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## Clinical Condition: Post-treatment Follow-up of Renal Cell Carcinoma

**Variant 1:** Asymptomatic patient; no known metastases.

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray chest</td>
<td>8</td>
<td>This procedure is not necessary if a chest CT is performed.</td>
<td>☀</td>
</tr>
<tr>
<td>CT abdomen and pelvis with IV contrast</td>
<td>8</td>
<td>This procedure is particularly appropriate if the primary disease was high stage and/or high grade. CT and MRI are alternative examinations.</td>
<td>☢☢☢☢</td>
</tr>
<tr>
<td>MRI abdomen and pelvis without and with IV contrast</td>
<td>8</td>
<td>This procedure is equivalent to CT.</td>
<td>O</td>
</tr>
<tr>
<td>CT abdomen and pelvis without and with IV contrast</td>
<td>6</td>
<td>This procedure is particularly appropriate if the patient is postablation or has a hereditary renal cancer syndrome. The noncontrast scan is not needed in the pelvis.</td>
<td>☢☢☢☢</td>
</tr>
</tbody>
</table>
| CT chest with IV contrast                           | 6      | This procedure is particularly appropriate if patients are considered at high risk for metastatic disease. | ☢☢|max
| CT chest without IV contrast                        | 5      | This procedure is particularly appropriate if patients are considered at high risk for metastatic disease. | ☢☢|
| MRI abdomen and pelvis without IV contrast          | 5      |                                                                           | O    |
| CT abdomen and pelvis without IV contrast           | 4      |                                                                           | ☢☢☢☢ |
| FDG-PET/CT whole body                               | 4      | This procedure may have a role when CT and bone scan findings are equivocal. | ☢☢☢☢ |
| US kidney retroperitoneal                           | 3      |                                                                           | O    |
| CT chest without and with IV contrast               | 2      |                                                                           | ☢☢|
| X-ray intravenous urography                         | 2      |                                                                           | ☢☢|
| Tc-99m bone scan whole body                         | 2      |                                                                           | ☢☢|
| MRI head without and with IV contrast               | 1      |                                                                           | O    |
| MRI head without IV contrast                        | 1      |                                                                           | O    |
| X-ray abdomen                                       | 1      |                                                                           | ☢☢|
| CT head without and with IV contrast                | 1      |                                                                           | ☢☢|
| CT head without IV contrast                         | 1      |                                                                           | ☢☢|
| CT head with IV contrast                            | 1      |                                                                           | ☢☢|
| X-ray skeletal survey                               | 1      |                                                                           | ☢☢|

**Rating Scale:** 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

*Relative Radiation Level

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POST-TREATMENT FOLLOW-UP OF RENAL CELL CARCINOMA

Expert Panel on Urologic Imaging: David D. Casalino, MD; Erick M. Remer, MD; Jay T. Bishoff, MD; Courtney A. Coursey, MD; Manjiri Dighe, MD; Howard J. Harvin, MD; Marta E. Heilbrun, MD; Massoud Majd, MD; Paul Nikolaidis, MD; Glenn M. Preminger, MD; Steven S. Raman, MD; Sheila Sheth, MD; Raghunandan Vikram, MD; Robert M. Weinfeld, MD.

Summary of Literature Review

Introduction/Background

In this document we address the appropriate imaging examinations for asymptomatic patients who have been treated for renal cell carcinoma (RCC) by radical nephrectomy or nephron-sparing surgery. We do not deal with patients who are undergoing systemic therapy for known recurrent RCC, patients in whom specific symptoms, signs, or laboratory studies suggest recurrent malignancy at a specific site, or patients for whom surgery is known to have left a residual tumor [1-6]; we do not address the imaging of nononcologic complications of surgery.

Follow-up is important for patients who have had radical or partial nephrectomy for RCC. Although patients may have been initially considered cured, local or distant metastatic recurrences may develop in 20%–50% of cases and require further management. Solitary metastasis may occasionally be treated by resection [7]. Until recently, systemic treatment for metastatic RCC was limited primarily to cytokine therapy, including interferon alfa and interleukin-2, [8,9]; however, the use of these agents has been limited by their toxicity as well as generally poor response rates. Targeted therapy using tyrosine kinase inhibitors is now available and has shown significant antitumor effects and meaningful clinical benefit [10,11].

Common anatomic locations of recurrences dictate the choice of imaging modalities. The tumor may recur in the resection site, especially if the primary tumor is large, high grade, or has a higher tumor (T) stage [4,12]. The incidence of tumor recurrence in the resection site is similar to or only slightly higher in patients who have had partial nephrectomy, compared with those who have had radical nephrectomy [7,13,14]. More commonly, however, tumor recurrence appears as distant metastases.

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 [15,16]. For instance, the risk of metastatic disease after nephrectomy increases with the higher stage of the primary tumor. In decreasing order of frequency, metastases most commonly appear in the lung (with or without mediastinal or hilar nodes), bone, 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) [4,16].

