



NCCN Clinical Practice Guidelines in Oncology™

Kidney Cancer

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NCCN Kidney Cancer Panel Members

* Robert J. Motzer, MD/Chair † ‡
Memorial Sloan-Kettering Cancer
Center

Graeme B. Bolger, MD †
University of Alabama at Birmingham
Comprehensive Cancer Center

Barry Boston, MD † £
St. Jude Children's Research
Hospital/University of Tennessee
Cancer Institute

Michael A. Carducci, MD †
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

Mayer Fishman, MD, PhD † ‡ †
H. Lee Moffitt Cancer Center &
Research Institute at the University of
South Florida

Steven L. Hancock, MD § †
Stanford Hospital and Clinics

Ralph J. Hauke, MD †
UNMC Eppley Cancer Center at The
Nebraska Medical Center

Gary R. Hudes, MD † ‡
Fox Chase Cancer Center

Eric Jonasch, MD †
University of Texas M. D. Anderson
Cancer Center

Philip Kantoff, MD †
Dana-Farber/Partner's CancerCare

Timothy M. Kuzel, MD ‡
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Paul H. Lange, MD ☉
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Ellis G. Levine, MD †
Roswell Park Cancer Institute

Chris Logothetis, MD ☉
The University of Texas M. D. Anderson
Cancer Center

Kim A. Margolin, MD † ‡
City of Hope Cancer Center

Kamal Pohar, MD ☉
Arthur G. James Cancer Hospital &
Richard J. Solove Research
Institute at The Ohio State
University

Bruce G. Redman, DO †
University of Michigan
Comprehensive Cancer Center

Cary N. Robertson, MD ☉
Duke Comprehensive Cancer
Center

Wolfram E. Samlowski, MD †
Huntsman Cancer Institute at the
University of Utah

Joel Sheinfeld, MD ☉
Memorial Sloan-Kettering Cancer
Center

† Medical oncology
‡ Hematology/hematology oncology
§ Radiotherapy/Radiation oncology
£ Supportive Care including Palliative,
Pain Management, Pastoral care and
Oncology social work
† Internal medicine
☉ Urology
* Writing committee member

Continue

Table of Contents

[NCCN Kidney Cancer Panel Members](#)

[Workup, Primary Treatment, and Follow-up \(KID-1\)](#)

[First- and Second-Line Therapy for Relapse and Stage IV](#)

[Medically or Surgically Unresectable Disease \(KID-2\)](#)

[Guidelines Index](#)

[Print the Kidney Cancer Guideline](#)

[For help using these documents, please click here](#)

[Staging](#)

[Manuscript](#)

[References](#)

Clinical Trials: The NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, [click here: nccn.org/clinical_trials/physician.html](http://nccn.org/clinical_trials/physician.html)

NCCN Categories of Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Consensus](#)

[Summary of Guidelines Updates](#)

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representations or warranties of any kind, regarding their content use or application and disclaims any responsibility for their application or use in any way. These guidelines are copyrighted by National Comprehensive Cancer Network. All rights reserved. These guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2007.

