

**American College of Radiology
ACR Appropriateness Criteria®**

Clinical Condition: Follow-up of Renal Cell Carcinoma

Variant 1: Asymptomatic patient; no known metastases.

Radiologic Procedure	Rating	Comments	<u>RRL*</u>
X-ray chest	8	Not necessary if CT chest performed.	Min
CT abdomen and pelvis with contrast	8	Particularly if primary was high stage and/or high grade.	High
MRI abdomen and pelvis without and with contrast	6	See statement regarding contrast in text under "Anticipated Exceptions."	None
CT chest with or without contrast	6		Med
FDG-PET whole body	4	May have a role when CT and/or bone scan findings are equivocal.	High
US kidney retroperitoneal	3		None
X-ray intravenous urography	2		Med
Tc-99m bone scan whole body	2		Med
MRI head without and with contrast	1		None
X-ray abdomen	1		Med
CT head without and with contrast	1		Med
X-ray radiographic survey whole body	1		Med
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate			*Relative Radiation Level

FOLLOW-UP OF RENAL CELL CARCINOMA

Expert Panel on Urologic Imaging: David D. Casalino, MD¹; Isaac R. Francis, MD²; Ronald S. Arellano, MD³; Deborah A. Baumgarten, MD, MPH⁴; Nancy S. Curry, MD⁵; Manjiri Dighe, MD⁶; Pat Fulgham, MD⁷; Gary M. Israel, MD⁸; John R. Leyendecker, MD⁹; Nicholas Papanicolaou, MD¹⁰; Srinivasa Prasad, MD¹¹; Parvati Ramchandani, MD¹²; Erick M. Remer, MD¹³; Sheila Sheth, MD.¹⁴

Summary of Literature Review

This narrative addresses appropriate imaging examinations to follow patients who have been treated for renal cell carcinoma by radical nephrectomy or nephron-sparing surgery. It specifically deals with asymptomatic patients; it does not deal with imaging of nononcologic complications of surgery; with patients undergoing systemic therapy for known recurrent renal cell carcinoma; with patients in whom specific symptoms, signs, or laboratory studies suggest recurrent malignancy at a specific site; or with patients whose surgery is known to have left residual tumor [1-6].

Follow-up is important for patients who have had radical or partial nephrectomy for renal cell carcinoma [7]. Although they may be thought to have been initially cured, local or metastatic recurrences may develop in 20%-50% of them and require management. Solitary metastasis may occasionally be treated by resection [8,9]. A nonspecific immune approach with cytokines has been used to treat metastatic disease [10,11], yet the use of these agents has been limited by their toxicity as well as generally poor response rates. Recently, several new agents that inhibit vascular endothelial growth factor signaling have shown significant antitumor effects and meaningful clinical benefit [12]. Imaging is essential in evaluating the response to these therapies.

The anatomic location of recurrences clearly dictates the choice of imaging modalities. The tumor may recur in the resection site, especially if the primary is large, high grade, or has a higher tumor (T) stage [4,13,14]. The incidence of tumor recurrence in the resection site is

similar or only slightly higher in patients who had partial nephrectomy compared to those who had radical nephrectomy [9,15,16]. More commonly, however, the tumor recurrence appears as distant metastases [17].

Several studies have suggested surveillance protocols based on patterns of tumor recurrence, including where and when metastases occur, and the primary tumor's size, stage, and nuclear grade at the time of resection [18,19]. For instance, the risk of metastatic disease after nephrectomy increases with higher stage of the primary tumor [20,21]. In decreasing order of frequency, metastases most commonly appear in lung (with or without mediastinal or hilar nodes) [22], bone, the upper abdomen (including the resection bed, adrenal gland, contralateral kidney, and liver), brain, and a multitude of other sites (including skin, spleen, heart, diaphragm, gut, connective tissue, and pancreas) [4,19].

Other characteristics of metastatic disease from renal cell carcinoma are worth consideration. Most lung metastases are (at least early in their history) asymptomatic [2,23]. Metastases in thoracic nodes usually indicate a very short survival time [22]. Most bone metastases are symptomatic at the time of discovery; they can appear anywhere in the skeleton [24], but frequently appear in the lumbar spine, thoracic spine, and ribs — that is, the areas likely to be included in chest and abdomen examination [25]. Most recurrences appear within 2-3 years after the initial resection, but they may not occur until decades later [5,26]. Tumor recurrences tend to occur earlier in patients with higher T stages, and those that appear after a long interval appear to be associated with a better prognosis [15]. Therefore it may be argued either that routine follow-up should be limited to only a few years (especially if the chosen modalities are expensive) or that to halt follow-up after a brief period may deprive those patients who might benefit most from treating recurrences of the advantage of an early diagnosis.

