) is significantly lower for pRCC than for nonpapillary histology, with sensitivity and specificity of 86% and 85%, respectively (cutoff, 0.25).⁹ Similarly, Sun et al¹⁰ confirmed higher MRI enhancement levels during corticomedullary and nephrographic phases in ccRCC (205.6% and 247.1%, respectively) compared with pRCC (32.1% and 96.6%), whereas chromophobe RCC exhibited intermediate enhancement (109.9% and 192.5%).

Although percutaneous biopsies are highly accurate for RCC diagnosis, a recent meta-analysis reported a 14% nondiagnostic rate, 4% false-positive rate, and 3.1% false-negative rate.¹¹ Furthermore, harms associated with biopsies are infrequent but not negligible.¹¹ A composite MRI phenotype can predict RCC histology¹² (Appendix Table A1; Fig 1) and help with management decisions. By using a predefined algorithm that was based on multiparametric MRI, Kay et al¹³ reported a sensitivity and specificity of 85% and 76%, respectively, for ccRCC and 80% and 94%, respectively, for pRCC. With the same algorithm, Canvasser et al¹⁴ reported a multiparametric MRI likelihood score of clear cell histology (cCLS). Sensitivity, specificity, and the positive predictive value for ccRCC using cCLS ≥ 4 was 78%, 80%, and 80%, respectively. On the basis of these results and the high specificity (95%) and positive predictive value (93%) for non-ccRCC in cCLS 1 or 2, a recommendation of surgical resection for patients with cCLS 4 or 5 lesions, active surveillance for patients with cCLS 1 to 2 lesions, and biopsy for patients with cCLS 3 lesions (particularly if renal mass < 3 cm) would result in a 20% biopsy rate; unnecessary treatment of oncocytoma and AML in 4.5% and 1.7%, respectively; and placement of 4.4% of patients with ccRCC on active surveillance.¹⁴ SRMs on active surveillance with homogeneous signal intensity on T2-weighted images exhibit a slower growth rate (ie, tumor doubling time > 2 years) and thus, may be better candidates for active surveillance.¹⁵

Contrast-enhanced ultrasound (CEUS) is an alternative to CECT for renal mass characterization,¹⁶ particularly in patients with renal impairment in whom administration of iodinated contrast is undesirable. Dual-energy CT technology, introduced in the past decade, can reduce some limitations of standard CECT, such as lesion pseudoenhancement and detection of enhancement in hypoenhancing tumors (eg, pRCC).¹⁷ Diffusion-weighted MRI offers information about cellular density. A meta-analysis reported significantly lower apparent diffusion coefficients (ADCs) derived from diffusion-weighted imaging in RCC (95% CI, 1.45 to 1.77 $\times 10^{-3}$ mm²/s) compared with benign lesions (95% CI, 1.92 to 2.28 $\times 10^{-3}$ mm²/s). Oncocytomas had significantly higher ADCs than malignant lesions (1.84 to 2.17 $\times 10^{-3}$ mm²/s).¹⁸ Arterial spin labeled (ASL) MRI provides measures of tissue perfusion without the

need of an exogenous contrast agent. Lanzman et al¹⁹ confirmed lower mean perfusion in pRCC compared with other RCC subtypes and high perfusion in oncocytomas using ASL MRI.

In general, state-of-the-art multiparametric MRI protocols are superior to CT scans for renal mass characterization in cooperative patients because of superior soft tissue contrast, characterization of fatty elements, and detection of enhancement. However, when MRI is not available, CECT is an excellent alternative to multiparametric MRI in patients with contraindication to MRI or poor breath-hold capacity. To date, positron emission tomography (PET)/CT does not play a role in the evaluation of primary tumors.

RADIOLOGIC ASSESSMENT OF CYSTIC RENAL LESIONS

A radiologic definition of cystic RCC currently is lacking. Previous reports have proposed the inclusion of neoplasms with $\geq 75\%$ cystic components at histopathology.²⁰ This distinction is important because increasing data indicate that cystic renal neoplasms demonstrate more indolent behavior and favorable prognosis than solid renal tumors.

Currently, patients with cystic renal lesions are managed on the basis of radiologic complexity (eg, wall thickness, internal septations, nodularity). The Bosniak classification is a well-established five-tier scale that reflects the increasing likelihood of malignancy as the lesion exhibits greater imaging complexity.²¹ Bosniak I (simple) and II (mildly complicated) cysts are considered benign, and Bosniak IIF (follow-up) cysts deserve longitudinal monitoring with imaging.²² The rate of malignancy in Bosniak IIF (complicated), III (indeterminate), and IV (malignant) cystic lesions is approximately 11% (range, 5% to 38%), 50% (range, 25% to 100%), and 80% (range, 67% to 100%), respectively.²³ Although the Bosniak classification was developed for CECT, similar principles are applicable to ultrasound and MRI. MRI is particularly helpful to distinguish solid from cystic lesions when enhancement is equivocal on CT (ie, between 10 and 20 Hounsfield units).²⁴ CEUS also is helpful to characterize complex cystic lesions.¹⁶

Although the Bosniak classification is an excellent tool to estimate the risk of malignancy, direct extrapolation between the Bosniak category and the need for treatment is likely not appropriate. Historically, surgical treatment was recommended for Bosniak III and IV lesions. Increasing evidence suggests that predominantly cystic renal neoplasms (ie, > 45% cystic) are more indolent than solid tumors, and have low metastatic potential.²⁵ Moreover, the risk of metastasis may be lower than the risk of complications after surgery or ablation.^{26,27} Accordingly, many Bosniak category III and IV lesions, presumed to represent malignancies, may be safely followed with imaging, particularly in patients with comorbidities and/or a minimal solid component. Patients on active surveillance should undergo an initial 6-month follow-up and subsequent annual imaging follow-up.