Summary of the Guidelines updates

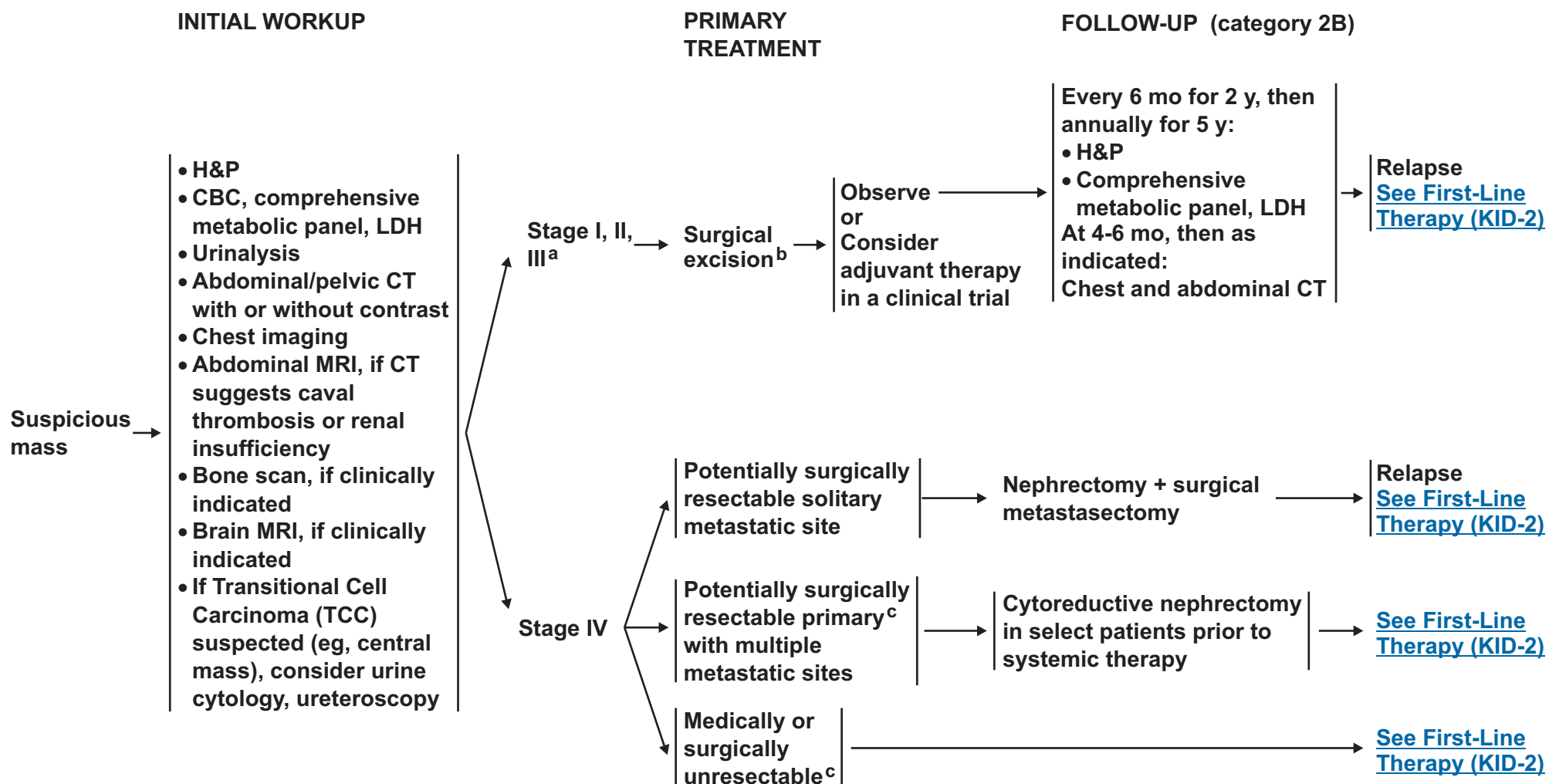
The 2.2007 version represents changes to the manuscript discussion of temsirolimus. ([MS-6](#))

Summary of changes in the 1.2007 version of the Kidney Cancer Guidelines from the 2.2006 version include:

- The recommendations in the workup section were modified. An abdominal/pelvic CT can be performed without contrast. The chest x-ray and chest CT recommendations were changed to chest imaging. The MRI was clarified that it is an abdominal MRI. A bullet was added to consider urine cytology and ureteroscopy if transitional cell carcinoma is suspected. ([KID-1](#))
- The Primary Treatment recommendation is now the same for Stage I, II, and III. The recommendation is a surgical excision with reference to the Principles of Surgery attachment. ([KID-1](#))
- Chest-x-ray was removed from the list of Follow-up recommendations. Chest CT was added with abdominal CT. ([KID-1](#)).
- In the Stage IV section, the category of "Potentially surgically resectable primary and good performance status" was changed to "Potentially surgically resectable primary with multiple metastatic sites". ([KID-1](#))
- For patients with relapse or stage IV and medically or surgically unresectable, the recommendations for IFN and Low dose IL-2 were removed as treatment options in first-line therapy for predominant clear cell histology. ([KID-2](#))
- Second-line therapy was changed to Subsequent therapy and the category designations for sunitinib and sorafenib were clarified to state category 1 following cytokine therapy and category 2B following tyrosine kinase inhibitor therapy. ([KID-2](#))
- In the Principles of Surgery attachment ([KID-A](#)), the size requirement was removed for selected patients with small unilateral tumors. A bullet was added that observation or emerging ablative techniques can be considered for patients who are not surgical candidates.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