Several stage-based surveillance protocols for renal cell carcinoma after radical or partial nephrectomy have been proposed. They can be summarized as follows [1-6,16,19,27,28]:

- **For T1 tumors.** As the risk of metastases is low, most surveillance protocols recommend that history, physical examination, laboratory tests, and a chest radiograph be obtained every 6 to 12 months for 3 years and then yearly until year 5. Others have suggested no imaging if the tumor is <2.5 cm. Most protocols do not recommend surveillance with abdominal computed tomography (CT) for patients with T1 tumors.
- **For T2 primary tumors.** Most protocols recommend that history, physical examination, laboratory tests and a chest radiograph be obtained annually or every 6 months for 3 years, then annually thereafter till year 5. Protocols vary widely regarding the use of abdominal CT. Some do not recommend CT at all,

¹Principal Author and Panel Vice-chair, Northwestern University, Chicago, Illinois.

²Panel Chair, University of Michigan, Ann Arbor, Michigan.

³Massachusetts General Hospital, Boston, Massachusetts.

⁴Emory University Hospital, Atlanta, Georgia.

⁵Medical University of South Carolina, Charleston, South Carolina.

⁶University of Washington Medical Center, Seattle, Washington.

⁷Presbyterian Hospital of Dallas, Dallas, Texas, American Urological Association.

⁸Yale University School of Medicine, New Haven, Connecticut.

⁹Wake Forest University School of Medicine, Winston Salem, North Carolina.

¹⁰Hospital of University of Pennsylvania, Philadelphia, Pennsylvania.

¹¹University of Texas Health Science Center, San Antonio, Texas.

¹²University of Pennsylvania Hospital, Philadelphia, Pennsylvania.

¹³Cleveland Clinic Foundation, Cleveland, Ohio.

¹⁴Johns Hopkins Hospital, Baltimore, Maryland.

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while others recommend CT at year 2 and year 5. Still others recommend a CT every other year or annually for 3 years following surgical removal, then annually thereafter.

- **For T3 or T4 primary tumors.** Most protocols recommend that history, physical examination, laboratory tests, and a chest radiograph be obtained every 6 months for a few years, then annually thereafter. The vast majority of protocols recommend abdominal CT, with most recommending more frequent (every 3-6 months) CT imaging for 3 years after surgery and less frequently (yearly or every other year) thereafter.

It is likely that the incorporation of molecular biomarkers, such as IMP-3 and p53, into prognostic models will improve their accuracy and allow more individualized postoperative surveillance protocols in the future [29].

Pulmonary Metastases

Given the fact that pulmonary metastases are often asymptomatic, routine imaging of the chest is usually performed. The major modalities used to search for metastases in the chest are the chest radiograph and chest CT [2,3,5,23,30-33]. Certainly, if the chest radiograph is chosen and is positive, CT almost inevitably follows in order to plan for and monitor the results of further therapy. The chest radiograph is less expensive and less likely to display incidental findings unrelated to metastatic disease. CT is more likely to display metastases earlier (in particular, it is more likely to demonstrate metastatic disease when there is just one lesion that might be amenable to resection than when there are several) and is probably more sensitive than chest radiograph in detecting metastases in thoracic spine, ribs, bones of the shoulder, and nodes. But CT is also more likely to display small granulomas that may masquerade as metastases and require further workup. While the extra yield from chest CT compared to chest radiography is probably too small to warrant its use in routine surveillance [34], some oncologists prefer to use chest CT, especially for patients with T3 or T4 primary tumors or nodal disease. A few studies have shown fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) to be highly specific in detecting chest metastases, but the sensitivity is limited [35-37]. No role for magnetic resonance imaging (MRI), angiography, or ultrasound (US) has been claimed in screening for metastases to the chest.

Abdominal Recurrences

Abdominal recurrences may occur at the surgical site or metastasize to the liver, lymph nodes, adrenal glands, bones, etc. While a few studies have argued against routine imaging of the abdomen in patients after resection of low-stage tumors (T1 and certain T2 tumors) [1,3,5,6], abdominal surveillance is commonly performed with CT. CT is quite sensitive in detecting metastases in the resection site, contralateral kidney, adrenal glands, liver, and bones included in the examination, [4,25,37-41]. MRI should be considered in place of CT in younger patients who will likely require multiple scans and in patients with

renal dysfunction or a history of allergy to iodinated contrast. Radiography is likely to be insensitive for all but the largest of masses and bone metastases. FDG-PET can be a useful adjunct to CT or MRI, particularly when a local recurrence is suspected in a renal fossa that may have postoperative and postradiation changes [37,42-44]. Performing separate nuclear medicine liver-spleen, bone, and renal scans is not practical. Angiography is too invasive. Urography is likely to be less sensitive than CT; it may be falsely negative in patients with small intrarenal masses, and it is likely to miss all but the largest extrarenal masses. US has demonstrated some success in detecting intra-abdominal recurrences [45], but it has never been shown to be as sensitive as CT, and it is likely to be less sensitive in detecting small resection bed metastases, especially if the nephrectomy has been performed on the left side and if bowel occupies the surgical site.

Follow-up of Renal Cell Carcinoma after Ablative Therapies

Energy-ablative therapies, such as cryoablation and radiofrequency (RF) ablation, are increasingly used in treating small renal cell carcinomas as an alternative to partial nephrectomy. These therapies have been shown to be effective and safe [46-51]. Postablative CT and MRI play an important role in the evaluation of the ablation zone, surveillance for residual or recurrent tumor, and identification of procedure-related complications [46-50,52].

