Complete Summary

GUIDELINE TITLE

Follow-up of renal cell carcinoma.

BIBLIOGRAPHIC SOURCE(S)

Casalino DD, Francis IR, Baumgarten DA, Bluth EI, Bush WH Jr, Curry NS, Israel GM, Jafri SZ, Kawashima A, Papanicolaou N, Remer EM, Sandler CM, Spring DB, Fulgham P, Expert Panel on Urologic Imaging. Follow-up of renal cell carcinoma. [online publication]. Reston (VA): American College of Radiology (ACR); 2007. 5 p. [60 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Casalino DD, Choyke PL, Bluth EI, Bush WH Jr, Francis IR, Jafri SZ, Kawashima A, Kronthal A, Older RA, Papanicolaou N, Ramchandani P, Rosenfield AT, Sandler CM, Segal AJ, Tempany C, Resnick MI, Expert Panel on Urologic Imaging. Follow-up of renal cell carcinoma. [online publication]. Reston (VA): American College of Radiology (ACR); 2005. 4 p. [44 references]

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Renal cell carcinoma

GUIDELINE CATEGORY

Evaluation

CLINICAL SPECIALTY

Nephrology
Nuclear Medicine
Oncology
Pulmonary Medicine
Radiology
Surgery

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To evaluate the appropriateness of follow-up radiologic examinations for patients with renal cell carcinoma

TARGET POPULATION

Patients with renal cell carcinoma

INTERVENTIONS AND PRACTICES CONSIDERED

1. X-ray
    - Chest
    - Intravenous urography (IVU)
    - Abdomen
    - Radiographic survey, whole body
2. Computed tomography (CT)
    - Abdomen and pelvis
    - Chest
    - Head
3. Magnetic resonance imaging (MRI)
    - Abdomen and pelvis
    - Head
4. Fluorodeoxyglucose positron emission tomography (FDG-PET), whole body
5. Ultrasound (US) kidney transabdominal view
6. Nuclear medicine (NUC) bone scan whole body

MAJOR OUTCOMES CONSIDERED

Utility of radiologic procedures in follow-up evaluation of patients with renal cell carcinoma

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals, and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi

technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table and narrative as developed by the topic leader(s). Questionnaires are completed by the participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1 to 9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by this Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Follow-up of Renal Cell Carcinoma

Variant: Asymptomatic patient; no known metastases.

Radiologic Procedure	Rating	Comments	RRL*

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	8	Not necessary if CT chest performed.	Min
CT abdomen and pelvis	8	Particularly if primary was high stage and/or high grade.	High
MRI abdomen and pelvis	6	See comments regarding contrast in text under "Anticipated Expectations."	None
CT chest	6		Med
FDG PET, whole body	4	May have a role when CT and/or bone scan findings are equivocal.	High
US kidney transabdominal	3		None
X-ray intravenous urography	2		Low
NUC bone scan whole body	2		Med
MRI, head	1		None
X-ray abdomen	1		Low
CT, head	1		Low
X-ray radiographic survey whole body	1		Low
Rating Scale: 1=Least appropriate, 9=Most appropriate			***Relative Radiation Level**

Note: Abbreviations used in the table are listed at the end of the "Major Recommendations" field.

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.

Follow-up is important for patients who have had radical or partial nephrectomy for renal cell carcinoma. Although they may be thought to have been initially cured, local or metastatic recurrences may develop in 20% to 50% of them and

require management. Solitary metastases may occasionally be treated by resection. A nonspecific immune approach with cytokines has been used to treat metastatic disease, 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. 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. 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. More commonly, however, the 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. For instance, the risk of metastatic disease after nephrectomy increases with higher stage of the primary tumor. In decreasing order of frequency, metastases most commonly appear in lung (with or without mediastinal or hilar nodes), 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).

Other characteristics of metastatic disease from renal cell carcinoma are worth consideration. Most lung metastases are (at least early in their history) asymptomatic. Metastases in thoracic nodes usually indicate a very short survival. Most bone metastases are symptomatic at the time of discovery; they can appear anywhere in the skeleton, but frequently appear in the lumbar spine, thoracic spine, and ribs–that is, the areas likely to be included in chest and abdomen examination. Most recurrences appear within 2 to 3 years after the initial resection, but they may not occur until decades later. 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. 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:

- **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 less than 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, 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 or 6 months) CT imaging for 3 years after surgery and less frequently (yearly or every other year) thereafter.

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 x-ray and chest CT. Certainly, if the chest x-ray is chosen and is positive, CT almost inevitably follows in order to plan for and monitor the results of further therapy. The chest x-ray 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 x-ray 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. The extra yield from chest CT compared to chest radiography is probably too small to warrant its use in routine surveillance. While 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, the sensitivity is limited. 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 metastatic 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), 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. 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. Plain 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 post-radiation changes. 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, 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 loops of gut occupy 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 of small renal cell carcinomas as an alternative to partial nephrectomy. These therapies have been shown to be effective and safe. 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.

