Imaging for Metastatic Renal Cell Carcinoma

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KEYWORDS

• Metastatic disease • Renal cell carcinoma • MRI • CT • PET

KEY POINTS

- Imaging modalities for metastatic renal cell carcinoma offer synergistic soft tissue characterization for staging evaluation.
- Clinical suspicion for osseous or central nervous system metastasis remains the recommended driver for imaging specific to these organ systems.
- Imaging criteria for tumor assessment during systemic therapy and for likelihood of response to first-line antiangiogenic agents may need to account for markers of vascularity rather than size alone for prognostication.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 5% of adult cases of cancer in men and 3% in women and is the second most common urologic neoplasm found in both sexes.[1] Approximately 33% to 50% of patients have metastatic disease at the time of detection.[2] In addition, 20% to 40% of patients with RCC develop metastatic disease after radical nephrectomy.[3,4] Approximately 25% to 50% of those treated for localized disease develop metastatic disease.[2] Monitoring for metastatic disease development and progression relies mostly on imaging. The increasing use of diagnostic imaging has resulted in tumors being diagnosed incidentally at an earlier stage and smaller size, but dedicated staging protocols may still be needed to provide accurate staging evaluation once RCC is suspected.[5] The stage of disease is the most important factor in determining prognosis and determining the risk of relapse.

Imaging plays a key role in surveillance and assessment of treatment response after the diagnosis of metastatic disease by aiding clinicians in tailoring treatments.[3] Systemic therapies for metastatic RCC have evolved from the earliest forms in the 1980s based on adoptive immunotherapy. By the early 1990s, interleukin-2, interferon, or a combination of the two were widely adopted.[6] Immunotherapy with interferon or interleukin-2 was the standard of care, but with response rates of only 10% to 20%.[3,7] However, with newer agents, such as tyrosine kinase inhibitors, patients have partial response rates of 4% to 40% and more than 75% demonstrate minor response or stabilization of disease.[8] Randomized trials have also shown promising results with vascular endothelial growth factor inhibitors and anti–programmed death ligand in molecular targeted therapies.[9,10] With such treatment advances, imaging evaluation of response may play an increasingly crucial role in decision-making about available systemic therapies. This review article provides updates on the role of imaging in metastatic RCC and describes newer techniques under investigation for staging and treatment response.

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ROLE OF DIAGNOSTIC RADIOLOGY IN EVALUATION FOR METASTATIC DISEASE: COMPUTED TOMOGRAPHY AND MRI

Abdominal computed tomography (CT) and MRI are the mainstay of staging the primary tumor at initial diagnosis, including evaluation for locoregional nodal or abdominal visceral metastases.[11] Protocols are designed to fully evaluate the extent of the primary tumor and for metastatic RCC. The recommended CT technique for the initial staging evaluation includes arterial and nephrographic/portal venous phases to identify hypervascular tumors and also delineate arterial and venous structures.[11] Imaging is acquired at 15 to 30 and 80 to 90, seconds, respectively, to capture these phases.

Clear cell carcinoma is the most common subtype of RCC and demonstrates avid arterial enhancement as opposed to papillary or chromophobe subtypes (**Fig. 1**). These differences are related to intratumoral vascularity. Therefore, clear cell metastases generally also demonstrate avid arterial enhancement and can be undetectable in nephrographic phases.[1] However, non–clear cell subtypes may enhance to a lesser degree and are better detected on nephrographic phases.[1] The nephrographic/portal venous phase is used to evaluate the venous system to evaluate for invasion and/or surgical planning. Additional delayed excretory phase images, captured at 180 seconds, can also be obtained if there is concern for extension into the collecting system.[11] Excretory images are helpful in detecting identifying filling defects in the ureters and can supplement routine surveillance when there is a clinical concern. Other helpful study components include multiplanar reformatted images and three-dimensional volume-rendered images, with the latter helpful in visualization of the relationships of structures for preoperative planning. In addition, these images can help assess tumor stage, delineating the tumor with particular attention to the relationship of the tumor to adjacent structures, including vascular relationships.[11] Such reformations are best obtained with the thinnest possible images (typically <1.5-mm interval and 10%–50% overlap).[11]