A multi-institutional study [53] reported that 63 of 616 patients (10.2%) were found to have residual or recurrent tumor after primary ablation. Residual tumor was defined as enhancement in the vicinity of the treated tumor on the first imaging study after the ablative procedure, and recurrent tumor was defined as enhancement after an initially negative imaging study. Thirty-seven of 46 patients who received salvage ablative therapy for residual or recurrent disease had no further evidence of disease over a mean follow-up period of 2 years. Seventy percent of the initial treatment failures were detected within the first 3 months after therapy, and 92% were detected within the first 12 months. The proposed surveillance protocol consisted of a minimum of 3 to 4 imaging studies (CT or MRI) in year one after ablative therapy, with studies being performed at months 1, 3, 6 (optional), and 12. The CT or MRI should be a dedicated renal examination using thin cuts and precontrast and postcontrast imaging. The study did not make a specific recommendation for surveillance beyond the first year; although, all the participating institutions reported follow-up imaging with CT or MRI in the range of every 6 to 12 months after year 1. The required duration of follow-up is still unknown.

While US contrast agents are not yet approved for clinical applications outside of cardiology in the United States, Meloni et al [54] from Vimercate General Hospital in Milan, Italy, showed contrast-enhanced US to be effective in the follow-up of patients with renal cell carcinoma following RF ablation. There was concordance between

the results of contrast-enhanced US and CT or MRI findings for 27 of 28 treated tumors. Contrast-enhanced US missed only one of seven cases of local tumor progression. Concordant results of absence of tumor recurrence were noted for the remaining 21 tumors.

Osseous Metastases

Surveillance for the appearance of metastases to the skeleton might be done by serial radionuclide bone scans [55-58], or it might not be done at all unless the patient develops specific symptoms, usually local pain or abnormal alkaline phosphatase levels. Most authors do not suggest routine bone scanning to search for metastases without symptoms [2,3,5,15,41], because the vast majority of bone metastases are symptomatic and bone metastases are not curable. When a bone metastasis is suspected, a bone scan is preferable to MRI or CT because it can survey the entire skeleton. If the bone scan is positive, a radiograph might be considered to exclude impending fracture. Identification of bone metastases may facilitate treatment for pain relief and prevention of pathologic fracture.

Relatively little has been written regarding the use of radiography or scintigraphy to monitor patients in the postoperative phase. FDG-PET may have a role when CT and/or bone scan findings are equivocal [37]. FDG-PET may reveal bone metastases not detected on bone scan, but false-negative results have also been reported [35,59,60].

Brain Metastases

Surveillance protocols for renal cell carcinoma have not supported routine imaging of the brain to search for metastases in asymptomatic patients [3,5,15]. While this narrative is not intended to address imaging of patients with metastatic disease, Shuch et al [61] in a recent study of 138 patients with renal cell carcinoma brain metastases (RCCBM) suggested that such patients should undergo central nervous system screening to identify smaller brain lesions that are more amenable to treatment. The recommendation is based in part on the following observations: one-third of the patients with RCCBM did not have symptoms in the central nervous system; 95% of the patients had synchronous extracranial metastases; and in selected patients with RCCBM, aggressive therapy was associated with prolonged survival.

Summary

- Tumor recurrences, whether metastatic or local, are not uncommon after resection of localized renal cell carcinoma.
- The intensity and length of follow-up in these patients are largely dependent on the stage of the primary tumor.
- The follow-up generally includes a history and physical examination, complete blood count, liver function tests, and chest radiography.
- While there is no clear consensus regarding the timing of abdominal CT in routine surveillance, it is

generally included in the follow-up evaluation of patients after resection of T2-T4 primary tumors.

- The literature does not support the routine use of bone scans or brain imaging in asymptomatic patients.
- FDG-PET appears to be a useful adjunct to conventional imaging.

Anticipated Exceptions

Nephrogenic systemic fibrosis (NSF) is a disorder with a scleroderma-like presentation and a spectrum of manifestations that can range from limited clinical sequelae to fatality. It appears to be related to both underlying severe renal dysfunction and the administration of gadolinium-based contrast agents. It has occurred primarily in patients on dialysis, rarely in patients with very limited glomerular filtration rate (GFR) (ie, <30 mL/min/1.73m²), and almost never in other patients. There is growing literature regarding NSF. Although some controversy and lack of clarity remain, there is a consensus that it is advisable to avoid all gadolinium-based contrast agents in dialysis-dependent patients unless the possible benefits clearly outweigh the risk, and to limit the type and amount in patients with estimated GFR rates <30 mL/min/1.73m². For more information, please see the [ACR Manual on Contrast Media](#) [62].

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. 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	Effective Dose Estimate Range
None	0
Minimal	< 0.1 mSv
Low	0.1-1 mSv
Medium	1-10 mSv
High	10-100 mSv

Supporting Document(s)

- [ACR Appropriateness Criteria® Overview](#)
- Evidence table under review

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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.