NCCN Kidney Cancer Panel Members

* Robert J. Motzer, MD/Chair † Memorial Sloan-Kettering Cancer Center
    Neeraj Agarwal, MD ‡ Huntsman Cancer Institute at the University of Utah
    Clair Beard, MD § Dana-Farber/Brigham and Women’s Cancer Center
    Sam Bhayani, MD ω Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine
    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
    Sam S. Chang, MD ω Vanderbilt-Ingram Cancer Center
    Toni K. Choueiri, MD †§ Dana-Farber/Brigham and Women’s Cancer Center
    Robert A. Figlin, MD † City of Hope Comprehensive Cancer Center
    Mayer Fishman, MD, PhD †§ ‡ H. Lee Moffitt Cancer Center & Research Institute
    Steven L. Hancock, MD § ‡ Stanford Comprehensive Cancer Center
    Gary R. Hudes, MD †§ Fox Chase Cancer Center
    Eric Jonasch, MD † The University of Texas M. D. Anderson Cancer Center
    Timothy M. Kuzel, MD †§ Robert H. Lurie Comprehensive Cancer Center of Northwestern University
    Paul H. Lange, MD ω Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance
    Ellis G. Levine, MD † Roswell Park Cancer Institute
    Kim A. Margolin, MD †§ Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance
    M. Dror Michaelson, MD, PhD † Massachusetts General Hospital Cancer Center
    Thomas Olencki, DO ‡ The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute
    Roberto Pili, MD † Roswell Park Cancer Institute
    Bruce G. Redman, DO † University of Michigan Comprehensive Cancer Center
    Cary N. Robertson, MD ω Duke Comprehensive Cancer Center
    Charles J. Ryan, MD † UCSF Helen Diller Family Comprehensive Cancer Center
    Lawrence H. Schwartz, MD ‡ Memorial Sloan-Kettering Cancer Center
    Joel Sheinfeld, MD † memorial Sloan-Kettering Cancer Center
    Jue Wang, MD † UNMC Eppley Cancer Center at The Nebraska Medical Center

† Medical oncology ‡ Hematology/hematology oncology § Radiotherapy/Radiation oncology ω Urology
§ Radiotherapy/Radiation oncology † Medical oncology £ Supportive Care including Palliative, Pain Management, Pastoral care and Oncology social work £ Supportive Care including Palliative, Pain Management, Pastoral care and Oncology social work
† Internal medicine
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### Summary of the Guidelines updates

Summary of changes in the 2.2010 version of the Kidney Cancer Guidelines from the 1.2010 version include:

**KID-2:**
- For predominant clear cell histology, first-line therapy, “pazopanib” was added as an option with a category 1 designation.
- For non-clear cell histology, first-line therapy, “pazopanib” was added as an option with a category 3 designation.
- Footnote f, “Category 1 recommendations are listed in order of FDA approval” is new to the page.

**KID-3:**
- For predominant clear cell histology, subsequent therapy, “pazopanib” was added as an option with a category 1 designation following cytokine therapy and category 3 designation following tyrosine kinase inhibitor therapy.
- Footnote i, “Tyrosine kinase inhibitors with a category 1 designation are listed in order of FDA approval” is new to the page and footnote ‘j’ was modified by adding “or pazopanib.”

Summary of changes in the 1.2010 version of the Kidney Cancer Guidelines from the 2.2009 version include:

**KID-1:**
- For stage I-III, after primary treatment of surgical excision, “Consider adjuvant therapy in a clinical trial” was clarified as “clinical trial”.
- For stage I-III follow-up “Abdominal/renal ultrasound and chest x-ray” were added as an option for imaging.
- Footnote a, “Biopsy may be considered to confirm malignancy and guide surveillance strategies” was added to the page.
- Footnote d, “UCLA Integrated Staging System (UISS) surveillance protocol based on risk group stratification of high, intermediate, low, or nodal status has been published and may be considered as an alternate to the listed follow-up for patients with localized or locally advanced RCC. See Surveillance Protocol Based on UISS Risk (KID-B)” was added to the page.
- Footnote e, “No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient and tumor characteristics.”