MRI is generally used when iodinated contrast is contraindicated or when further characterization of soft tissue is needed to determine disease extent. For MRI, protocols should include gadolinium-enhanced and noncontrast T1 sequences.[12] Just as in CT, arterial phase imaging is useful in detection of clear cell type metastases. For example, one can see an avidly arterially enhancing focus in the left adrenal gland, which was biopsy proven as metastatic clear cell RCC. Arterial phase imaging can be used in initial staging and recurrence as commonly done with CT; tumor proximity

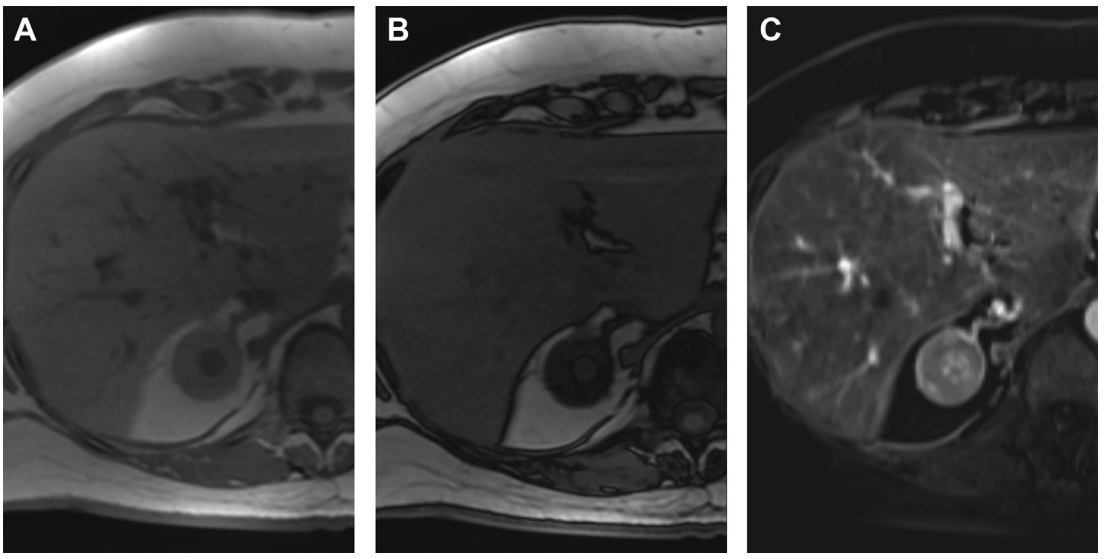

Fig. 1. Adrenal collision tumor with clear cell RCC. A 69-year-old man with history of left clear cell RCC status postnephrectomy in 1987. He was found to have a right adrenal adenoma. T1-weighted in-phase (*A*) and out-of-phase (*B*) sequences demonstrate loss of signal on out-of-phase images, suggestive of microscopic fat as seen in adrenal adenomas. However, a central portion demonstrates India ink artifact, suggesting an interface of fat with nonfatty soft tissue. The center also avidly enhances on postcontrast imaging (*C*), suggesting metastasis. Pathology confirmed adrenal adenoma containing metastatic RCC.

vasculature is important in surgical planning. Other useful sequences in MRI can also help identify RCC metastases. For example, diffusion weighting is used to more easily identify lymph nodes in the retroperitoneum, which may be less conspicuous on other sequences; use of diffusion-weighted imaging can increase sensitivity to detect smaller lymph nodes and those that may have less contrast to abutting structures.[13] RCC are cellular tumors that demonstrate diffusion restriction.[13] In addition, they contain intravoxel fat, which occasionally is seen in metastasis. Papillary subtype to be specific may not demonstrate avid arterial enhancement but demonstrates diffusion restriction.[13] Therefore, diffusion imaging aids in the detection of metastatic non–clear cell subtype RCC.

RCC typically metastasizes to the lung, bone, lymph nodes, liver, adrenal glands, and brain.[1] More rare sites include skeletal muscle, bowel, gallbladder, pancreas, and orbits (**Fig. 2**). Depending on the organ system in which the metastasis may be suspected clinically, various imaging modalities are superior to others in detecting metastasis. CT and MRI play critical but distinctive roles in detection and surveillance of metastatic RCC. Guidelines slightly vary among the American Urologic Association (AUA), European Association

