

American College of Radiology ACR Appropriateness Criteria®

Clinical Condition: **Renal Cell Carcinoma Staging**

Radiologic Procedure	Rating	Comments	RRL*
CT abdomen without and with IV contrast	9	This procedure is complementary to x-ray chest.	☼☼☼☼
X-ray chest	8	This procedure is complementary to CT.	☼
MRI abdomen without and with IV contrast	8	This procedure is an alternative to CT.	○
CT abdomen with IV contrast	7	This procedure is an alternative to CT without and with contrast.	☼☼☼
CT chest without IV contrast	6		☼☼☼
CT chest with IV contrast	6		☼☼☼
CT abdomen and pelvis with IV contrast	5		☼☼☼
CT abdomen and pelvis without and with IV contrast	5	This procedure may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating.	☼☼☼☼
MRI abdomen without IV contrast	5		○
Bone scan whole body	5		☼☼☼
MRI head without and with IV contrast	4		○
CT head with IV contrast	4		☼☼☼
CT abdomen and pelvis without IV contrast	3		☼☼☼
CT chest without and with IV contrast	3		☼☼☼
MRI head without IV contrast	3		○
CT head without IV contrast	3		☼☼☼
CT head without and with IV contrast	3		☼☼☼
US abdomen	3		○
FDG-PET/CT skull base to mid-thigh	3		☼☼☼☼
CT abdomen without IV contrast	2		☼☼☼
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

RENAL CELL CARCINOMA STAGING

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Summary of Literature Review

Introduction/Background

Renal cell carcinoma (RCC) accounts for 2%–3% of all visceral malignancies. It is estimated that approximately 61,560 new cases of RCC are diagnosed per year in the United States, resulting in approximately 14,080 deaths [1] due to cancers of the kidney and renal pelvis. The incidence of RCC appears to be increasing in the United States over the past decade [2]. The incidence in men is 1.6 times greater than in women. Metastatic disease at presentation varies with the patient series but typically occurs in about 1 in 10 patients [3,4]. The most common sites of distant metastases, in descending order, are the lungs, bone, retroperitoneal and mediastinal nodes, liver, brain, or in multiple sites [5,6].

The TNM staging system developed by the American Joint Committee on Cancer (AJCC) is now used almost universally and allows determination of prognosis [7-9].

Tumor size is critical to staging RCC for tumors confined to the kidney. In patients with T1 stage classification of RCC, there is an overall improved survival in patients with tumors <4 cm compared with those whose tumors measure 4–7 cm [7]. In a large study evaluating 47,909 cases from the National Cancer Database, patients with tumors <4 cm in diameter had a 75% 5-year survival rate, whereas tumors >10 cm in diameter yielded a median survival rate of 47.5% at 5 years [10].

Extrarenal tumor extension, such as infiltration into the perinephric or renal sinus fat and venous infiltration, is also a significant prognostic factor [11]. Hence, tumors with these characteristics are assigned stages of T3 and above. Prognosis is related to several other factors, including the tumor subtype, the stage, and the nuclear grade. Several prognostic nomograms based on staging information at the time of diagnosis have been proposed [12-15]. These models are valuable not only in patient counseling but also in risk stratification, patient selection for trials, and formulating follow-up strategies. Furthermore, recent advances in whole-genome sequencing have revealed specific genetic mutations that are associated with poor prognosis [16-18]. Future refinements of these models will probably take into consideration these genomic characteristics and may be sufficiently flexible to allow widening treatment options. Although incidentally discovered small tumors have a much better prognosis than symptomatic tumors, nonaggressive biologic behavior cannot be assumed. Klatte et al [19] showed that 7% of patients with primary tumors <4 cm had metastatic disease at presentation in a series of 1067 patients. Locally aggressive stages (pT3a and above) have been reported in 5.6% to 8% of patients with RCCs <4 cm [20-22].