**KID-2:**
- For predominant clear cell histology, subsequent therapy:
  - “Preferred” was removed from clinical trial.
  - “IFN, low dose IL-2 ± IFN, and high dose IL-2” regimens were modified as “IFN or IL-2” and is a category 2B recommendation.

**KID-A:**
- Principles of Surgery:
  - Second bullet was modified by adding, “regional” to lymph node dissection is optional.
  - Last bullet was modified by adding “Biopsy of small lesions may be considered to confirm diagnosis of malignancy and guide surveillance strategies.”

**KID-B:**
- An alternate surveillance protocol based on the UCLA Integrated Staging System (UISS) for patients following surgical resection for localized and locally advanced renal cell cancer is new to the guidelines.

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.
INITIAL WORKUP

**Suspicious mass**

- H&P
- CBC, comprehensive metabolic panel, LDH
- Urinalysis
- Abdominal/pelvic CT or abdominal MRI with or without contrast depending on renal insufficiency
- Chest imaging
- Bone scan, if clinically indicated
- Brain MRI, if clinically indicated
- If urothelial carcinoma suspected (e.g., central mass), consider urine cytology, ureteroscopy
- Consider needle biopsy, if clinically indicated

**Stage I, II, III**

- Surgical excision (See KID-A)

**Stage IV**

- Potentially surgically resectable solitary metastatic site
- Potentially surgically resectable primary with multiple metastatic sites
- Medically or surgically unresectable

PRIMARY TREATMENT

- Observation or Clinical trial

FOLLOW-UP (category 2B)

- Every 6 mo for 2 y, then annually for 5 y:
  - H&P
  - Comprehensive metabolic panel, LDH
  - At 4-6 mo, then as indicated:
    - Chest and abdominal CT or abdominal/renal ultrasound and chest x-ray

Relapse

- See First-Line Therapy (KID-2)

**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.

- Biopsy of small lesions may be considered to confirm diagnosis of malignancy and guide surveillance strategies.
- Patients are encouraged to participate in clinical trials.
- Individualized treatment based upon symptoms and extent of metastatic disease.
- UCLA Integrated Staging System (UISS) surveillance protocol based on risk group stratification of high, intermediate, low, or nodal status has been published and may be considered as an alternate to the listed follow-up for patients with localized or locally advanced RCC. See Surveillance Protocol Based on UISS Risk (KID-B)
- No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient and tumor characteristics.
FIRST-LINE THERAPY

- Predominant clear cell histology
  - Clinical trial
  - Sunitinib (category 1)
  - Temsirolimus (category 1 for poor-prognosis patients, category 2B for selected patients of other risk groups)
  - Bevacizumab + IFN (category 1)
  - Pazopanib (category 1)
  - High dose IL-2 for selected patients
  - Sorafenib for selected patients
  - Best supportive care: See NCCN Palliative Care Guidelines

- Non clear cell histology
  - Relapse or Stage IV and medically or surgically unresectable
    - Clinical trial (preferred)
    - Temsirolimus (category 1 for poor-prognosis patients, category 2A for other risk groups)
    - Sorafenib
    - Sunitinib
    - Pazopanib (category 3)
    - Chemotherapy (category 3): gemcitabine or capecitabine or flocuridine or 5-FU or doxorubicin (in sarcomatoid only)
    - Best supportive care: See NCCN Palliative Care Guidelines

- See Subsequent Therapy (KID-3)

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.

Category 1 recommendations are listed in order of FDA approval.
Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival (KID-C).

Best supportive care can include palliative RT, metastasectomy, or bisphosphonates for bony metastases.
**Subsequent Therapy**

<table>
<thead>
<tr>
<th>Predominant clear cell histology</th>
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</table>

**Clinical trial**
- or
- Everolimus (category 1 following tyrosine kinase inhibitor)\(^i\)
- or
- Sorafenib (category 1 following cytokine therapy and category 2A following other tyrosine kinase inhibitor)\(^i\)
- or
- Sunitinib (category 1 following cytokine therapy and category 2A following other tyrosine kinase inhibitor)\(^i\)
- or
- Pazopanib (category 1 following cytokine therapy and category 3 following other tyrosine kinase inhibitor)\(^i\)
- or
- Temsirolimus (category 2A following cytokine therapy and category 2B following tyrosine kinase inhibitor)\(^i\)
- or
- Bevacizumab (category 2B)
- or
- IFN or IL-2 (category 2B)
- and
- Best supportive care: \(^h\) See NCCN Palliative Care Guidelines

\(^h\)Best supportive care can include palliative RT, metastasectomy, or bisphosphonates for bony metastases.