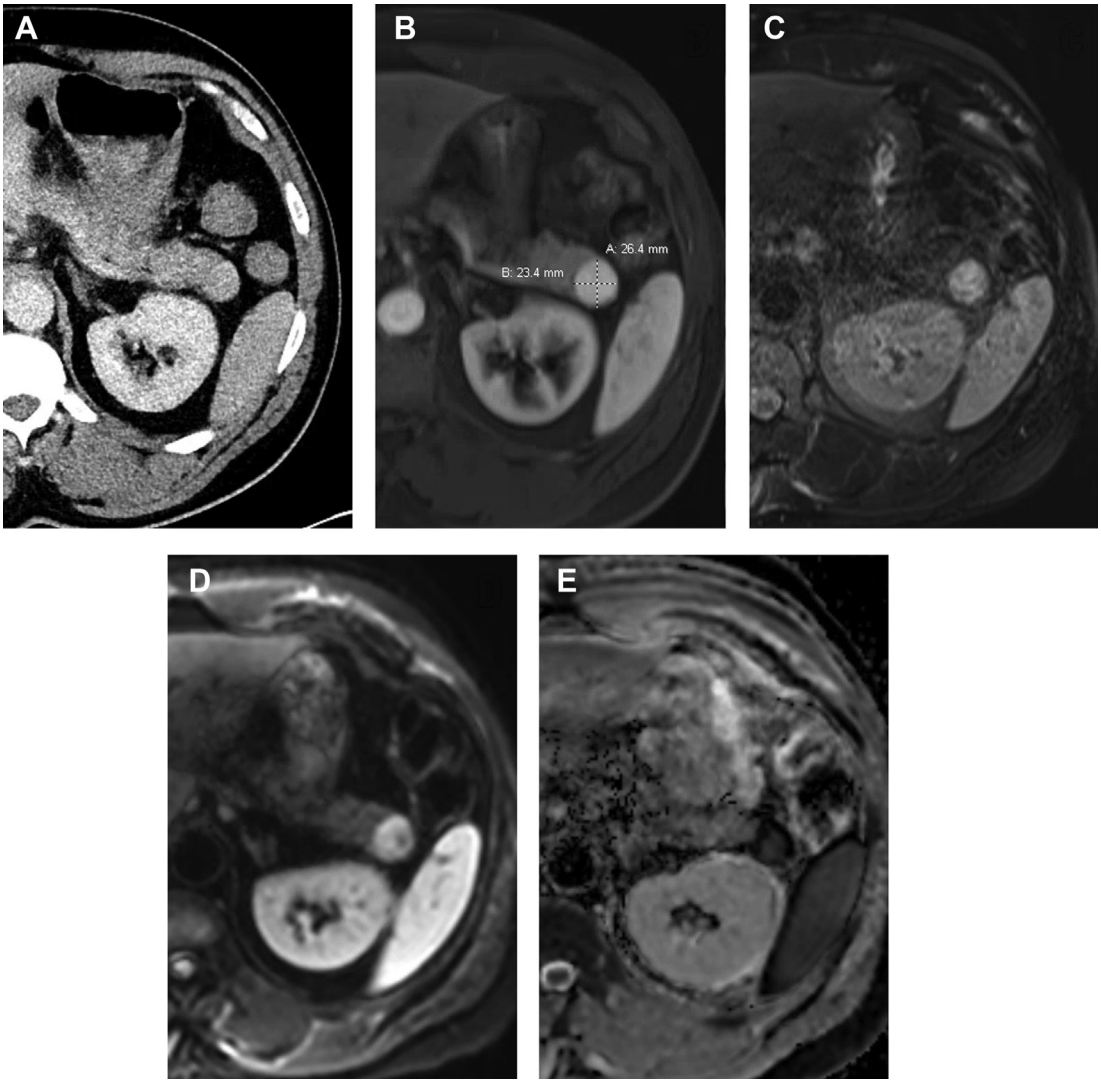

Fig. 2. Pancreatic metastasis. Patient with history of RCC was found to have a growing pancreatic tail mass on routine CT of the abdomen and pelvis. The mass enhances avidly on arterial phase images on CT (*A*) and arterial phase on MRI (*B*). On MRI, the lesion is T2 hyperintense to surrounding tissue on T2-weighted fat-saturated images (*C*). Diffusion restriction entails high signal on high b value images (*D*) and low signal on the ADC map (*E*).

of Urology, and National Comprehensive Cancer Network. AUA defines certain symptoms that should be followed by specific imaging.[8] However, the European Association of Urology and National Comprehensive Cancer Network make general recommendations, stating that bone scan, brain CT, or MRI may be used in the presence of specific clinical or laboratory signs and symptoms (Table 1).[14,15] The AUA also recommends specific time intervals for surveillance for metastatic disease based on the TNM stage of disease at presentation (Table 2).[15]