A recent multi-institutional study 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 two 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 exam 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 one. The required duration of follow-up is still unknown.

Osseous Metastases

Surveillance for the appearance of metastases to the skeleton might be done by serial radionuclide bone scans, or it might not be done at all unless the patient develops specific symptoms. Most authors do not suggest routine bone scanning to search for metastases without symptoms, 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 pending 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. FDG-PET may reveal bone metastases not detected on bone scan, but false negative results have also been reported.

Brain Metastases

There has been no literature that supports employing routine imaging of the brain to search for metastases from renal cell carcinoma in asymptomatic patients.

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, CBC, LFTs, and chest radiography. While there is no clear consensus regarding the timing of abdominal CT in routine surveillance, abdominal CT is generally included in the follow-up evaluation of patients after resection. 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, also known as nephrogenic fibrosing dermopathy) was first identified in 1997 and has recently generated substantial concern among radiologists, referring doctors and lay people. Until the last few years, gadolinium-based MR contrast agents were widely believed to be almost universally well tolerated, extremely safe and non-nephrotoxic, even when used in patients with impaired renal function. All available experience suggests that these agents remain generally very safe, but recently some patients with renal failure who have been exposed to gadolinium contrast agents (the percentage is unclear) have developed NSF, a syndrome that can be fatal. Further studies are necessary to determine what the exact relationships are between gadolinium-containing contrast agents, their specific components and stoichiometry, patient renal function and NSF. Current theory links the development of NSF to the administration of relatively high doses (e.g., >0.2 mM/kg) and to agents in which the gadolinium is least strongly chelated. The FDA has recently issued a "black box" warning concerning these contrast agents (http://www.fda.gov/cder/drug/InfoSheets/HCP/gcca_200705HCP.pdf).

This warning recommends that, until further information is available, gadolinium contrast agents should not be administered to patients with either acute or significant chronic kidney disease (estimated GFR <30 mL/min/1.73m^2), recent liver or kidney transplant or hepato-renal syndrome, unless a risk-benefit assessment suggests that the benefit of administration in the particular patient clearly outweighs the potential risk(s).

Abbreviations

- CT, computed tomography
- FDG PET, fluorodeoxyglucose positron emission tomography
- Med, medium
- Min, minimal
- MRI, magnetic resonance imaging
- NUC, nuclear medicine
- US, ultrasound

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Selection of appropriate radiologic imaging procedures for evaluation of patients with renal cell carcinoma

POTENTIAL HARMS

- Urography is likely to be less sensitive than computed tomography (CT) in the evaluation of abdominal recurrences; it may be falsely negative in patients with small intrarenal masses, and it is likely to miss all but the largest extrarenal masses.
- While fluorodeoxyglucose positron emission tomography (FDG PET) may reveal bone metastases not detected on bone scan, false negative results have also been reported.
- The relative radiation level is high for CT of the abdomen and pelvis and FDG-PET whole body; medium for CT of the chest and NUC bone scan whole body; and low for X-ray intravenous urography, X-ray of the abdomen, and X-ray radiographic survey of the whole body, and CT of the head.
- Some patients with renal failure who have been exposed to gadolinium contrast agents (the percentage is unclear) have developed nephrogenic systemic fibrosis, a syndrome that can be fatal.
- Until further information is available, gadolinium contrast agents should not be administered to patients with either acute or significant chronic kidney disease (estimated GFR <30 mL/min/1.73m^2), recent liver or kidney transplant or hepato-renal syndrome, unless a risk-benefit assessment suggests that the benefit of administration in the particular patient clearly outweighs the potential risk(s).

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (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 radiologist, radiation oncologist, 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 exams 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 U.S. Food and Drug Administration (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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Casalino DD, Francis IR, Baumgarten DA, Bluth EI, Bush WH Jr, Curry NS, Israel GM, Jafri SZ, Kawashima A, Papanicolaou N, Remer EM, Sandler CM, Spring DB, Fulgham P, Expert Panel on Urologic Imaging. Follow-up of renal cell carcinoma. [online publication]. Reston (VA): American College of Radiology (ACR); 2007. 5 p. [60 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 (revised 2007)

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

SOURCE(S) OF FUNDING

American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Urologic Imaging

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: David D. Casalino, MD; Isaac R. Francis, MD; Deborah A. Baumgarten, MD; Edward Bluth, MD; William H. Bush, Jr., MD; Nancy S. Curry, MD; Gary M. Israel, MD; S. Zafar H. Jafri, MD; Akira Kawashima, MD, Nicholas Papanicolaou, MD; Erick M. Remer, MD; Carl M. Sandler, MD; David B. Spring, MD; Pat Fulgham, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

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The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® *Anytime*, *Anywhere*™ (PDA application). Available from the ACR Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.
- ACR Appropriateness Criteria®. Relative radiation level information. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

PATIENT RESOURCES

None available

NGC STATUS

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