\(^i\)Tyrosine kinase inhibitors with a category 1 designation are listed in order of FDA approval.

\(^j\)For example, sorafenib, sunitinib, or pazopanib.
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PRINCIPLES OF SURGERY

- Nephron-sparing surgery is appropriate in selected patients, for example:
  - Multiple primaries
  - Uninephric state
  - Renal insufficiency
  - Selected patients with small unilateral tumors

- Regional 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 (e.g., cryosurgery or radiofrequency ablation) can be considered for patients who are not surgical candidates.

- Emerging energy ablative techniques (e.g., cryosurgery or radiofrequency ablation) are currently considered an option by some experts for selected small tumors. Though a rigorous comparison with surgical resection (i.e., total or partial nephrectomy by open or laparoscopic techniques) has not been done. Biopsy of small lesions may be considered to confirm diagnosis of malignancy and guide surveillance strategies.
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* Includes complete blood count, serum chemistries and liver function tests.
† A chest radiograph can be alternated with a chest CT after 3 years of follow-up.


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.
Flow chart for determination of UISS risk group assignment of patients with localized or locally advanced RCC. Start from left to right using 1997 AJCC N stage and T stage, Fuhrman grade, and ECOG-PS.

PREDICTORS OF SHORT SURVIVAL

Poor-prognosis patients are defined as those with ≥ 3 predictors of short survival.

- Lactate dehydrogenase level > 1.5 times upper limit of normal
- Hemoglobin level < lower limit of normal
- Corrected serum calcium level > 10 mg/dl (2.5 mmol/liter)
- Interval of less than a year from original diagnosis to the start of systemic therapy
- Karnofsky performance score ≤ 70
- ≥ 2 sites of organ metastasis

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## Table 1

**AJCC Staging of Renal Cell Carcinoma**

### Primary Tumor (T)

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastases</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases in a single regional lymph node</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in more than one regional lymph node</td>
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</tbody>
</table>

*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)

<table>
<thead>
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<th>Stage</th>
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<td>Distant metastasis cannot be assessed</td>
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<tr>
<td>M0</td>
<td>No distant metastasis</td>
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<tr>
<td>M1</td>
<td>Distant metastasis</td>
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### Stage Grouping

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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 overall 5-year relative survival rate of patients with renal and pelvic cancers for the period between 1999-2005 from 17 SEER geographic areas was 69.4%.$^5$ 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.$^4$

Initial Evaluation and Staging

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 VHL 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., abdominal/pelvic 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.

Overview

An estimated 57,760 Americans will be diagnosed with renal cancer and 12,980 will die of the disease in the United States in 2009.$^1$ Renal cell carcinoma (RCC) comprises approximately 2-3% 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 RCC, 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.
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 (KID-1).

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 urothelial cell carcinoma; if so, urine cytology or uroscopy 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.

Fine-needle biopsy has been shown to have a limited role in the work-up of patients with RCC, but may be considered in selected cases.

Primary Treatment and Staging
CT-guided needle biopsy of small lesions in the kidney or other accessible sites or cytoreductive nephrectomy can be used to diagnose patients with suspected RCC (KID-1). 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. Nephron-sparing surgery is most appropriate for tumors located over the upper or lower pole or in a peripheral...
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, minimally invasive techniques, such as radiofrequency ablation or cryoablation (KID-A).

The estimated average 5-year survival rates in renal cell carcinoma is 96% for patients presenting with stage I disease, 82% for stage II, 64% for stage III, and 23% for stage IV.

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. 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 currently 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 alpha (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. Observation remains standard care after nephrectomy, and eligible patients should be enrolled in randomized clinical trials, if available. There are a number of ongoing clinical trials exploring the role of targeted therapy in the adjuvant setting. 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 clinically indicated. Chest x-ray and ultrasound may also be performed to assess patients especially in patients with small tumors with a low risk of recurrence. No single follow-up plan is appropriate for all patients therefore individual follow-up plan should be developed depending on size of the primary tumor, the extent of extent of extrarenal spread, histology, and relative risk of relapse. Patients are seen every 6 months for the first 2 years after surgery and annually thereafter 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).