ORGAN-SPECIFIC EVALUATION FOR METASTASIS

Pulmonary

Pulmonary metastases account for 45% of metastatic RCC and are usually asymptomatic.[1] Controversies exist as to whether and how to evaluate for the possibility of intrathoracic metastases based on stage of tumors. For small primary tumors (T1), where the risk of metastatic disease is small, simple chest radiography may be satisfactory. For stage T2 or higher primary tumors, and because small pulmonary metastases are missed on radiographs, chest CT should probably be performed.[11,16] Lesions on CT are usually small, well circumscribed, and in subpleural locations. However, in RCC, patients can have "cannonball" metastases that are large (>5 cm) rounded pulmonary metastases.[1]

Bone

The second most common site of RCC spread is to bones. Compared with other malignancies, the distribution of bone metastases varies and common sites include the pelvis, spine, and ribs. Solitary bone metastases are rare.[1] For bone metastases, compared with CT, MRI is useful in detecting smaller lesions and lesions adjacent to the bones.[16] Bone scan is recommended for patients with bone pain or elevated increased alkaline phosphatase (Fig. 3).[17]

Table 1
Imaging recommendations based on clinical suspicion for metastatic RCC

Symptom	Imaging Modality Recommended
Bone pain or elevated alkaline phosphatase	Bone scan
Pulmonary symptoms	Chest radiograph or CT chest
Neurologic symptoms	CT or MRI of the brain/spine

Data from Campbell S., Uzzo R G., Allaf M E., et al., Renal Mass and Localized Renal Cancer: AUA Guideline. J Urol., 2017. 198(3); p. 520-529.

Lymph Nodes

Lymph node metastases are the third most common site of metastasis in RCC, accounting for 22% of cases. Diagnosis of lymph node involvement is based on morphologic criteria, especially size increase seen at CT (discussed later). Both CT and MRI are equally adequate in identifying metastatic lymph nodes; however, CT is generally the mainstay in assessing lymph node sizes and locations. Staging accuracy of lymph nodes has been shown to be approximately 83% to 88% on CT and MRI, without difference between modalities, although a head-to-head comparison has not been published.[3] PET has shown moderate ability to detect lymph node metastases in RCC[18]; a study by Kang and colleagues[19] found that 18F-fluorodeoxyglucose (FDG)-PET was 75% sensitive and 100% specific for retroperitoneal lymph node metastases.

Liver

Liver metastases carry poor prognosis and multiphase contrast-enhanced abdominal CT is preferred in most surveillance regimens.[2] Most patients with liver metastases from RCC develop metastases in other locations; the metastatic disease is limited to the liver in only a small portion of these patients. Only 2% to 4% of patients with metastatic RCC have operable liver metastases without additional sites of disease.[20]

Brain

Given the low incidence of brain metastases, the literature does not support the routine use of CT/MRI or bone scans for asymptomatic patients.[16] The AUA recommends reserving brain imaging for only those who have neurologic symptoms. To date, there are no standardized imaging protocols for screening the central nervous system in patients with metastatic RCC.[17]

IMAGING ASSESSMENT TO RESPONSE TO THERAPY

Imaging has played an increasing role in monitoring response to treatment in patients on chemotherapy. Previously, metastatic RCC was treated primarily with immunotherapy with interleukin-β and interferon-α; however, the mainstay has now become antiangiogenic agents and combination with immune check point inhibitors.[21] On CT,

Table 2
The American Urologic Association categorizes follow-up imaging recommendations based on risk criteria

Low Risk (pT1N0Nx)	Moderate/High Risk (pT2-pT4 N0, Nx, or Any Stage N+)
Baseline abdominal scan (CT or MRI) for nephron-sparing surgery and abdominal imaging (US, CT, or MRI) for radical nephrectomy within 3–12 mo after surgery	Moderate- to high-risk patients are recommended to have a baseline chest and abdominal scan (CT or MRI) within 3–6 mo following surgery with continued imaging (US, CXR, CT, or MRI) every 6 mo for at least 3 y and yearly thereafter to year 5
Additional abdominal imaging (US, CT, or MRI) may be performed in patients with low-risk disease following a radical nephrectomy if the initial postoperative baseline image is negative	Site-specific imaging may be performed if clinical symptoms are suggestive of recurrence or metastatic spread
Abdominal imaging (US, CT, or MRI) may be performed annually for 3 y in patients with low-risk disease following a partial nephrectomy based on individual risk factors if the initial postoperative scan is negative	In moderate- to high-risk patients, imaging (US, CXR, CT, or MRI) beyond 5 y may be performed at the discretion of the clinician
Those with history of low-risk RCC are recommended to have annual CXR to assess for pulmonary metastases for 3 y and only as clinically indicated beyond that time period	Routine FDG-PET scan is not indicated in the follow-up for RCC