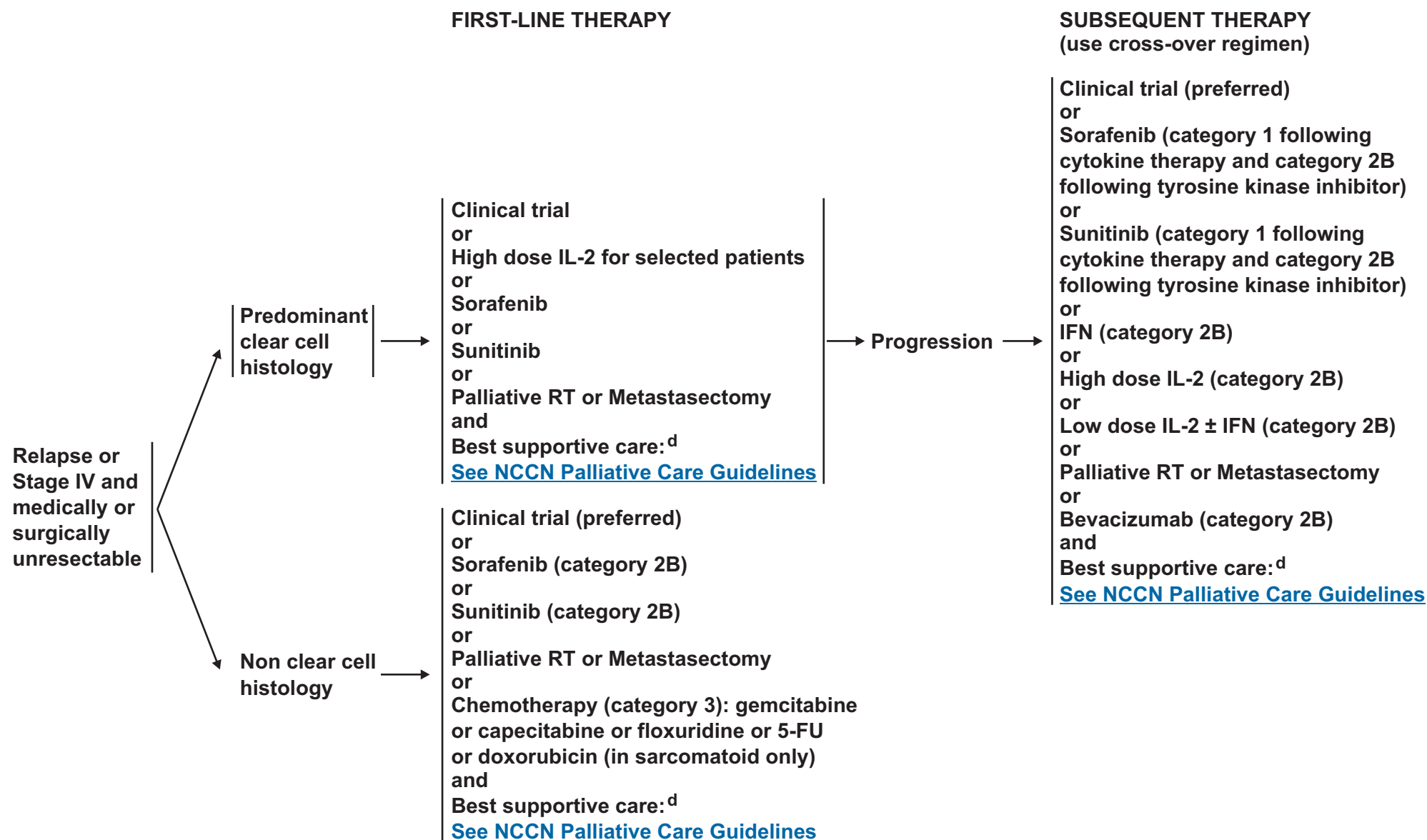
^aPatients are encouraged to participate in clinical trials.