Other characteristics of metastatic disease from RCC are worth considering. Most lung metastases are (at least early in their history) asymptomatic [2]. Metastases in thoracic nodes usually indicate a short survival time. Most bone metastases are asymptomatic at the time of discovery; they can appear anywhere in the skeleton, but frequently appear in the lumbar spine, thoracic spine, and ribs (ie, the areas likely to be included in chest and abdomen examination). Most recurrences appear within 2–3 years after the initial resection but may not occur until decades later [5,17]. Tumor recurrences tend to occur earlier in patients who have higher T stages; tumors that appear after a long interval seem to be associated with a better prognosis [13]. Therefore, one can argue either that routine follow-up should be limited to only a few years or that halting follow-up after a brief period can deprive those patients, who might benefit most from treating recurrences, of an early diagnosis.

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Several stage-based surveillance protocols for RCC after radical or partial nephrectomy have been proposed. They are summarized as follows [1-6,14,16,18,19]:

- **For T1 tumors:** Because the risk of metastasis is low, most surveillance protocols recommend that history, physical examination, laboratory tests, and a chest radiograph be obtained every 6–12 months for 3 years and then annually until year 5. Others have suggested that no imaging be performed if the tumor is <2.5 cm. Most protocols do not recommend surveillance with abdominal computed tomography (CT) for patients who have T1 tumors.

- **For T2 primary tumors:** Most protocols recommend that history, physical examination, laboratory tests, and a chest radiograph be obtained every 6 months or annually for 3 years and then annually until year 5. Protocols vary widely regarding the use of abdominal CT. Some do not recommend CT at all, while others recommend CT at years 2 and 5. Still others recommend a CT annually or every other year for 3 years after surgery and 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 the first few years and annually thereafter. The vast majority of protocols recommend abdominal CT, with most recommending CT imaging every 3–6 months for 3 years after surgery and annually or every other year thereafter.

It is likely that incorporating molecular biomarkers, such as IMP-3 and p53, and microvascular invasion into prognostic models will improve their accuracy and allow for more individualized postoperative surveillance protocols in the future [20,21].

Preliminary studies suggest that fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) can be used to evaluate tumor recurrence in patients who have undergone surgery for RCC [22]. Park et al [23] showed FDG-PET/CT to be comparable to conventional imaging methods (chest radiography or chest CT, abdominal CT, and bone scan) in the postoperative surveillance of patients who have a higher risk RCC (T2, T3, and T4 tumors).

### Pulmonary Metastases

Because 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 [2,3,5,24,25]. If the chest radiograph is positive, CT almost inevitably follows in order to plan for and monitor 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 if there is just one lesion, which might be amenable to resection, than if there are several) and is probably more sensitive than chest radiograph in detecting metastases in the thoracic spine, ribs, shoulder bones, and nodes. CT is also more likely to display small granulomas that can masquerade as metastases and require further workup. Although the extra yield from chest CT compared to chest radiography is probably too small to warrant its use in routine surveillance [26], some physicians prefer to use chest CT, especially for patients who have T3 or T4 primary tumors or nodal disease. Mediastinal and hilar lymph node metastases are an independent prognostic factor for decreased survival after pulmonary metastasectomy in patients who have RCC, and systematic lymphadenectomy can potentially prolong survival [27]. A few studies have shown FDG-PET to be highly specific in detecting chest metastases, but the sensitivity is limited [28-30]. With advancements in MRI, whole-body MRI is feasible in the follow-up of patients who have RCC, but the accuracy of MRI for detecting pulmonary metastases is inferior to that of CT (71.9% versus 88.5%, P<0.001) [31].

### Abdominal Recurrences

Abdominal recurrences may occur at the surgical site or metastasize to the liver, lymph nodes, adrenal glands, bones, etc. Although a few studies have argued against routine imaging of the abdomen after resection of low-stage tumors (T1 and certain T2 tumors) [1,3,5,6], abdominal surveillance is commonly performed with a contrast-enhanced CT of the abdomen and pelvis. Although 2 retrospective studies concluded that CT imaging of the pelvis has limited value for RCC staging, the value of imaging the pelvis during follow-up after RCC treatment has not been determined [32,33]. CT is sensitive in detecting metastases in the resection site, contralateral kidney, adrenal glands, liver, and bones included in the examination [4,30,34,35]. In a recent study, Jain et al [36] suggested that an arterial phase of imaging is complementary to the portal venous phase in detecting RCC metastases to the liver and pancreas. In their study of 100 patients, 9 patients had metastases
detected only in the arterial phase, and management was changed for 2 patients. Use of MRI, preferably with contrast, should be considered in place of CT for younger patients, who will likely require multiple scans, and for patients with a history of allergy to iodinated contrast.