LOCAL STAGING AND SURGICAL PLANNING

The TNM classification remains the most commonly used tool to stage kidney cancer. CT and MRI are used for local staging and accurate tumor measurements. Determination of extension

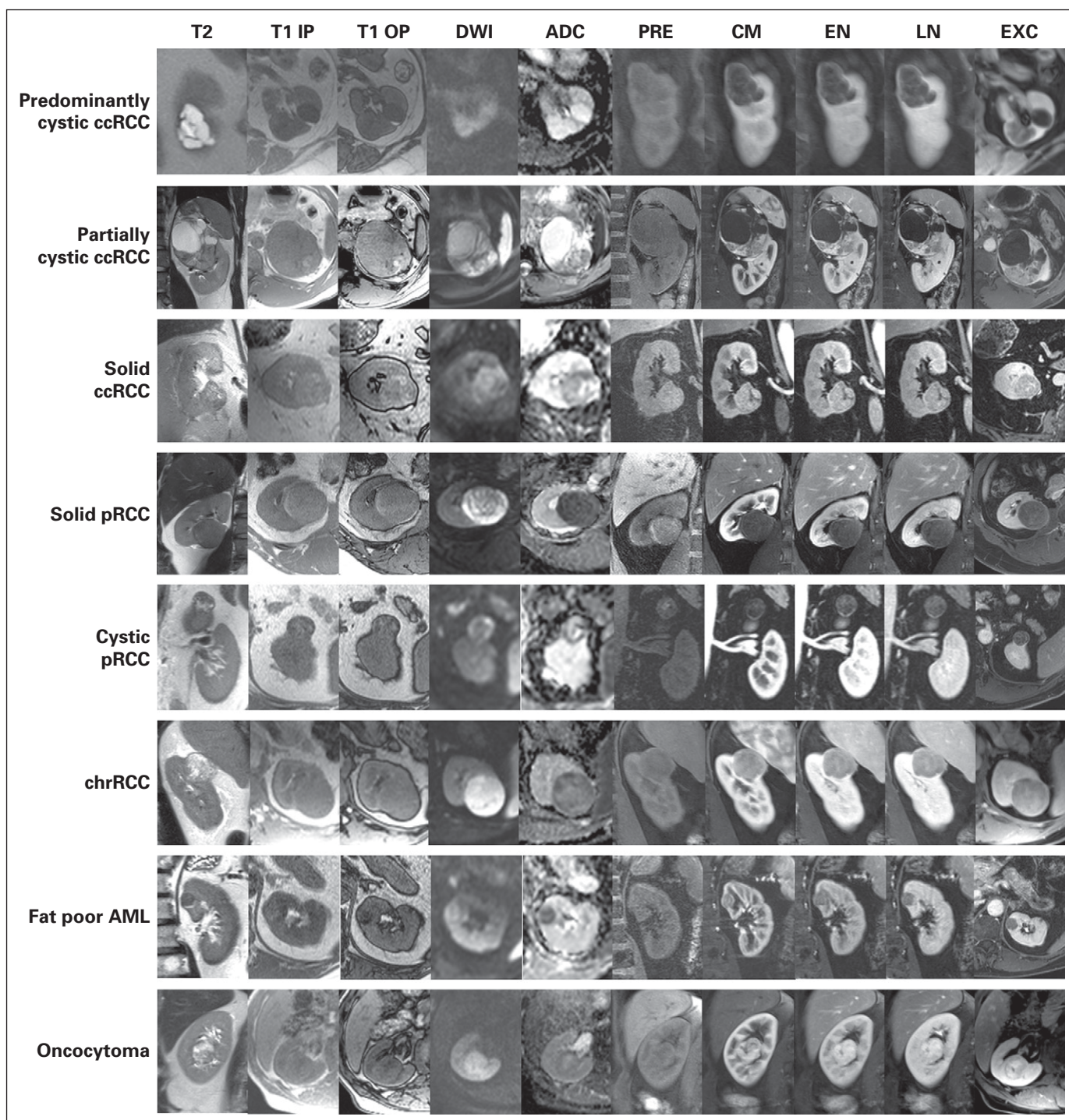


Fig 1. Prototypical imaging phenotype of most common renal masses on multiparametric magnetic resonance imaging. Representative examples of most common histologic subtypes in renal masses. ADC, apparent diffusion coefficient; AML, angiomyolipoma; ccRCC, clear cell renal cell carcinoma; chrRCC, chromophobe renal cell carcinoma; CM, contrast-enhanced fat-saturated T1-weighted spoiled gradient echo during corticomedullary phase; DWI, diffusion-weighted imaging ($b = 800$); EN, contrast-enhanced fat-saturated T1-weighted spoiled gradient echo during the early nephrographic phase; EXC, contrast-enhanced fat-saturated T1-weighted spoiled gradient echo during the excretory phase; LN, contrast-enhanced fat-saturated T1-weighted spoiled gradient echo during the late nephrographic phase; pRCC, papillary renal cell carcinoma; PRE, precontrast fat-saturated T1-weighted spoiled gradient echo; T1 IP, T1-weighted in-phase gradient echo; T1 OP, T1-weighted opposed phase gradient echo; T2, T2-weighted single-shot fast spin echo.

beyond the kidney may be challenging. A well-defined tumor pseudocapsule is present in 66% of SRMs and better appreciated on T2-weighted imaging and contrast-enhanced MRI. This

pseudocapsule is associated with low-grade histology²⁸ and a high negative predictive value for tumor extension into perirenal and hilar fat.²⁹ Conversely, infiltrating margins correlate with

aggressive histology and behavior in pRCC and ccRCC.³⁰⁻³² CT and MRI are accurate in excluding local invasion (T4 disease) when a fat plane is visualized between the renal mass and adjacent organs. Separate deposits in the perirenal fat likely indicate aggressive behavior but represent a challenge for staging (Fig 2).