As an alternate protocol, the NCCN Kidney Cancer panel members suggest the surveillance protocol based on UCLA Integrated Scoring System (UISS) (KID-B page 1 of 2). It is an evidence based surveillance protocol in which patients are stratified (KID-B page 2 of 2) based on the 1997 TNM stage, grade, and Eastern Cooperative Oncology Group (ECOG) performance status into low-, intermediate-, and high risk groups for developing recurrence or metastases post-surgical treatment of localized or locally advanced RCC. The use of this protocol allows selective use of imaging and appropriately targeting those patients most in need of intensive surveillance. For example, according to the UISS protocol, in patients with low risk, chest CT scans can be performed annually following surgery for up to 5 years and abdominal CT performed at 24 and 48 months following surgery. Whereas, in patients with nodal disease, chest and abdominal CT must be performed 3, 6, 12, 18, 24 and 36 months after surgery and annually thereafter.
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. 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).

Patient selection is important to identify those 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. The role of cytoreductive nephrectomy and patient selection may warrant assessment in the setting of targeted therapy.

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 Guidelines).

First-line therapy

Until recently, systemic treatment options for metastatic RCC were limited to cytokine therapy and clinical trials of novel agents. For patients with metastatic, recurrent, or unresectable clear cell RCC (KID-2) various combinations and dosages of IL-2 and IFN were studied in randomized trials. These studies have suggested that high-dose IL-2 results in higher response rates compared with low-dose IL-2. High-dose IL-2 has been shown to produce high response rates including complete remission in some patients. This is the only drug reported in literature to produce durable remissions. 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. Enrolling patients in clinical trials and high-dose IL-2 therapy for selected patients are category 2A recommendations.

Although cytokines have been standard of care for about 15 years, recently targeted therapy utilizing tyrosine kinase inhibitors are used in first and second-line treatments. To date, five such agents have been approved by the FDA for the treatment of advanced RCC: sunitinib malate, sorafenib tosylate, temsirolimus, everolimus, and recently bevacizumab in combination with interferon. Risk stratification of patients is important in therapy selection. The most widely used model for risk stratification is the Memorial Sloan-Kettering Cancer Center criteria (MSKCC). The risk factors or predictors of short survival (KID-C) include, high blood LDH level (>1.5 times upper limit of...
normal), high blood calcium level (corrected Ca\(^{++}\) >10 mg/dL or 2.5 mmol/L), anemia, time of less than a year from diagnosis to the need for systemic treatment, and low performance status (KPS < 80%). Patients with none of the above mentioned risk factors are placed in the favorable or good risk group, with 1 to 2 risk factors in the intermediate group, and those with 3 or more risk factors are placed in the poor risk group.

**Treatment for clear cell carcinoma**

Sunitinib malate is multi-kinase inhibitor. It selectively inhibits a number of receptor tyrosine kinases, platelet-derived growth factor (PDGFR-\(\alpha\), PDGFR-\(\beta\)), vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), stem cell factor receptor (c-KIT), FMS-like tyrosine kinase (Flt3), colony stimulating factor (CSF-1R), and the neurotrophic factor receptor (RET). Preclinical data suggested that sunitinib malate has anti-tumor activity that may result from both inhibition of angiogenesis and inhibition of cell proliferation.\(^{32-33}\) To further evaluate the efficacy of sunitinib in previously untreated patients with metastatic RCC; a large multinational phase III trial was conducted.\(^{34}\) A total of 750 patients with metastatic (all risk) clear cell histology RCC were randomized to receive either sunitinib or IFN \(\alpha\). The patients selected for the trial had no prior treatment with systemic therapy, had a good performance status and measurable disease. The primary endpoint was progression free survival (PFS), and secondary endpoints were patient-related outcomes, overall survival (OS), response rate, and safety. Stratification factors were lactate dehydrogenase levels, ECOG performance status of 0 or 1, and nephrectomy status. Patients were randomized to receive oral sunitinib (n = 375) or IFN \(\alpha\) (n = 375). The treatment arms were well balanced; patients had a median age of 60 years, and 90% had undergone prior nephrectomy. Approximately 90% of patients on the trial had either “favorable” or “intermediate” MSKCC risk features. The median PFS was 11 months for the sunitinib arm and 5 months for the IFN \(\alpha\) arm.