Abbreviations: CXR, chest radiograph; US, ultrasound.
Data from Campbell S., Uzzo R G., Allaf M E., et al., Renal Mass and Localized Renal Cancer: AUA Guideline. J Urol., 2017. 198(3); p. 520-529.

successful treatment is seen as diminished vascularity, attenuation and enhancement, and size; therefore, attenuation and size should be used as criteria for assessment of response to treatment.[12] Frequency and duration of follow-up imaging is not yet standardized, although a schedule of contrast-enhanced CT scans every 3 months has been reported.[12] Because of the increasing use of imaging in monitoring treatment response, various criteria have been developed over the years to help clinicians in treatment plans (**Table 3**).

Since the initial introduction of Response Evaluation Criteria in Solid Tumors (RECIST) in 2000, RECIST has been widely adopted and applied by the oncology and radiology communities to define response to treatment in clinical trials. It was created to assess objective changes in tumor size as affected by therapy and to compare the changes to tumor from future therapies with current standards of care. In 2009, the revised RECIST 1.1 guidelines were formed to simplify, optimize, and further standardize assessments of tumor burden and became the most widely used method for assessing treatment response.[22] In particular, these guidelines were more applicable to antiangiogenic agents, because the RECIST 1.0 system was originally created to assess response to cytotoxic agents.[23,24] The RECIST 1.1 criteria were based on one-dimension measurements to quantify changes in tumor size, obtained by summing the longest diameters of the target lesions in the axial plane.[1] Lesion response is classified using four categories: (1) partial, (2) progressive, (3) stable, and (4) complete response. Partial response is defined as 30% decrease in sum of the longest diameters of the target lesions. Progressive disease is defined as at least 20% increase in the sum of the longest diameters of the target lesions. Complete response is defined as disappearance of all target lesions and any pathologic lymph nodes must have reduction in short axis of less than 10 mm. Stable disease is considered when there is neither sufficient decrease to qualify for partial response nor sufficient increase to qualify for progressive disease. Thus, limitations of RECIST 1.1 stem from changes in size being better attuned to assess tumor response to cytotoxic agents. RECIST does not consider other features, such as tumor attenuation, and underestimates the response of malignancies to cytostatic therapies, such as antiangiogenic agents.[23]

Choi proposed updated criteria that incorporated some of the limitations of RECIST. Choi

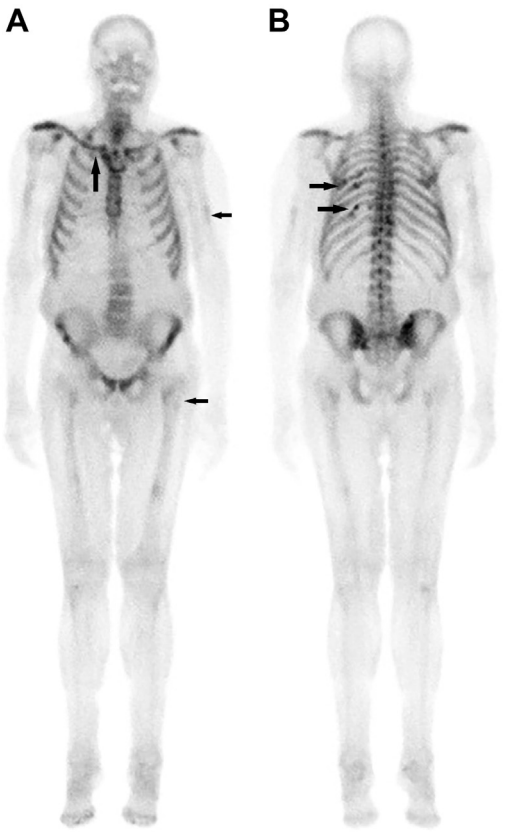

Fig. 3. Bone scan of diffuse metastatic RCC. A 68-year-old man with history of metastatic RCC, clear cell type, had a right nephrectomy in 1986. A subsequent cancer was discovered in the contralateral kidney and treated with partial nephrectomy in 2012, later requiring a complete nephrectomy because of recurrence. The patient later developed metastasis to lymph nodes, liver, and bone. A bone scan was performed to assess the metastatic disease. (A) Focal uptake represents metastases of the axial skeleton, upper and lower extremities (arrows), and (B) metastatic lesions in the ribs (arrows). The patient is status post bilateral nephrectomy with no visualization of kidneys or bladder uptake.