Tumor thrombus in the renal vein and inferior vena cava (IVC) has prognostic implications and affects the surgical approach.³³ Tumor thrombus can be differentiated from bland thrombus when vascularity is present within (ie, flow on Doppler ultrasound, enhancement on CEUS, CECT, or MRI). MRI is more accurate than conventional venography and CT in delineating the extent of IVC tumor thrombus³⁴ (Fig 3). However, determination of renal vein and IVC wall invasion remains challenging. Right-sided tumors, anteroposterior IVC diameter at the renal vein ostium of ≥ 24.0 mm, and complete occlusion of the IVC at the same level are associated with a significantly increased risk of IVC resection during nephrectomy.³⁴

Several systems have been proposed to assess the difficulty of surgical resection of renal masses. R.E.N.A.L (radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior, location relative to polar lines) is a popular image-based scoring system that provides objective information on anatomic complexity of a renal mass and predicts complications and warm ischemia time during minimally invasive nephron-sparing surgery.³⁵ The PADUA (preoperative aspects and dimensions used for anatomical score) and centrality index (C-Index) are alternative scoring systems to predict the complexity of surgery.

DIAGNOSIS OF METASTATIC DISEASE

Approximately 16% of patients with RCC have metastatic disease at diagnosis.³⁶ Of patients with surgically excised localized tumors, 20% to 30% eventually relapse.³⁷ The risk of metastatic disease is greatest in the 3 years after diagnosis, although late recurrences are possible, especially in younger patients with few comorbidities and larger tumors.³⁸ Risk and/or stage-based imaging surveillance strategies have been incorporated into the National Comprehensive Cancer Network (NCCN) and American Urological Association guidelines.^{37,39}

CECT is a mainstay imaging technique for surveillance because it is widely available and depicts lung, soft-tissue, and bone pathology. This is useful because RCC metastases involve numerous organs, including lungs, bone, nodes, liver, adrenals, and brain.⁴⁰ CT limitations include radiation exposure and contrast allergies or contraindications in patients with renal impairment. According to American College of Radiology (ACR) contrast media guidelines, serum creatinine (with or without estimated glomerular filtration rate) should be available or obtained before the injection of iodinated contrast medium in all patients considered at risk for contrast-induced nephropathy; in patients older than 60 years of age; and/or in patients with a history of renal disease (including renal cancer, single kidney, renal surgery, dialysis, and renal transplant), history of hypertension that requires medical therapy, diabetes, and/or treatment with metformin or a metformin-containing regimen.⁴¹ At present, little evidence indicates that intravenous iodinated contrast material is an independent risk

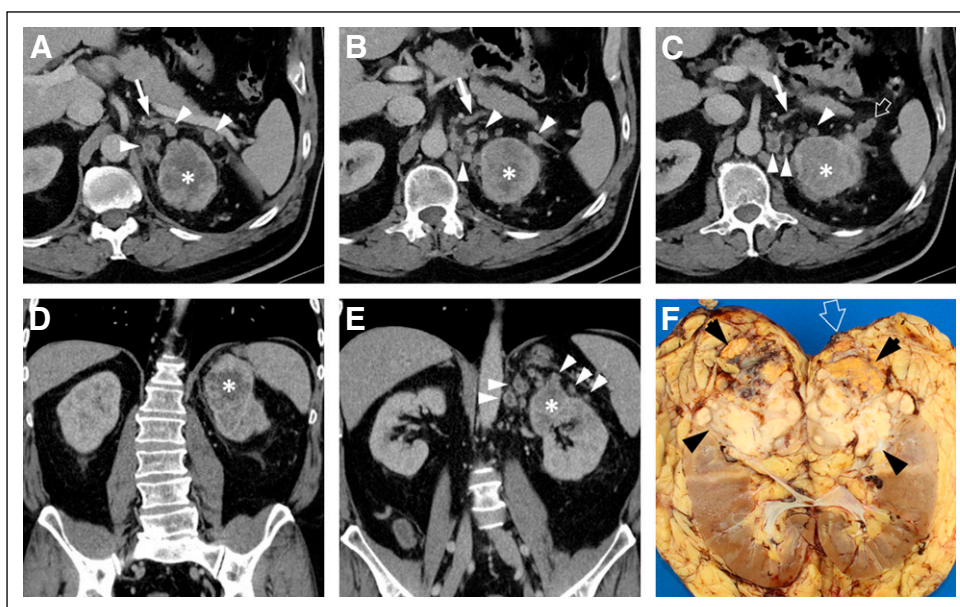


Fig 2. Fifty-nine-year-old patient with left renal mass. (A, B, C) Axial contrast-enhanced computed tomography images and (D, E) coronal reconstructions show an ill-defined mass (asterisk) with central hypo-enhancement suggestive of necrosis. The left adrenal gland is seen (arrow) surrounded by multiple heterogeneous nodules (arrowheads) in the perirenal fat. (C) A soft tissue deposit is extending beyond Gerota's fascia (open arrow). (F) Bivalved gross specimen after radical nephrectomy that demonstrates a large infiltrative mass (arrowheads) replacing the left upper pole. A separate nodule (open arrow) is visible at the surgical margin. At histopathology, the mass was consistent with clear cell renal cell carcinoma with sarcomatoid differentiation (International Society of Urological Pathology nucleolar grade 4 [out of 4]). Invasion of the perirenal and hilar fat and lymphovascular invasion were present. Perirenal soft tissue nodules are likely intravenous tumor spread to the perirenal fat. Contrary to direct tumor spread into the perirenal fat (ie, T3 disease), noncontiguous spread to perirenal fat is not clearly typified in TNM staging. A separate nodule was present in the left adrenal gland and surgical resection of a left lung nodule identified at presentation (not shown) confirmed metastatic disease.