^b[See Principles of Surgery \(KID-A\)](#).

^cIndividualized treatment based upon symptoms and extent of metastatic disease.

Note: All recommendations are category 2A unless otherwise indicated.

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^dBisphosphonates for bony metastases.

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PRINCIPLES OF SURGERY

- Nephron-sparing surgery may be indicated in selected patients, for example:
 - ▶ Multiple primaries
 - ▶ Uninephric state
 - ▶ Renal insufficiency
 - ▶ Selected patients with small unilateral tumors
- Lymph node dissection is optional
- Adrenal gland may be left if uninvolved and tumor is not high risk, on the basis of size and location
- Special teams may be required for extensive inferior vena cava involvement
- Observation or emerging energy ablative techniques can be considered for patients who are not surgical candidates.

[Back to Primary Treatment \(KID-1\)](#)

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Staging (2002 AJCC 6th Edition)

Table 1

AJCC Staging of Renal Cell Carcinoma

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T3	Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
T3a	Tumor directly invades the adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or vena cava below the diaphragm
T3c	Tumor grossly extends into vena cava above diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia

Regional Lymph Nodes (N)*

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in a single regional lymph node
N2	Metastases in more than one regional lymph node

* *Note:* Laterality does not affect the N classification

Note: If a lymph node dissection is performed, then pathologic evaluation would ordinarily include at least eight nodes.

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
Stage IV	T3	N0	M0
	T3	N1	M0
	T3a	N0	M0
	T3a	N1	M0
	T3b	N0	M0
	T3b	N1	M0
	T3c	N0	M0
	T3c	N1	M0
	T4	N0	M0
	T4	N1	M0
Any T	N2	M0	
Any T	Any N	M1	

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Manuscript

NCCN Categories of Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

An estimated 38,890 Americans will be diagnosed with kidney cancer and 12,840 will die of the disease in the United States in 2006.¹ Renal cell carcinoma (RCC) comprises approximately 2% of all malignancies, with a median age at diagnosis of 65 years. The rate of RCC has increased by 2% per year for the past 65 years. The reason for this increase is unknown. Approximately 90% of renal tumors are RCCs, and 85% of these are clear cell tumors.² Other less common cell types include papillary, chromophobe, and Bellini duct (collecting duct) tumors. Collecting duct carcinoma comprises less than 1% of kidney cancer cases. Medullary renal carcinoma is a variant of collecting duct renal carcinoma and was initially described as occurring in patients who are sickle-cell–trait positive.

Smoking and obesity are among the risk factors for RCC development. Several hereditary types of RCC also exist, with von Hippel-Lindau disease (VHL) the most common, caused by a mutation in the *VHL* gene predisposing to clear cell carcinoma.^{3,4}

The most important prognostic determinants of 5-year survival are the tumor grade, local extent of the tumor, presence of regional nodal metastases, and evidence of metastatic disease at presentation. RCC primarily metastasizes to the lung, bone, brain, liver, and adrenal gland.³

Initial Evaluation and Staging (KID-1)

Patients with RCC typically present with a suspicious mass involving the kidney that has been visualized using a radiographic study, often a computed tomographic (CT) scan. Common complaints that lead to the detection of a renal mass are hematuria, flank mass, and flank pain. Less frequently, patients present with signs or symptoms resulting from metastatic disease, including bone pain, adenopathy, and pulmonary symptoms attributable to lung parenchyma or mediastinal metastases. Other presentations include fever, weight loss, anemia, or a varicocele. RCC in younger patients may indicate von Hippel-Lindau disease, and these patients should be referred to a hereditary cancer clinic for further evaluation.

Renal tumors may also be identified on an imaging study (e.g., CT or ultrasound) performed to evaluate other conditions. As the use of imaging methods has become more widespread, the frequency of incidental detection of RCC has increased. These small low-stage carcinomas may be treated with more conservative surgical

approaches, such as nephron-sparing techniques, discussed in later sections.

A thorough physical examination should be performed with special attention to detecting supraclavicular adenopathy, an abdominal mass, lower extremity edema, a varicocele, or subcutaneous nodules.