Overview of Imaging Modalities

Computed Tomography

Computed tomography (CT) is a noninvasive imaging modality that uses ionizing radiation to characterize renal masses. Use of iodinated contrast material significantly improves the ability to characterize and stage the primary tumor and nodal and distant metastases. In general, 100–150 mL of iodinated intravenous (IV) contrast medium is used, with a flow rate of 2–3 mL/s. A noncontrast scan followed by a contrast-enhanced scan improves detection

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of small lesions in the kidney. Lack of soft-tissue contrast limits the sensitivity of CT scanning without IV contrast as a stand-alone examination.

Chest CT is useful to detect small pulmonary metastases and metastatic mediastinal lymph nodes. Use of IV contrast does not improve detection of intrathoracic metastasis.

CT scanning of the brain may be useful in detecting brain metastasis. Noncontrast CT scanning of the brain may not be effective in detecting lesions that are small or lack mass effect or significant vasogenic edema. Use of contrast increases the accuracy of CT scans of the brain.

Magnetic Resonance Imaging

MRI provides excellent soft-tissue contrast resolution and provides radiation-free multiplanar anatomic evaluation of the abdominal organs. MRI is generally used when optimal CT cannot be performed, as in the case of pregnancy or severe allergy to iodinated contrast medium. MRI is also useful in instances where there is equivocal contrast enhancement on CT or in instances of hemorrhagic lesions. MRI has similar reported overall staging accuracies compared with CT.

A MRI protocol for renal mass evaluation should include T2-weighted images, in- and opposed-phase T1-weighted gradient echo images to detect intravoxel fat, and dynamic contrast-enhanced 3-D T1-weighted gradient echo images in arterial, nephrographic, and excretory phases. Due to its superior contrast resolution, MRI of the brain is very useful in detecting brain metastasis and for detecting meningeal tumor seeding. Compared to CT, MRI is useful in detecting smaller lesions and lesions adjacent to the bones [23]. In one study, approximately 20% of patients who demonstrated a single lesion on CT demonstrated multiple lesions on MRI [24].

Chest Radiography

Chest radiography uses ionizing radiation and is useful as a screening tool to detect pulmonary metastasis. Small pulmonary metastases are easily missed on chest radiographs. In high-risk patients, a chest CT is preferred.

Ultrasonography

Ultrasound (US) is an imaging modality free of ionizing radiation. US can be useful in differentiating solid and cystic renal masses. However, US is operator dependent and is challenging in obese patients who provide poor acoustic windows. Some of the challenges in the use of US may be related to incomplete visualization of the mass, acoustic shadowing from partially calcified cysts or masses, variability in echogenicity of hemorrhagic cysts, and poor sensitivity in diagnosing isoechoic small renal tumors. Hence, US is seldom used for local staging of RCC other than for clarification of potentially cystic tumors [25].

Bone Scans

Tc-99m methylene diphosphonate bone scans provide a survey of the entire skeleton to detect bone metastases. Bone scans involve injection of a radioisotope and use ionizing radiation. Bone scans are nonspecific in determining the cause of increased tracer uptake, particularly in solitary lesions, and may occasionally require an accompanying radiograph or cross-sectional imaging to further characterize the lesion. When available, single-photon emission computed tomography fused with CT can be utilized to provide detailed anatomic localization of the abnormal radiotracer uptake and further improve the characterization of the nature of the abnormality [26]. They also have poor spatial resolution and contrast resolution. However, the ability to survey the entire skeleton at a relatively low cost and wide availability make it a useful tool in initial screening for bone metastasis.

Arteriography

Fluoroscopy and radiography are used while performing renal arteriography after inserting a catheter into the renal artery or the aorta for injection of contrast. It is an invasive procedure and is performed when therapeutic interventions at the same setting, such as embolization of the tumor, are planned. Diagnostic arteriography is rarely performed as a stand-alone procedure.