criteria were initially developed to assess the efficacy of using imatinib to treat gastrointestinal stromal tumors.[25,26] It was the first classification to use tumor attenuation measurements (in Hounsfield Units). Partial response was defined as greater than or equal to 10% decrease in tumor size or greater than or equal to 15% decrease in tumor attenuation in the portal phase with the region of interest placed surrounding the entire lesion. Progression was defined as greater than or equal to 10% increase in tumor size without taking tumor attenuation into account. A study done with sunitinib validated the Choi criteria, having a significantly better predictive value for overall survival over RECIST 1.1.[23]

In 2010, Nathan and colleagues[1] proposed a combined assessment of size and arterial phase attenuation of target lesions in patients with metastatic RCC and developed the modified Choi criteria. It compared data with Choi and RECIST 1.1 and found the modified Choi to be a better predictor of clinical response, as defined by time to progression and survival in patients with metastatic RCC.

Smith and colleagues[27] proposed the Size and Attenuation CT (SACT) criteria, which like the modified Choi criteria evaluated changes in tumor size and attenuation, and also defined specific patterns of contrast enhancement in target lesions that were indicative of disease progression. Changes from central necrosis to nearly complete central enhancement were described. The proposed SACT criteria were able to stratify patients with progression-free survival greater than 250 days with those with earlier progression with a sensitivity of 75% and specificity of 100%. This was compared with RECIST 1.1, which had sensitivity and specificity of 16% and 100%, respectively, and modified Choi with 93% and 44%, respectively. However, the criteria required three-dimensional volumetric evaluation that required proprietary software, limiting adoption for clinical use.[1]

The Morphology, Attenuation, Size, and Structure criteria were developed to overcome limitations of the SACT criteria. It eliminated three-dimensional analysis and defined specific patterns that were based on changes in lesion morphology, attenuation, and size of target lesions in the portal venous phase of CT. This set of criteria separated response into favorable, indeterminate, and unfavorable categories. A major change from the others was that greater than or equal to 40% decrease in attenuation or marked necrosis was considered a favorable response.[28]

Given the development of antiangiogenic drugs that induce stabilization rather than tumor regression, criteria of RECIST 1.1 may be inadequate in early detection of progressive disease because it is based only on tumor size. Therefore, these alternate classifications that incorporate attenuation, morphology, and structural changes are likely to provide more accurate indication of response. However, there are limitations in reproducibility and the prognostic value of these imaging-based tumor response criteria may differ based on clinical risk status.[23] Therefore, it is yet to be determined how the changes in imaging appearance should guide the management of patients with metastatic RCC, to

Table 3
The development of various tumor response assessment systems reflects the advancement of pharmaceutical agents

System	Criteria/Target Lesions	Complete Response	Partial Response	Stable Disease	Progressive Disease
RECIST 1.1	Tumor size ≥10 mm Maximum of 5 target lesions (maximum 2 per organ)	Disappearance of all target lesions Any pathologic lymph nodes (TL or NTL) must have reduction in short axis to <10 mm	≥30% decrease in the sum of the longest dimensions of the target lesions, with the baseline sum of the diameters as reference	Does not qualify as partial disease or progressive disease	≥30% increase in the sum of the longest diameters of the target lesions, with the smallest sum as reference Sum must also have absolute increase of a minimum of 5 mm New lesions
Choi	Tumor size ≥15 mm Maximum of 10 target lesions Lesion attenuation as measured on portal venous phase	Disappearance of all lesions No new lesions	≥10% decrease in size (unidimensional in axial) OR a decrease in tumor attenuation of ≥15% HU No new lesions No obvious progression of measurable disease	Does not meet the criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression	≥10% increase in tumor size (unidimensional in axial) and does not meet criteria of PR by tumor attenuation New lesions
Modified Choi	Tumor size ≥15 mm Maximum of 10 target lesions Lesion attenuation as measured on arterial phase	Disappearance of all lesions No new lesions	≥10% decrease in size (unidimensional in axial) AND a decrease in tumor attenuation of ≥15% HU No new lesions No obvious progression of measurable disease	Does not meet the criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression	≥10% increase in tumor size (unidimensional in axial) and does not meet criteria of PR by tumor attenuation New lesions New intratumoral nodules or increase in the size of the existing intratumoral nodules