The objective response rate assessed by independent review was 31% for the sunitinib arm vs. 6% for the IFN \(\alpha\) arm. Severe adverse events (grade 3–4 toxicities) were acceptable, with neutropenia (12%), thrombocytopenia (8%), hyperamylasemia (5%), diarrhea (5%), hand-foot syndrome (5%), and hypertension (8%) being noteworthy in the sunitinib arm and fatigue more common with IFN \(\alpha\) (12% vs. 7%). Updated results demonstrate an overall survival advantage of sunitinib in the first-line setting. The overall survival of patients treated with sunitinib was longer (26.4 months vs. 21.81 months).\(^{35}\) Based on these studies and its tolerability, sunitinib has been given a category 1 recommendation for first line treatment of patients with relapsed or medically unresectable stage IV renal cancer with predominant clear cell and for non-clear cell histology it is a category 2A recommendation. Recent data from an expanded access trial revealed that sunitinib is safe and efficacious in subgroups of patients with brain metastases, non-clear-cell histology, and poor performance status.\(^{36}\)

Sorafenib tosylate is small molecule that inhibits multiple isoforms of the intracellular serine/threonine kinase Raf (including c-raf and b-raf) and also other receptor tyrosine kinases, including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-\(\beta\), Flt3, and c-kit.\(^{37-41}\) A randomized phase II trial investigated the efficacy and safety of sorafenib vs. IFN in previously untreated patients with clear-cell RCC.\(^{42}\) Patients (n=189) were randomized to continuous oral sorafenib (400 mg bid) or IFN, with an option of dose escalation of sorafenib to 600 mg bid or crossover from IFN to sorafenib (400 mg bid) upon disease progression. The primary endpoint was PFS. In the IFN arm, 90 out of 92 patients received treatment; 56 had disease progression, of which 50 crossed to sorafenib (400 mg bid). All 97 patients in the sorafenib arm received treatment; median PFS was 5.7 months vs. 5.6 months for sorafenib (400 mg bid) vs. IFN, respectively. Overall, the incidence of adverse events was similar between both treatment arms, although skin toxicity (rash and hand-foot skin reaction) and diarrhea occurred more
frequently in patients treated with sorafenib, and flu-like syndrome occurred more frequently in the IFN group. Median PFS was 5.3 months in patients (n = 50) who crossed from IFN to sorafenib (400 mg bid). The median PFS for patients (n = 44) with dose escalation to 600 mg bid was 3.6 months. The 600 mg bid dose was well tolerated. Further analyses of possible benefit from sorafenib dose escalation are required in a larger number of patients. According to the NCCN Kidney Cancer panel members, sorafenib is recommended for selected patients as first line treatment with relapsed or medically unresectable stage IV renal cancer with both predominant clear cell and non-clear cell RCC and it is a category 2A recommendation.