Fluorine-18-2-fluoro-2-deoxy-D-glucose–positron emission tomography/computed tomography

Positron emission tomography (PET)/CT sequentially acquires PET scans and a CT scan, usually in a single system wherein both scanners are fitted into a single gantry. This enables the ability to provide coregistered images of both PET and CT scans. The most widely used tracer for PET scanning is fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG), which is a positron emitter. PET/CT scanners involve exposure to ionizing radiation. Use of PET/CT is controversial in renal cell carcinoma. PET/CT appears to have a better sensitivity for detecting distant metastasis than for detecting and staging RCC in the kidney [27-30]. PET/CT with 18F-sodium fluoride

(NaF) has been shown to be more sensitive in detecting bone metastasis. NaF PET/CT had the greatest impact in initial staging and in monitoring of treatment in patients with bony metastasis. Its role in staging and metastatic workup in RCC is yet to be defined [31,32].

Discussion of Imaging Modalities by Variant

Variant: Renal cell carcinoma staging

Staging of primary tumor

Preoperative imaging can provide important staging and anatomic information to the surgeon. Both CT and MRI are equally accurate in staging of the primary tumor [33,34]. It is important to be aware that a change in the pathologic stage of malignant renal neoplasms postoperatively is common, mainly due to disparities in radiographic and pathologic size or the pathologic presence of perinephric or renal sinus fat invasion that is not easily detected on imaging [35-37]. RCC can be multifocal. One of the important roles of preoperative imaging studies is also to look for synchronous primary tumors. Hence, it is important to obtain an adequately designed CT and MRI protocol that includes the nephrographic phase to optimize detectability and characterize small lesions.

Size of the primary tumor and degree of local invasion determines the T stage classification in the AJCC TNM staging system [8]. Tumors confined to the kidneys are staged as T1 or T2, depending on the size. Tumors <7 cm are staged as T1, with a further subclassification into T1a and T1b based on a cut-off of 4 cm. Tumors >7 cm in maximum diameter, confined to the kidneys, are staged T2. Extrarenal extension into the perinephric/renal sinus fat or renal vein is staged as T3a; extension of tumor thrombus into the inferior vena cava (IVC) is staged T3b or T3c. Adjacent organ involvement, including extension beyond the Gerota fascia or involvement of the ipsilateral adrenal gland, is T4 disease.

Perinephric tumor extension (T3a) is difficult to discriminate from nonspecific perinephric stranding due to edema, vascular engorgement, or fibrosis. High-resolution CT using thin sections appears to improve detection of perinephric infiltration, although false positives are common [33,34,38]. Breath-hold MRI showing lack of perinephric fat involvement is reported to have a high negative predictive value for no perinephric tumor invasion [39]. In a study of 73 RCCs, Roy et al [40] showed that the presence of a pseudocapsule on MRI had an accuracy of 93% for clear-cell carcinomas in separating T1/T2 tumors from T3a tumors.

Renal sinus fat invasion (T3a) is also difficult to accurately detect on CT [41]. It is considered the most common site for extrarenal extension of RCC [42,43]. The clinical significance of this finding is controversial. Several authors believe that the presence of renal sinus fat invasion heralds a poorer prognosis compared with perinephric fat invasion [44,45]. However, Margulis et al [46] found no significant difference in outcomes. Nevertheless, the presence of renal sinus fat invasion poses special challenges in planning nephron-sparing procedures; hence, special caution should be taken when evaluating these structures. Some urologists rely on intraoperative frozen sections, when available, to make these determinations. [47].

Direct contiguous spread to the adrenal gland is classified as T4. CT has a high sensitivity and nearly a 100% negative predictive value in detecting direct contiguous spread to the ipsilateral adrenal gland [22,48]. However, the positive predictive value of CT is lower, as it may be difficult to distinguish abutment from direct invasion.