System	Criteria/Target Lesions	Favorable Response	Indeterminate Response	Unfavorable Response
SACT	Tumor size ≥10 mm Maximum of 10 target lesions (maximum 5 per organ) Patterns of contrast enhancement as determined on portal venous phase VOI Lung lesions are not measured using attenuation or volume	Decrease in tumor size VOI of 20% Decrease in tumor size (VOI) of ≥10% AND a. ≥20 HU decrease in mean attenuation of half or more of the nonlung target lesions ≥40 HU decreased mean attenuation of ≥1 nonlung target lesions	Does not fit criteria for favorable or unfavorable response	Increase in tumor size (VOI) of ≥20% New metastases Marked central fill-in New enhancement of a previously homogenous hypoattenuating nonenhancing mass
MASS	Tumor size ≥10 mm Maximum of 10 target lesions (maximum 5 per organ) Lesion attenuation as measured on portal venous phase Brain lesions excluded Lung lesions were not assessed for marked central necrosis or marked decreased attenuation	No new lesion AND a. Decrease in tumor size (longest axial dimension) of ≥20% ≥1 predominantly solid enhancing lesions with marked central necrosis or marked decreased attenuation (≥40 HU)	Does not fit criteria for favorable or unfavorable response	Increase in tumor size (longest axial dimension) of ≥20% New metastases Marked central fill-in New enhancement of a previously homogenous hypoattenuating nonenhancing mass

Several systems incorporate features other than lesion size, given the cytostatic nature of current first-line therapeutic agents.

Abbreviations: CR, complete response; NTL, non-target lesion; PD, progressive disease; PR, partial response; TL, target lesion; MASS, Morphology, Attenuation, Size, and Structure; RECIST 1.1, Response Evaluation Criteria in Solid Tumors 1.1; SACT, Size and Attenuation CT; VOI, volume of interest.

maximize cancer-specific outcomes.[1] Despite its shortcomings, RECIST 1.1 remains the widely accepted standardized method in most trials of solid tumors.[29]

OTHER IMAGING MODALITIES

Role of Ultrasound

Ultrasound is rarely used for staging evaluation of RCC. There are many challenges in ultrasound and image quality is user dependent. Challenges include incomplete visualization of masses, acoustic shadowing from partially calcified cysts or masses, variability in echogenicity of hemorrhagic cysts and malignant tumors, and poor sensitivity in diagnosing isoechoic small renal tumors. Hence, ultrasound seldom is used for local staging of RCC,[16] and when iodinated contrast used for CT is contraindicated, MRI is favorable as compared with ultrasound.

Role of Nuclear Medicine

The role of PET/CT staging and metastatic workup in RCC is evolving.[16] PET/CT sequentially acquires PET images and a CT scan, usually in a single system where both scanners are fitted into a single gantry, which allows coregistered images of PET and CT scans to be provided.[16] FDG accumulation inside RCC cells depends on the expression of glucose transporter-1.[4] 18F-FDG-PET/CT is a useful adjunct to conventional imaging in establishing metastatic disease in lesions detected by CT, MRI, or bone scan. 18F-FDG-PET/CT is used in high-risk RCC patients with better sensitivity for detecting distant metastasis, providing anatomic and metabolic information.[4] However, the high background of renal pelvis from physiologic excretion of FDG limits evaluation of small primary RCC.[16] Although the usefulness of 18F-FDG-PET/CT in primary RCC remains unclear, and FDG-PET/CT is not currently recommended for the diagnosis and staging of RCC based on updated national and international guidelines.[4] Another PET agent, 18F-NaF, was Food and Drug Administration approved in 2016, and has been shown to be more sensitive in detecting bone metastasis with the greatest impact in initial staging and monitoring of bone lesions.[16]