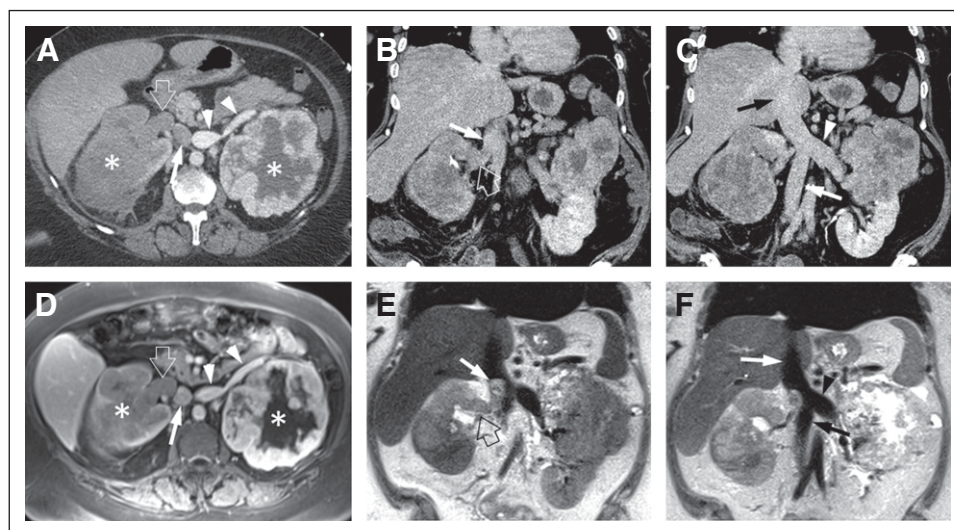


Fig 3. Fifty-seven-year-old patient with bilateral renal masses and inferior vena cava (IVC) tumor thrombus. (A) Axial contrast-enhanced computed tomography (CT) image obtained during the corticomedullary phase shows bilateral renal masses (asterisks) and optimal opacification of the left-side renal vein (arrowheads). The right renal vein (open arrow) demonstrates lower attenuation, similar to that of the right renal mass, which is suspicious for tumor thrombus. The infrarenal IVC (arrow) is poorly opacified. (B, C) Coronal CT reconstructions from an acquisition during the venous phase shows subtle hypoenhancement of (B) the right renal vein (open arrow) and normal enhancement of the suprarenal, infrahepatic IVC (arrow); there is normal enhancement of the (C) left renal vein (arrowhead) and infrarenal IVC (white arrow). Assessment of the (C) intrahepatic IVC (black arrow) is challenging. (D) Axial contrast enhanced magnetic resonance image shows both renal masses (asterisks) and confirms the presence of hypoenhancing tumor thrombus in the right renal vein (open arrow). There is normal enhancement of the infrarenal IVC (arrow) and left renal vein (arrowheads). (E) Coronal T2-weighted images demonstrate extension of the right renal vein tumor thrombus (open arrow) into the suprarenal, infrahepatic IVC (arrow), which was not visualized on the CT examination. (F) The intrahepatic IVC (white arrow), left renal vein (arrowhead), and infrarenal IVC (black arrow) are free of tumor. Unclassified renal cell carcinoma (International Society of Urological Pathology grade 3 [out of 4]) with right renal vein and infrahepatic IVC tumor thrombus was confirmed after right radical nephrectomy. Left partial nephrectomy revealed clear cell renal cell carcinoma (International Society of Urological Pathology grade 4 [out of 4]). The left renal vein and intrahepatic and infrarenal IVC were free of tumor thrombus at surgery.

factor for postcontrast acute kidney injury in patients with an estimated glomerular filtration rate ≥ 30 mL/min/1.73 m².⁴² However, the risks and benefits of iodinated contrast media must be considered on a case-by-case basis.

NCCN guidelines recommend chest radiographs or CT scans in patients with up to stage III disease,³⁷ although chest CT is more sensitive for lung nodules. CECT or MRI can be used to monitor the abdomen. Contrast-enhanced MRI is uniquely suited to detect enhancement that represents recurrent disease after ablation. Because the risk of nephrogenic systemic fibrosis is sufficiently low or possibly nonexistent in patients imaged with standard or lower-than-standard doses of group II gadolinium-based contrast agents for contrast-enhanced MRI, renal function assessment with a questionnaire or laboratory testing is now considered optional in this setting according to ACR guidelines.⁴¹ Patients who may be administered group I or group III gadolinium-based agents still should be screened for renal impairment.

Detection of liver and pancreatic ccRCC metastases is improved with arterial phase and portal venous phase abdominal CT or MRI.^{43,44} Adrenal masses can present a diagnostic dilemma at initial diagnosis when no prior imaging is available. ccRCC adrenal metastases must be differentiated from lipid-poor adenomas, which can demonstrate overlapping imaging features on a dedicated adrenal CT protocol.⁴⁵ Furthermore, ccRCC metastasis may exhibit lipid content that mimics lipid-rich adenomas. Increased T2-weighted imaging hyperintensity and heterogeneity on MRI recently have been shown to differentiate adrenal metastasis from adenomas; additional studies are needed to assess the role of MRI to replace tissue diagnosis.⁴⁶

[^{99m}Tc]Technetium methylene diphosphate bone scans are standard of care for metastatic bone disease. However, bone scanning is of limited utility, even in patients with high pretest probability given the commonly lytic nature of this disease. In a small cohort of 36 patients with RCC with clinical suspicion for bone metastases, bone scan sensitivity ranged from 10% to 60%, depending on the applied threshold.⁴⁷ Furthermore, CT is less sensitive than MRI, with a reported sensitivity of 66% for spinal metastasis.⁴⁸

Although not recognized in the NCCN guidelines, [¹⁸F]fluorodeoxyglucose PET/CT or PET/MRI may be useful for the identification of metastases to peritoneum, bone, muscle, and adrenals as well as in problem solving, biopsy site selection, prognostication, and monitoring response to therapy^{49,50} (Appendix Fig A1, online only).