The extent of venous invasion of tumor is an important factor in the T stage classification in the current TNM staging system. Tumor extension into segmental branches or the main renal vein is seen in approximately 20% of cases and has been reclassified as T3a in light of recent evidence that this group of patients tends to have a better prognosis compared with those with extension of tumor into the IVC, which is seen in up to 10% of patients [49-51]. Not only must the involvement of the renal veins and IVC be identified but the cephalad extent of the tumor must also be correctly assessed for preoperative planning. Depending on the level of the IVC thrombus, the surgeon may need to perform more extensive mobilization of the liver in order to obtain suprahepatic IVC access. An intra-atrial thrombus may require cardiac bypass. A thrombus limited to the renal vein ostium can be retracted back into the vein without the need to perform temporary ligation of the IVC and cavotomy. Rarely, transmural invasion of the caval wall might necessitate a graft placement. Therefore, accurate assessment of the extent of the caval thrombus is important. The prognostic significance of the extent of venous thrombus is still a topic of controversy, but recent evidence shows that supradiaphragmatic extension of an IVC thrombus heralds a poorer prognosis than does subdiaphragmatic extension [49,51,52].

Venous thrombus in the renal vein or IVC can usually be identified on the venous phase or delayed phase of the initial diagnostic CT. In cases where the findings are equivocal, MRI may be helpful. Tumor thrombus in the segmental branches of the renal vein may be more difficult to determine than thrombus in the main renal vein and IVC [41]. Both contrast-enhanced multidetector CT and MRI have equal sensitivity in detecting venous involvement, particularly in the main renal vein and the IVC [38,53]. Signs suggestive of renal vein or caval thrombus include filling defects, enlargement of the vessel, and rim enhancement. The pitfalls in CT occur with technically inadequate boluses of contrast media, motion, and flow artifact.

Due to its higher tissue contrast, noncontrast MRI has a higher sensitivity and specificity for detecting venous extension than does noncontrast CT. Pitfalls of MRI include the potential for large tumors to compress the vena cava and cause flow-related artifacts. Such artifacts can be reduced with appropriate saturation pulses. With bright-blood techniques, rapid or turbulent flow can also lead to artifacts. Diagnostic accuracy is improved with gadolinium-enhanced MR venography. The highest sensitivity and specificity in assessing venous involvement are achieved with a gradient-echo sequence [34,54]. Bland thrombus featuring a uniform signal intensity and lack of enhancement after gadolinium can be distinguished from tumor thrombus, which exhibits intermediate or high signal intensity, heterogeneous intensity, and, more reliably, the presence of small vessels. However, if a good-quality CT is obtained with adequate venous opacification, MRI is usually not needed. Invasion of the renal vein is better recognized on MRI studies. Diameter of the IVC and renal vein, presence of signal alterations in the vessel wall, flow around the tumor thrombus, and mobility in different phases are some of the signs that are useful [55,56].

Venous anomalies should be identified, specifically the presence of a retroaortic left renal vein or circumaortic left renal vein, as these have surgical implications. CT and MR angiograms can be incorporated in any staging study to determine any arterial or venous anomalies that may be helpful in surgical planning. US and color duplex US can be used to study venous invasion and venous anatomy, but this technique is of limited value in obese patients and in the presence of bowel gas, which interferes with the ability to image the renal vein–IVC junction. US is also highly dependent on the expertise of the operator.

Catheter angiography is insensitive for tumor thrombus. Its main roles are for preoperative embolization to control the renal artery in anticipation of a thrombectomy and for palliation of hematuria in inoperable tumors [57,58].

Contiguous invasion of the adrenal gland, liver, diaphragm, psoas muscles, pancreas, and bowel is seen in advanced T4 tumors and usually portends a poor prognosis. Both CT and MRI have poor positive predictive value for distinguishing invasion from mere abutment. However, CT offers a high negative predictive value in excluding direct contiguous invasion [22,48].

Including the pelvis in a routine staging examination is of limited value and is not likely to yield any significant results unless in rare instances of ectopic kidneys located in the pelvis. Two retrospective studies looking at a total of 519 staging CTs including both abdomen and pelvis reported that none of the pelvic CTs offered management-altering information not already known to the clinical team [59,60].