FDG-PET can be a useful adjunct to CT or MRI, particularly when a local recurrence is suspected in a renal fossa that could have postoperative and postradiation changes [30,37-39]. Performing separate nuclear medicine liver-spleen, bone, and renal scans is not practical. Ultrasound (US) has demonstrated some success in detecting intra-abdominal recurrences, but it has never been shown to be as sensitive as CT. Also, US is likely to be less sensitive in detecting small, resection-bed metastases, especially if the nephrectomy was performed on the left side and if the bowel occupies the surgical site. Radiography, angiography, and intravenous urography do not have a role in postoperative surveillance.

**Osseous Metastases**

Surveillance for metastases to the skeleton might be conducted using serial radionuclide bone scans [40-42] or not 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 [2,3,5,13,35], because the vast majority of bone metastases are symptomatic and incurable. When a bone metastasis is suspected, a bone scan is most often performed to survey the entire skeleton. If the bone scan is positive, a radiograph might be considered to rule out impending fracture. Whole-body MRI has a specificity similar to that of a bone scan (94% and 97%, respectively) and sensitivity (94%) superior to the bone scan (62%) for detecting bone metastases [43]. Identification of bone metastases can help facilitate treatment for pain relief and prevent pathologic fracture.

Relatively little has been written regarding the use of radiography or scintigraphy to monitor patients in the postoperative phase. FDG-PET can be used when CT or bone scan findings are equivocal [30]. FDG-PET can reveal bone metastases that are not detected by a bone scan; however, false-negative results have also been reported [28,44,45].

**Brain Metastases**

Surveillance protocols for RCC have not supported routine imaging of the brain to search for metastases in asymptomatic patients [3,5,13].

**Follow-up of Renal Cell Carcinoma After Ablative Therapies**

As an alternative to partial nephrectomy, energy-ablative therapies, such as cryoablation and radiofrequency ablation (RFA), are being used to treat small RCCs. These therapies have been shown to be effective and safe [46-52]. Cryoablation and RFA have similar efficacies for treating small renal masses [53], and the approach—percutaneous versus laparoscopic—does not seem to change oncologic efficacy [54,55]. Recent studies with follow-up data exceeding 5 years strongly support the long-term oncologic efficacy of RFA for RCCs under 4 cm [56-58]. Postablative CT and MRI play an important role in the evaluation of the ablation zone, surveillance for a residual or recurrent tumor, identification of procedure-related complications [46-50], and detection of new RCCs [59].

A multi-institutional study [60] found that 63 of 616 patients (10.2%) had residual or recurrent tumors after primary ablation. A residual tumor was defined as enhancement in the vicinity of the treated tumor on the first imaging study after the ablative procedure, and a 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 3-4 imaging studies (CT or MRI) in year 1 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 every 6–12 months after year 1. Zagoria et al [58] more recently suggested that patients be followed for at least 5 years with initial CT or MRI at 1–3 months postablation, then every 6 months for 3 intervals, and annually thereafter. Periodic chest radiography or CT was also recommended for thoracic surveillance. Others have suggested follow-up imaging at 4–6 weeks, 6 months, and annually thereafter [52,55,57]. Aron et al [61] reported that a history of contralateral radical nephrectomy for
RCC was an independent predictor of disease recurrence after cryoablation and that 1 patient who had preceding contralateral nephrectomy for RCC developed a duodenal metastasis 90 months after cryoablation.

Although US contrast agents have not yet been approved for clinical applications outside of cardiology in the United States, Meloni et al [62], from Vimercate General Hospital in Milan, Italy, showed that contrast-enhanced US, using a sulfur hexafluoride-filled microbubble contrast agent, was effective in patients following RFA. There was concordance between the results of contrast-enhanced US and contrast-enhanced CT or MRI findings for 27 of 28 treated tumors. Contrast-enhanced US missed only 1 of 7 cases of local tumor progression. Concordant results of the absence of tumor recurrence were noted for the remaining 21 tumors.

Summary
- Tumor recurrences, whether metastatic or local, are common after resection of localized RCC.
- The intensity and length of follow-up in patients who have RCC largely depends 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.
- Although there is no clear consensus regarding the timing of abdominal CT in routine surveillance, CT is generally included in the follow-up evaluation of patients after the resection of T2-T4 primary tumors.
- The literature does not support the routine use of bone scans or brain imaging for asymptomatic patients.
- FDG-PET appears to be a useful adjunct to conventional imaging.

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.

<table>
<thead>
<tr>
<th>Relative Radiation Level*</th>
<th>Adult Effective Dose Estimate Range</th>
<th>Pediatric Effective Dose Estimate Range</th>
</tr>
</thead>
<tbody>
<tr>
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<td>0 mSV</td>
<td>0 mSV</td>
</tr>
<tr>
<td>☢</td>
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<td>&lt;0.03 mSV</td>
</tr>
<tr>
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<td>0.03-0.3 mSV</td>
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<td>0.3-3 mSV</td>
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<tr>
<td>☢☢☢☢</td>
<td>10-30 mSV</td>
<td>3-10 mSV</td>
</tr>
<tr>
<td>☢☢☢☢☢</td>
<td>30-100 mSV</td>
<td>10-30 mSV</td>
</tr>
</tbody>
</table>

*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.
References


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.