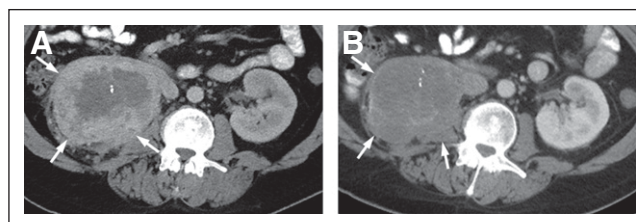


Fig 4. Forty-five-year-old man with metastatic clear cell renal cell carcinoma. (A) Baseline contrast-enhanced axial computed tomography scan shows a large, solid, peripherally enhancing right renal mass (arrows) that represents the primary tumor. (B) Follow-up contrast-enhanced axial computed tomography scan after 3 months of sunitinib therapy demonstrates mildly decreased size but significantly decreased enhancement within the primary renal mass (arrows), which represents a partial response according to Choi or MASS (morphology, attenuation, size, and structure) criteria.

Variable [^{18}F]fluorodeoxyglucose avidity of RCC metastases, cost, availability, and radiation dose are potential limitations to use. Gerety et al⁵¹ reported a 100% sensitivity of [^{18}F]sodium fluoride PET/CT for bone metastasis compared with 46% for CT and 29% for bone scanning. Availability, high cost, and limited reimbursement have challenged the implementation of [^{18}F]sodium fluoride PET/CT in clinical practice.

ASSESSMENT OF TUMOR RESPONSE

Given the array of treatments available for metastatic RCC (mRCC), including therapies targeted to vascular endothelial growth factor (VEGF) receptor and other ligands; immune checkpoint inhibitors; and metastasectomy, thermal ablation, and stereotactic body radiotherapy (SBRT), imaging follow-up for mRCC has become complex. Patients with mRCC are living longer and may undergo numerous therapies; radiologists must be cognizant of past and present therapy, expected post-therapy changes, and associated toxicities during interpretation.

For patients with RCC treated in clinical trials, Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 remains the most commonly used response assessment method (Appendix Table A2, online only). Secondary and exploratory end points may include class-specific response assessments (eg, immune-related response criteria). In routine care, treatment change decisions may be based on the presence or absence of progressive disease and other factors. Although the utility of RECIST is evident through its longevity and range of application in a variety of cancers and treatment settings, a limitation of RECIST is that a large proportion of patients with mRCC show stable disease on follow-up, especially in those treated with VEGF-targeted agents and mammalian target of rapamycin inhibitors.⁵² This category includes patients with 29% tumor shrinkage and 19% growth, a heterogeneous group with heterogeneous outcomes.⁵³

It is well established that the VEGF-targeted therapies can result in modest early size changes and/or changes in tumor vascularity, which have been associated with prolonged time to progression.^{54,55} Several groups have sought to better define responders and nonresponders to treatment. Choi and MASS (morphology, attenuation, size, and structure) criteria have been

applied to patients with mRCC treated with VEGF-targeted therapies, both of which incorporate size and density changes (Fig 4).^{56,57} Ten-percent tumor shrinkage also has been identified as a useful threshold indicator of response.^{54,55,58} Partial or favorable response according to various alternative criteria have been shown to better correlate with survival outcomes than RECIST partial response, although alternative response assessments have been less useful in early or optimally identifying progressive disease. Efforts to further improve the predictive value of response category designations have incorporated Memorial Sloan Kettering Cancer Center risk factors.⁵⁹ Recently, semiautomated quantification of initial changes in CT vascular tumor burden improved differentiation of responders and nonresponders to sunitinib compared with RECIST and other alternative criteria.⁶⁰

Response assessment in clinical trials that use immune checkpoint inhibitors has been based in RECIST. In the phase III study of nivolumab versus everolimus in advanced RCC, response assessment was according to RECIST 1.1, although patients could continue therapy after initial progression if the investigator perceived clinical benefit.⁶¹ A spectrum of changes in immune checkpoint inhibitor treatment of RCC has been described, including early complete response, pseudoprogression, disease stability before response, mixed response with new lesions, and early progression, although the incidence of each is not well understood.⁶² With the use of RECIST, patients with pseudoprogression or mixed response and new lesions may be characterized as having progressive disease and discontinued from potentially effective therapy (Fig 5). Several immune-related response assessment methods have been developed to capture these patterns (immune-related response criteria, immune-related RECIST, and immune RECIST), although they are not yet widely applied in RCC.^{63,64} Although some differences exist among these criteria, all advise confirmation of progressive disease on a short-interval follow-up scan.

Historically, RCC has been considered radioresistant, although SBRT is being effectively used for local control in selected scenarios, including the treatment of SRM, oligometastatic disease, and brain metastasis.^{65,66} Imaging interpretation of lesions treated with SBRT can be challenging because of the presence of persistent/delayed enhancement after treatment⁶⁷ and the lack of consensus in bone lesion response assessment on the basis of RECIST 1.1 and/

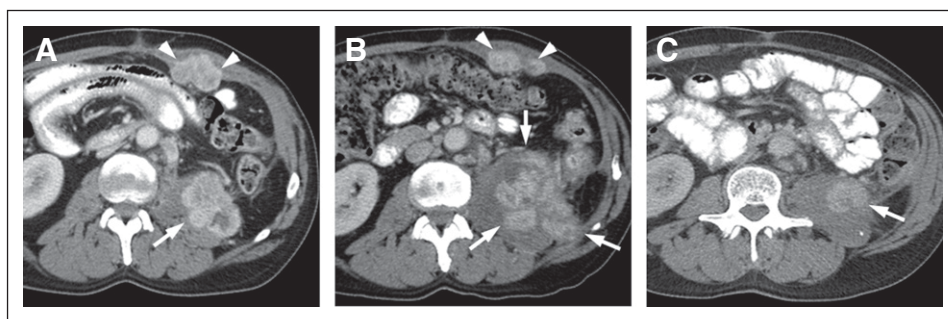


Fig 5. Fifty-four-year-old man with metastatic renal cell carcinoma and heterogeneous initial response to immunotherapy. (A) Baseline axial contrast-enhanced computed tomography (CT) scan demonstrates metastases to the left-side psoas (arrow) and left-side anterior abdominal wall (arrowheads). (B) First follow-up abdominal CT scan after 8 weeks of immune checkpoint inhibitor treatment demonstrates marked increased size of the left-side psoas mass (arrows) suggestive of progressive disease. Conversely, some separation and decreased size of the conglomerate of anterior abdominal wall nodules (arrowheads) are seen. (C) Second follow-up CT scan after 6 additional weeks of treatment shows a significant decrease in the left-side psoas metastasis (arrow) and resolution of the abdominal wall nodules. The pattern of response in the left-side psoas metastasis (initial increase in size after treatment followed by decrease in tumor burden) has been termed pseudoprogression.