Nodal staging

As the current methodology for detecting lymph node metastases is based only on size, all imaging is suboptimal for N staging. Cross-sectional imaging criteria for diagnosing metastatic lymph nodes include a short-axis diameter of >1 cm and disruption of the normal lymph node architecture. However, based on this criterion, CT has a false-negative rate of about 10%, and nearly 50% of enlarged lymph nodes tend to be benign [61]. MR lymphography with iron oxide nanoparticles shows promise, but the agent is not yet available in the United States [62]. CT-guided aspiration biopsies are an alternative and can be performed if documenting nodal metastases impacts clinical management decisions.

Distant metastases

Distant metastases are most commonly seen in lungs, bone, liver, and brain. Chest imaging is important to RCC staging. Routine chest radiographs are considered adequate, but the routine use of chest CT is more controversial. The risk of pulmonary metastasis increases with the size of the primary tumor, and although universally accepted guidelines do not yet exist [63], chest CT is justified for larger primary tumors. When the chest radiograph is suspicious or positive, chest CT is useful for confirming or excluding metastases and defining the extent of metastatic disease.

Bone metastasis has been identified as an independent prognostic variable associated with poor survival in patients with metastatic RCC. In symptomatic patients who have advanced primary tumors or who have abnormal laboratory findings such as elevated alkaline phosphatase, a bone scan may be helpful to establish the diagnosis of bone metastasis [64].

Brain metastasis is seen in up to 17% of patients with metastatic RCC. Patients with acute neurological signs or symptoms should receive prompt MRI of the brain or a contrast-enhanced CT scan of the head. There is no evidence to justify routine use of brain MRI; however, it can be used to detect asymptomatic occult brain metastasis in patients with advanced RCC [65].

PET does not have an established role in the initial staging of renal cancer, in part due to the low avidity of metastatic RCC lesions. It may be difficult to detect primary renal cancers against the normal background of high activity in the kidneys on FDG-PET [66]. PET may be helpful for establishing metastatic disease in lesions detected by CT, MRI, or bone scan, and it can be used to detect unsuspected metastases in high-risk patients [67,68]. Although negative PET results cannot exclude metastatic disease, a positive PET scan should be considered highly suspicious due its high specificity.

Summary of Recommendations

- Contrast-enhanced multiphase CT scanning of the abdomen is the diagnostic modality of choice for staging a primary renal tumor. MRI of the abdomen is a suitable substitute when the patient cannot undergo contrast-enhanced CT. If the status of the renal veins and IVC cannot be determined on CT, contrast-enhanced multiphase 3-D MR venography can be performed.
- CT of the chest should be used to detect pulmonary metastasis in patients with large or locally advanced tumors. Chest radiography may be sufficient in patients with small primary tumors.
- In patients with suspicion for metastatic disease based on symptoms, other sites of metastases, or abnormal laboratory findings, brain MRI and bone scans can be performed.

Summary of Evidence

Of the 68 references cited in the *ACR Appropriateness Criteria® Renal Cell Carcinoma Staging* document, 56 are categorized as diagnostic references including 1 well designed study, 12 good quality studies, and 24 quality studies that may have design limitations. Additionally, 10 references are categorized as therapeutic references including 5 good quality studies. There are 24 references that may not be useful as primary evidence. There are 2 references that are meta-analysis studies.

The 68 references cited in the *ACR Appropriateness Criteria® Renal Cell Carcinoma Staging* document were published from 1990-2015.

While there are references that report on studies with design limitations, 18 well designed or good quality studies provide good evidence.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the *ACR Appropriateness Criteria® [Radiation Dose Assessment Introduction](#)* document.

Relative Radiation Level Designations		
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
○	0 mSv	0 mSv
⊕	<0.1 mSv	<0.03 mSv
⊕⊕	0.1-1 mSv	0.03-0.3 mSv
⊕⊕⊕	1-10 mSv	0.3-3 mSv
⊕⊕⊕⊕	10-30 mSv	3-10 mSv
⊕⊕⊕⊕⊕	30-100 mSv	10-30 mSv

*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as “Varies”.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.