Laboratory evaluation includes a complete blood cell count, comprehensive metabolic panel (including serum calcium, liver function studies, lactate dehydrogenase [LDH], and serum creatinine), coagulation profile, and urinalysis.

CT of the abdomen and pelvis with and without contrast and chest imaging (either chest radiograph or CT scan) are essential studies in the initial workup. Abdominal magnetic resonance imaging (MRI) is used to evaluate the inferior vena cava if tumor involvement is suspected, or it can be used instead of CT for detecting renal masses and for staging ([ST-1](#)) when contrast material cannot be administered because of allergy or renal insufficiency. A central renal mass may suggest the presence of a transitional cell carcinoma; if so, urine cytology or uteroscopy should be considered. |

A bone scan is not routinely performed unless the patient has an elevated serum alkaline phosphatase or complains of bone pain. CT or MRI of the brain is performed if the history or physical examination suggests brain metastases. A positron emission tomography scan is not a routine part of the initial workup.

Primary Treatment and Staging ([KID-1](#))

CT-guided needle biopsy of the kidney or other accessible sites or cytoreductive nephrectomy can be used to diagnose patients with

suspected RCC. Selected patients with metastases can be diagnosed during cytoreductive nephrectomy.

Surgical resection remains the only effective therapy for clinically localized RCC; with options including radical nephrectomy and nephron-sparing surgery ([KID-A](#)). A radical nephrectomy includes a perifascial resection of the kidney, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland. The lymph node dissection is not considered therapeutic but does provide prognostic information, because virtually all patients with nodal involvement subsequently relapse with distant metastases despite lymphadenectomy. Also, ipsilateral adrenal gland resection may only be necessary for patients who have large upper-pole tumors or abnormal-appearing adrenal glands appearing on CT.

Radical nephrectomy is the preferred treatment if the tumor extends into the inferior vena cava. Approximately one half of patients with these tumors experience long-term survival. Resection of a caval or atrial thrombus often requires the assistance of cardiovascular surgeons and may entail the techniques of veno-venous or cardiopulmonary bypass, with or without circulatory arrest. Patients considered for resection of a caval or atrial tumor thrombus should undergo surgery performed by experienced teams because treatment-related mortality approaches 10%, depending on the local extent of the primary tumor and the level of vena caval extension.

Originally, nephron-sparing surgery was indicated only in clinical settings in which a radical nephrectomy would render the patient functionally anephric, necessitating dialysis ([KID-A](#)). These settings

include RCC in a solitary kidney, RCC in one kidney with inadequate contralateral renal function, and bilateral synchronous RCC. However, nephron-sparing surgery has been used increasingly in patients with T1a and T1b renal tumors (i.e., up to 7 cm in greatest dimension) and a normal contralateral kidney, with equivalent outcomes to radical nephrectomy.⁵⁻⁷ Nephron-sparing surgery is most appropriate for tumors located over the upper or lower pole or in a peripheral location. Patients with a hereditary form of RCC, such as VHL disease, also should be considered for nephron-sparing therapy.

Patients in satisfactory medical condition should undergo surgical excision of stage I through III tumors. However, a small set of elderly or infirm patients with small tumors may be offered surveillance alone or energy ablative techniques, such as radiofrequency ablation or cryoablation ([KID-A](#))

The estimated 5-year survival rate is 95% for patients presenting with stage I disease, 88% for stage II, 59% for stage III, and 20% for stage IV.³

Management After Surgical Excision of Stages I–III Tumors

After surgical excision, 20% to 30% of patients with localized tumors experience relapse. Lung metastasis is the most common site of distant recurrence, occurring in 50% to 60% of patients.⁸ The median time to relapse after surgery is 1 to 2 years, with most relapses occurring within 3 years. Longer disease-free intervals between diagnosis and recognition of metastatic disease are associated with longer projected survival.

Adjuvant treatment after nephrectomy has no established role in patients who have undergone a complete resection of their tumor. No systemic therapy has been shown to reduce the likelihood of relapse. Randomized trials comparing adjuvant interferon α (IFN- α) or high-dose interleukin (IL)-2 with observation alone in patients who had locally advanced, completely resected RCC showed that no delay in time to relapse or improvement in survival was associated with adjuvant therapy.⁹⁻¹¹ Observation remains standard care after nephrectomy, and eligible patients should be enrolled in randomized clinical trials, if available. Two kinase inhibitors, sunitinib and sorafenib, recently showed marked activity in treating metastatic RCC. This success has created interest in investigating these agents in the adjuvant setting, and participation in these clinical trials is recommended ([KID-1](#)). Radiation therapy after nephrectomy is not beneficial, even in patients with nodal involvement or who have undergone incomplete tumor resection.