99mTc-MDP bone scintigraphy is typically used for surveillance for skeletal metastases and is currently considered a sensitive but not specific tool for detecting metastatic bone lesions of RCC.[17] In a study of 124 patients with clinically localized, stages T1-2N0M0 disease, only six (5%) were found to have bone metastasis and it was therefore suggested that bone scans should be reserved for symptomatic patients who develop specific symptoms, such as local pain or abnormal alkaline phosphatase levels.[16]

Newer PET agents, such as prostate-specific membrane antigen (PSMA) targeting, are being researched to aid in detection of metastatic RCC. PSMA is a type II transmembrane protein with high expression in prostate carcinoma cells and has been suggested as a novel tracer that can detect prostate carcinoma relapses and metastases with high target-to-background ratio. PSMA-PET has shown promising results in clinical trials for detecting the recurrence of prostate cancer, although it is not yet Food and Drug Administration approved in the United States. In addition to prostate cancer, PSMA is expressed in the endothelial cells within the neovasculature of various solid malignant tumors including clear cell RCC.[30] In a case report by Demirci and colleagues[28] multiple pathologic bone lesions were found to have better visual detectability on 68-Ga-PSMA over FDG-PET.[30] Rowe and colleagues[31] reported five patients with metastatic RCC with more accurate staging for metastatic RCC. In all five patients, sites of metastatic disease were easily detectable through abnormal uptake of ^{18}F-DCFPyL (inhibitor of PMSA), with more lesions detected than on conventional imaging. PET-detected sites included lymph nodes, pancreatic parenchymal lesions, lung parenchymal lesions, a brain parenchymal lesion, and other soft tissue sites. However, the subtype of RCC seems to play a role in PSMA receptor expressivity because PSMA-based PET (18F-DCFPyL) may show uptake infrequently in non–clear cell RCC. PSMA binds to endothelial cells within the tumor microenvironment. Therefore, it is proposed that higher pretreatment levels of radiotracer uptake may identify lesions that are more likely to respond to angiogenesis-targeted therapies and thereby aiding clinicians in treatment strategies.[31]

Another novel radiotracer, ^{124}I-cG250, used in conjunction with PET/CT has been reported to assist in characterizing clear cell subtype RCC. G250 and its chimeric form cG250 (girentuximab) are monoclonal antibodies that recognize CAIX (carboxyl anhydrase IX transmembrane) on the cell membrane of clear cell RCC, and CAIX is known to be highly expressed in clear cell subtype RCC.[32] Two clinical trials by Divgi and colleagues[33,34] investigate this agent and have shown promising results in distinguishing clear subtype, but predominantly on larger masses, where the sensitivity was 89.4% in 2- to 4-cm tumors but only 70.8% in tumors less than 2 cm. The size

limitation, in fact, may be driven by the ^{124}I PET imaging properties, such as long-range positron emission in tissue (3 mm) and emission of 50% of positrons simultaneously with high-energy (603 keV) photons, which leads to increase in background counts and degradation of image contrast. Thus, sensitivity and specificity for detecting small (<4 cm) clear cell RCC lesions is yet to be determined and more investigative work needs to be conducted in a larger study with histologic reference.[32]

SUMMARY

Because metastatic disease is common in RCC at initial presentation and even after surgical treatment, accurate staging evaluation is important for suitable treatment. In addition, assessment of response to therapy is an important indicator for change in the choice of systemic therapeutic agents. CT and MRI are the mainstay of imaging tests for metastatic RCC evaluation, with other modalities being used only for symptomatic patients. The complementary strengths of different imaging modalities may assist with determination of disease extent and treatment selection as application of the most sensitive imaging modality based on organs of concern can aid detection of metastatic disease. Understanding the accuracy of the available imaging options may in part mitigate against unnecessarily frequent screening for metastatic disease. For assessment of response to systemic therapy, evidence suggests that considering size and attenuation may provide more prognostic information but a single system for such evaluation is not yet widely established. As disease-specific outcomes of new chemotherapeutic agents become clearer, the data may guide more precise imaging assessment of tumor response. One imaging technique under active investigation is nuclear medicine, because newer agents, such as PMSA, show potential for improved detection of metastases and further studies are needed to establish clinical utility.

DISCLOSURE

Dr S.K. Kang reports royalties from Wolters Kluwer for unrelated work. Dr E. Zan is involved in clinical trial support at AAA/Novartis and Perlmutter Cancer Center for unrelated work, and acting as a Co-PI in a study at the NIH for unrelated work. Dr S.V.L. Vig has no disclosures.

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