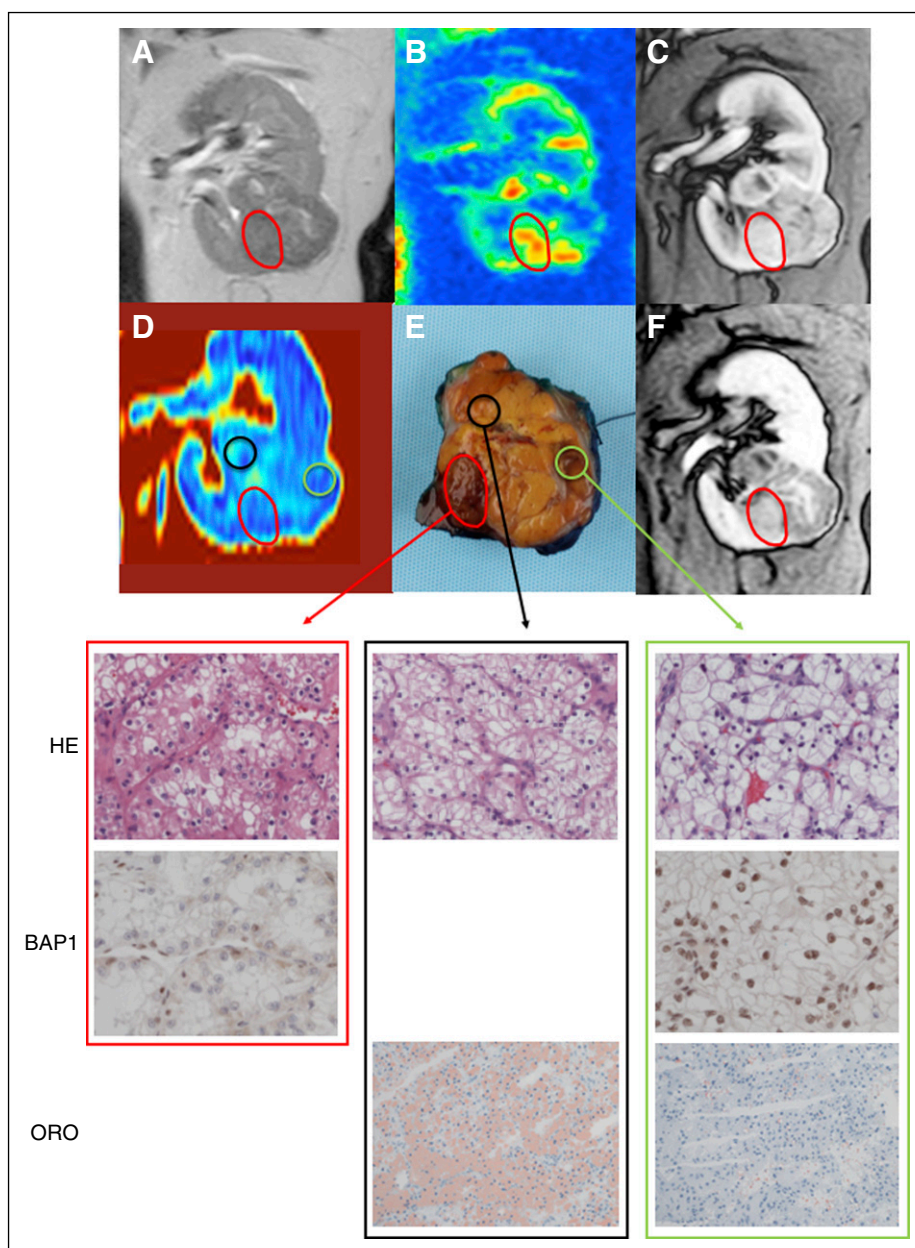


Fig 6. Use of multiparametric magnetic resonance imaging (MRI) as a radiomics platform for assessment of intratumor heterogeneity in clear cell renal cell carcinoma (ccRCC). (A) Coronal T2-weighted image, (B) arterial spin labeled (ASL) perfusion map, (C, F) corticomedullary and delayed venous phase from dynamic contrast-enhanced MRI, (D) Dixon fat fraction (FF) map, and (E) gross pathologic specimen. Histologic and immunohistochemical analysis revealed ccRCC grade 2 (out of 4) and BAP1 retained nuclear staining in the majority of the tumor. However, a distinct tumor nodule (red circle) demonstrates features consistent with ccRCC grade 3 and negative BAP1 nuclear staining (ie, BAP1 mutation). Multiparametric MRI in this nodule revealed (B) higher ASL perfusion (ie, 264 mL/100 g/min in nodule v 157 mL/100 g/min in the rest of the tumor), (C) increased enhancement during the corticomedullary phase, (F) retention of contrast during the delayed venous phase, and (D) decreased FF compared with the rest of the tumor. Oil red O staining (ORO) confirms (D) high-fat content in areas with high FF (black circle; FF, 8%) compared with areas with low FF (green circle; FF, 2%) on Dixon MRI. ORO staining in distinct tumor nodule (red circle) and BAP1 immunohistochemistry in superior tumor area (black circle) were not performed. HE, hematoxylin and eosin.

or MD Anderson bone criteria.⁶⁸ A potential application of SBRT in advanced RCC/mRCC is in alteration of the immune landscape to promote efficacy of immunotherapies (ie, abscopal effect) wherein imaging response assessment may be complicated further.