Follow-up for patients with completely resected disease includes an abdominal and chest CT scan obtained approximately 4 to 6 months after surgery to serve as a baseline, and then as indicated. Patients are seen periodically and each visit should include a history, physical examination, and comprehensive metabolic panel (e.g., blood urea nitrogen, serum creatinine, calcium levels, LDH, liver function tests) ([KID-1](#)).

Management of Stage IV Disease

Patients with stage IV disease are also candidates for surgery. For example, lymph nodes suspected for disease on CT may be hyperplastic and not involved with the tumor; therefore, patients with

minimal regional adenopathy can be surgical candidates. In addition, the small subset of patients with potentially surgically resectable primary RCC and a solitary resectable metastatic site are candidates for nephrectomy and surgical metastasectomy. Candidates include patients who 1) initially present with primary RCC and a solitary site of metastasis or 2) develop a solitary recurrence after nephrectomy. Sites of solitary metastases that are amenable to this approach include the lung, bone, and brain. Both the primary tumor and the metastasis may be resected during the same operation or at different times. Most patients who undergo resection of a solitary metastatic site experience recurrence at the primary or metastatic site. However, long-term survival has been seen in some patients.¹² In some instances, radiation therapy may be administered after bone metastases.

Cytoreductive nephrectomy before systemic therapy is recommended in patients with a potentially surgically resectable primary and multiple metastases ([KID-1](#)). Randomized trials showed a benefit of cytoreductive nephrectomy followed by IFN therapy. The Southwest Oncology Group (SWOG 8949) and the European Organization for the Research and Treatment of Cancer randomized patients with metastatic disease to undergo either nephrectomy followed by IFN therapy or treatment with IFN therapy alone. A combined analysis of these trials showed that median survival favored the surgery plus IFN group (13.6 vs. 7.8 months for IFN alone).^{13–15}

Patient selection is important to identify patients who might benefit from cytoreductive therapy. Patients most likely to benefit from nephrectomy before systemic therapy are those with lung-only metastases, good prognostic features, and good performance status.

Patients with hematuria or other symptoms related to the primary tumor may be considered for palliative nephrectomy. Treatment for the palliation of symptoms, especially in patients with marginal performance status and evidence of metastatic disease, includes optimal pain management (See [NCCN Cancer Pain Guideline](#)).

Patients with metastatic, recurrent, or unresectable clear cell RCC should undergo first-line systemic therapy with either high-dose IL-2, sorafenib, or sunitinib ([KID-2](#)). Over the past 15 years, various combinations and dosages of IL-2 and IFN have been studied in randomized trials. These studies have suggested that high-dose IL-2 results in higher response rates compared with low-dose IL-2.^{16–18} Although toxicity is a concern, some patients may benefit with durable responses. Most recently, McDermott et al.¹⁹ compared a combination of outpatient IL-2 and IFN with high-dose IL-2 in a phase III trial of 192 patients with metastatic RCC. The response rate for the high-dose IL-2 group was 23.2% compared with 9.9% in the outpatient IL-2/IFN group. Therefore, patients with a high Karnofsky performance status (> 80), especially patients with low-volume or lung-predominant disease, may be offered high-dose IL-2.