In conclusion, the landscape of imaging in the management of kidney cancer is evolving rapidly with new acquisition techniques and postprocessing algorithms (Appendix, Fig 6). Each imaging modality has strengths and limitations. Noninvasive histologic diagnosis in SRMs (virtual biopsy) is now feasible. Rapid implementation of new treatment modalities with different effects in primary tumors and metastatic sites has led to the investigation of alternative response criteria for improved prediction of outcomes. Standardization of these remains a challenge in clinical practice and trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Imaging Advances in the Management of Kidney Cancer

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Appendix

Future Renal Cell Carcinoma Imaging and Radiomics

An important advantage of imaging is that it provides an analysis of the whole tumor burden in each patient. Notwithstanding the promising role of liquid biopsies, imaging is currently the only approach to assessing tumor heterogeneity in vivo. Contemporary efforts have focused on more-objective assessment of renal cell carcinoma (RCC) using quantitative techniques and/or extraction and subsequent analysis of high-dimensional data from images (ie, radiomics). Hudson et al¹⁷ compared a variety of dynamic contrast-enhanced parameters obtained from magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound in patients with metastatic RCC (mRCC) who receive sunitinib. Only a change in blood volume measured by dynamic contrast-enhanced ultrasound was predictive of progression-free and overall survival.

RCC genome sequencing and identification of multiple mutations with prognostic significance have brought about attempts to associate imaging features with mutations. The ability to noninvasively characterize the genetic milieu of tumors is of special interest in RCC given intratumoral and inpatient heterogeneity (Fig 6). Early radiogenomic studies in clear cell RCC have found associations between *KDM5C* and *BAP1* mutations and renal vein invasion and *BAP1* and ill-defined tumor margins and calcification, respectively.^{18,19} A challenge of such approaches is that, beyond Von Hippel-Lindau mutations, other mutations have a relatively low frequency and thus require larger data sets.

Jamshidi et al²⁰ evaluated a 28-trait image array from preoperative CT images of clear cell RCC and identified four features (ie, pattern of necrosis, sharp or infiltrating transition zone between tumor and normal renal parenchyma, discrete enhancing rim or hypoattenuating rim that circumscribes the tumor) that correlated with a previously validated prognostic gene signature. These four traits, when combined into a radiogenomic risk score, predicted outcomes in patients with surgically resected clear cell RCCs. The radiogenomic risk score was trained and validated in independent data sets and was predictive of disease-specific survival independent of stage, grade, and performance status.

Take-Home Points

1. Multiparametric MRI and contrast-enhanced CT are useful tools to predict histologic diagnosis in renal masses. Noninvasive renal mass characterization with imaging aids in management by avoiding unnecessary surgeries in benign masses (angiomyolipoma, oncocytoma) and improving candidate selection for active surveillance versus definitive treatment.
2. Imaging features of malignant renal masses and aggressive behavior have also been defined. CT and MRI of malignant renal masses aid in staging and surgical planning, and scoring systems have been developed to predict surgical complexity and the risk of complications.
3. In general, contrast-enhanced CT is the mainstay imaging technique for metastatic surveillance in patients without contraindications to contrast administration (patients with history of allergy to iodinated contrast and/or elevated estimated glomerular filtration rate). Contrast-enhanced MRI can be performed for surveillance in patients with renal impairment when group II gadolinium-based contrast agents are administered because of the sufficiently low or potentially nonexistent risks of nephrogenic systemic fibrosis associated with these agents.
4. Response assessment in patients with metastatic disease is conventionally according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, although adjunct methods have been developed to capture the spectrum of response and progression in patients treated with molecularly targeted therapies and immune checkpoint inhibitors.
5. Contemporary RCC imaging research efforts aim to develop quantitative techniques to noninvasively characterize tumors' genetic features and predict outcomes.

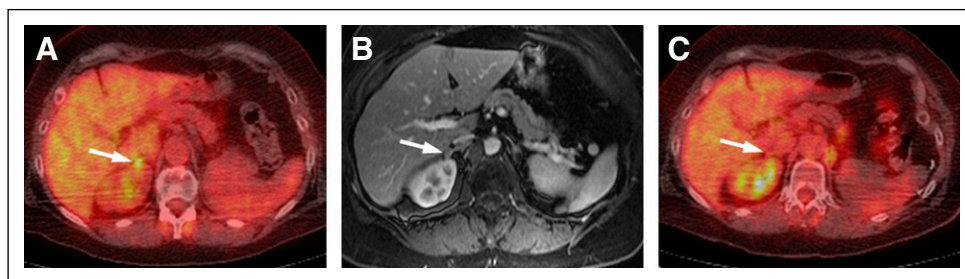


Fig A1. Fifty-seven-year-old woman with metastatic renal cell carcinoma to the right adrenal gland. (A) Axial fused [¹⁸F]fluorodeoxyglucose (FDG) positron emission tomography/computed tomography image demonstrates a new (ie, compared with prior imaging [not shown]), small, FDG-avid right-side adrenal nodule (arrow) that represents a new site of oligometastatic disease. (B) Axial fat-suppressed T1-weighted contrast-enhanced magnetic resonance image confirms the presence of a small, right-sided adrenal nodule (arrow). (C) Follow-up axial fused FDG positron emission tomography/computed tomography image after microwave ablation demonstrates resolution of the focal-intense FDG uptake (arrow), which suggests adequate coverage of the lesion. No new sites of disease were present elsewhere.

Imaging Advances in the Management of Kidney Cancer

Table A1. Characteristic Imaging Features of Most Common Epithelial Renal Neoplasms

Histology	Ultrasound/CEUS	CT	MRI	[⁹⁹ Tc]-Sestamibi
AML				
Classic	Hyperechoic (ie, isoechoic to hilar fat)	Fat-containing mass (areas < -10 HU) ²	Macroscopic fat ²	Low uptake
Fat poor AML	Variable echogenicity Most common hyperenhancement ¹	Hyperdense to renal parenchyma ² Moderate to intense enhancement ³	Hypo/isointense on T1 With or without microscopic fat ⁴ Homogeneous hypointense on T2 Hyperenhancing on CM, washout on delayed phase (ADER > 1.5) ⁵	Low uptake ⁶
Oncocytoma	Variable echogenicity, central stellate scar with spoke-wheel vascular pattern on Doppler Most common hyperenhancement ¹	Isodense precontrast Hyperenhancing with peak in NG phase ³ Central scar (delayed enhancement) Segmental enhancement inversion ⁷	Variable signal on T2 Mild to intense enhancement on CM Central scar (delayed enhancement) Segmental enhancement inversion ⁸	Intense uptake ⁶
Clear cell RCC	Variable echogenicity ⁹ Most common hyperenhancement ¹	Heterogeneous, Hyperenhancing with peak in CM phase ³ With or without hyperenhancing venous thrombus	Iso/hyperintense on T2 With or without intravoxel fat ^{4,10} Heterogeneous, hyperenhancing on CM phase ¹¹ Cystic component (fluid signal) Central scar (delayed enhancement) Necrosis (central heterogeneous nonenhancing area) With or without hyperenhancing venous thrombus ¹²	Low uptake ⁶
Papillary RCC				
Solid	Variable echogenicity ⁹ Most common hypoenhancing ¹	Homogenous hypoenhancing in CM With progressive enhancement on delayed postcontrast ³	Susceptibility (lower signal intensity on in-phase compared to opposed phased T1) Homogenous hypointense on T2 Hypoenhancing in CM phase with progressive enhancement on delayed postcontrast ¹¹	Low uptake ⁶
Cystic hemorrhagic	Heterogeneous cystic mass with solid components	Heterogeneous well-defined hyperdense cyst with peripheral hypoenhancement ¹³	Heterogeneous well defined on T2 and hyperintense on T1 Peripheral hypoenhancing areas with low signal intensity on T2 ¹⁵	Low uptake ⁶
Infiltrative		Ill-defined hypoenhancing ¹⁴ with or without hypoenhancing venous thrombus	Ill-defined hypoenhancing with or without hypoenhancing venous thrombus ¹⁵	Low uptake ⁶
Chromophobe RCC	Variable echogenicity ⁹ Variable enhancement ¹	Intermediate enhancement ³	Intermediate enhancement ¹¹ Segmental enhancement inversion ¹⁶	Intense uptake ⁶

NOTE. Macroscopic fat indicates high signal intensity on non-fat-suppressed T1- or T2-weighted images, with signal dropout on fat-suppressed images; India ink artifact seen at the interface between the hyperintense focus and adjacent renal parenchyma. Microscopic fat indicates signal dropout on opposed phase images compared with in-phase images. Segmental enhancement inversion indicates hyperenhancing areas during the CM phase with subsequent relative delayed washout and other areas in the same tumor exhibiting low-level enhancement during the CM phase and subsequent intense enhancement during the delayed postcontrast phase.

Abbreviations: ADER, arterial to delay enhancement ratio (difference in signal intensity between arterial and precontrast phase divided by the difference between delayed and precontrast phase); AML, angiomyolipoma; CEUS, contrast-enhanced ultrasound; CM, corticomedullary; CT, computed tomography; HU, Hounsfield units; MRI, magnetic resonance imaging; NG, nephrographic; RCC, renal cell carcinoma; T2, T2-weighted imaging.

Table A2. Imaging-Based Treatment Evaluation Criteria

Criteria	Target Lesions	CR	PR	SD	PD	Notes
RECIST 1.1	Metastases \geq 1 cm in long axis; Nodes \geq 1.5 cm in short axis Unidirectional measures of size	Disappearance of all lesions	\geq 30% decrease in target lesions	Neither PR nor PD	\geq 20% increase in target lesions from nadir, new lesions or unequivocal progression of nontargets	PD requires at least 5-mm increase from nadir PET/CT is incorporated
Choi	Defined per RECIST 1.0 Unidirectional measures of size	Disappearance of all lesions	\geq 10% decrease in size or \geq 15% decrease in tumor density on CT (in HU); no progression of nonmeasurable disease	Neither PR nor PD	\geq 10% increase in size and does not meet criteria for PR by tumor density; new lesion or new/increasing intratumoral nodule	
MASS	Defined per RECIST 1.0 Unidirectional measures of size		Favorable response: \geq 20% decrease in size or one or more predominantly solid-enhancing lesions with marked central necrosis or marked decreased attenuation (\geq 40 HU)	Neither favorable response nor unfavorable response	Unfavorable response: \geq 20% increase in size of a lesion not meeting favorable response criteria by density; new lesion, marked central fill-in or new enhancement in a previously hypoattenuating mass	Defined good clinical outcome: PFS > 250 days
irRC	As per RECIST 1.0 Bidimensional measures of size	Disappearance of all lesions in two consecutive scans 4 weeks apart	\geq 50% decrease in SPD of targets	Neither PR nor PD	\geq 25% increase from nadir on two consecutive scans not < 4 weeks apart	New lesions do not define PD; these are incorporated into the SPD
irRECIST	As per RECIST 1.1 Unidimensional measures of size	Disappearance of all lesions	\geq 30% decrease in size	Neither PR nor PD	\geq 20% and \geq 5-mm increase from nadir or nontarget PD	New lesions do not define PD, these are incorporated into the sum diameters
iRECIST	As per RECIST 1.1 Unidimensional measures of size	Disappearance of all lesions	\geq 30% decrease in size	Neither PR nor PD	\geq 20% AND \geq 5-mm increase from nadir or nontarget PD	New lesions result in unconfirmed PD; these are measured separately, and PD is confirmed by additional new lesions or growth in the new lesions on short interval follow-up (4-8 weeks)

Abbreviations: CR, complete response; CT, computed tomography; HU, Hounsfield units; iRECIST, immune Response Evaluation Criteria in Solid Tumors; irRC, immune-related Response Evaluation Criteria in Solid Tumors; MASS, morphology, attenuation, size, and structure; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SPD, sum of product diameters.

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