The U.S. Food and Drug Administration approved 2 kinase inhibitors, sorafenib and sunitinib, for treating patients with metastatic RCC. Escudier et al.²⁰ reported the results of a phase III study in which 884 patients with disease progression after 1 prior immunotherapy were randomized to treatment with sorafenib or placebo. Progression-free survival on the sorafenib arm was 24 weeks versus 12 weeks for patients treated with placebo; a statistically significant improvement. Although the objective response rate was 2% by independent review,

minor responses or stable disease were observed in 78% of the patients. Ratain et al.²¹ reported on the results of a phase II placebo-controlled “discontinuation trial” of sorafenib in 202 patients with metastatic RCC who were treated with sorafenib for 12 weeks and then reevaluated. Those who experienced at least a 25% tumor shrinkage continued on the sorafenib, and those with progressive disease discontinued the drug. The remaining “potential responders” were randomized to either continue or stop treatment with sorafenib. Therefore, only 65 of the original 202 patients were ultimately randomized. At 24 weeks, 50% of the sorafenib group was progression-free compared with 18% of the placebo group; a clinically and statistically significant difference. Both trials were conducted primarily in patients after progression to cytokine therapy. Data from sorafenib in the first-line setting are awaiting the results of a multicenter randomized phase II trial.

Motzer et al.²² reported on the results of 2 phase II studies of sunitinib. In one, 63 patients with metastatic RCC that had progressed on cytokine therapy underwent sunitinib monotherapy. A 40% partial response rate was observed and 27% of patients experienced stable disease lasting more than 3 months. The second study enrolled 106 patients who underwent failed prior cytokine therapy.²³ This single-arm study had a 34% partial response rate with a median progression-free survival of 8.3 months. Results of an interim analysis from a randomized phase III trial of sunitinib as first-line therapy for patients with previously untreated, metastatic disease were presented in 2006.²⁴ This study randomized 750 patients to undergo treatment with either sunitinib or IFN- α . The median progression-free survival was 47.3 weeks for the sunitinib group compared with 24.9 weeks for the IFN

group, and the objective response rates for sunitinib and IFN were 35.7% and 8.8%, respectively; a clinically and statistically significant difference.

These kinase inhibitors are generally well tolerated, with manageable toxicities reported in these early studies, representing a major addition to the oncology armamentarium in a disease state that has few other available therapies. Although the initial results of kinase inhibitors are very promising, mature data on overall survival are awaited. Additional studies evaluating sorafenib and sunitinib as combined therapy or in selected clinical settings are either planned or currently accruing.

The aforementioned studies focused on patients with the predominant histology of clear cell carcinoma, and all 3 treatment options (i.e., high-dose IL-2, sunitinib, and sorafenib) are considered category 2A. However, limited data are available regarding other histologies of RCC, and thus enrollment in clinical trials is the preferred strategy, and the same regimens for non-clear cell histologies are considered 2B ([KID-2](#)). Results of clinical trials evaluating gemcitabine with or without 5FU or capecitabine suggest minor activity in patients experiencing progression after treatment with cytokines, and can be considered category 3.^{25–28}

Clinical trials are preferred for second-line and subsequent therapy for metastatic disease. Sorafenib and sunitinib are also considered category 1 when used after cytokine therapy,^{20,22,23} and are considered category 2B when used after a prior kinase inhibitor therapy. IFN, IL-2, and bevacizumab are also considered a category 2B recommendation.

Other agents being evaluated for managing advanced RCC include AG013736 and temsirolimus (CCI-779), a mammalian target of rapamycin [mTOR] kinase inhibitor. Results of a phase III trial of temsirolimus, IFN, or a combination of temsirolimus plus IFN as first-line therapy for 626 patients with metastatic disease were reported in 2006.²⁹ The overall survival for those receiving temsirolimus monotherapy was 10.9 months compared with 7.3 months for those treated with IFN alone and 8.4 months for those receiving combination therapy. Overall survival was significantly longer for patients who received temsirolimus compared with those treated with interferon, but the difference in overall survival of combined temsirolimus and interferon compared with interferon alone was not significantly different. The results of a phase III study comparing IFN with IFN combined with bevacizumab are pending.

Supportive care remains a mainstay of therapy for patients with metastatic RCC. This includes surgery for patients with solitary brain metastasis, spinal cord compression, or impending or actual fractures in weight-bearing bones. Also, radiation therapy along with bisphosphonates is considered for palliation, particularly of painful bone metastases. The frequency of clinic visits or radiographic and laboratory assessments depends on the individual needs of the patient.

Disclosures for the NCCN Kidney Cancer Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers' bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiron Corporation, Genentech, Merck & Co., Pfizer, Sanofi-Aventis, Onyx Pharmaceuticals, Schering Plough, and Wyeth.

Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

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