Temsriolimus is a potent and specific inhibitor of the mammalian Target of Rapamycin (mTOR) protein and was approved for treatment of renal cell carcinoma by the U.S. FDA on May 30, 2007. mTOR regulates nutritional needs, cell growth, and angiogenesis by down-regulating or up-regulating a variety of proteins. Following the FDA approval, the NCCN Kidney Cancer panel added temsirolimus as an option in first-line therapy for patients with relapsed or medically unresectable stage IV renal cancer with both predominant clear cell histology and non-clear cell histology. Efficacy and safety of temsirolimus was demonstrated at a second interim analysis of the global ARCC trial, a phase III, multicenter, randomized, open-label study in previously untreated patients with advanced RCC who had 3 or more of 6 prognostic factors. The prognostic factors included: duration of less than one year from the time of diagnosis to start of systemic therapy, Karnofsky performance status of 60 or 70, hemoglobin less than the lower limit of normal, correct calcium of greater than 10 mm/dL, lactate dehydrogenase > 1.5 times the upper limit of normal, and/or more than one metastatic organ site. Six hundred and twenty six patients were randomized to one of following the three arms: IFN α alone (n = 207), temsirolimus 25 mg alone (n = 209), or the combination of temsirolimus 15 mg and IFN (n = 210). Patients were stratified for prior nephrectomy and geographic region. Seventy percent were less than 65 years old and 69% were male. Temsirolimus was infused intravenously over 30-60 minutes weekly either until disease progression or unacceptable toxicity. Premedication with an antihistamine was recommended. The group of patients who received temsirolimus alone showed a significant improvement in OS. The primary end-point of the study was OS. The median overall survival was 10.9 months for patients on temsirolimus alone versus 7.3 months for those treated with the interferon alone. The combination of temsirolimus and interferon did not result in a significant increase in overall survival when compared with interferon alone. Secondary end-point was PFS. The median PFS showed increase from 3.1 months on the interferon alone arm to 5.5 months on temsirolimus alone arm. The combination of temsirolimus and interferon did not result in a significant increase in OS when compared to IFN α alone and was associated with an increase in multiple adverse reactions. The most common grade 3 or 4 adverse events seen more in temsirolimus-treated patients versus IFN α-treated patients include rash, stomatitis, pain, infection, peripheral edema, thrombocytopenia and neutropenia, hyperlipidemia, hypercholesteremia, and hyperglycemia. Based on this data, the NCCN Kidney Cancer panel members have included temsirolimus as a category 1 recommendation as first-line treatment for poor prognosis patients with metastatic clear cell and non-clear cell RCC.

Bevacizumab is an anti-VEFG-A recombinant monoclonal antibody that binds and neutralizes circulating VEGF-A. The U.S. FDA approved bevacizumab in combination with interferon for treatment of advanced renal cell cancer on August 3, 2009. A multicenter, phase III trial (AVOREN) compared bevacizumab plus IFN α versus placebo plus IFN α. The trial was a randomized, double-blind trial. Six hundred and forty nine patients were randomized (641 treated). The addition of bevacizumab to IFN α significantly increased PFS (10.2 vs. 5.4 months) and objective tumor response rate (30.6% vs. 12.4%). No new
side-effects were observed with the combination, compared to that anticipated with each agent. A trend toward improved OS was also observed. Final results of the AVOREN trial showed a median OS of 23.3 months with bevacizumab plus IFN α, and 21.3 months for placebo plus IFN α. The difference did not reach statistical significance.45

In the United States, a similarly conducted trial was performed by the Cancer and Leukemia Group B (CALGB).46 In this CALGB 90206 study 732 previously untreated patients were randomized to receive either IFN α or the combination of bevacizumab plus interferon. Bevacizumab plus IFN α produced a superior PFS (8.5 months vs. 5.2 months) and higher objective response rate (25.5% vs. 13.1%) versus IFN α. Toxicity however was greater in the combination therapy arm. Data from this trial presented in a late-breaking abstract at the ASCO 2009 annual meeting showed a median overall survival of 18.3 months favoring bevacizumab plus IFN α vs. 17.4 months for IFN α plus placebo. In this trial too, the difference did not reach statistical significance.47

The NCCN Kidney Cancer panel members recommend bevacizumab in combination with IFN α as one of the first-line therapy options (category 1 recommendation).for patients with relapsed or medically unresectable stage IV disease with predominant clear cell histology.

Pazopanib, an oral multikinase angiogenesis inhibitor, received FDA approval on October 19, 2009 for treatment of patients with advanced renal cell carcinoma. The safety and effectiveness of pazopanib was evaluated in a phase III trail open-label, international, multi-center study (VEG105192). Patients with clear cell advanced RCC and measurable disease with no prior treatment or 1 prior cytokine-based treatment, randomized (2:1) to pazopanib 800 mg once daily or placebo. A total of 435 patents were enrolled were enrolled (290 to pazopanib; 145 to placebo). Progression free survival was significantly prolonged with pazopanib in the overall study population averaging to 9.2 months compared to 4.2 months for patients who did not receive the drug.48

Patients with progressive disease on placebo on this trial have the option to receive pazopanib 800 mg once daily in an ongoing extension study (VEG107769).49 The initial results of this study was presented during the 2009 ASCO annual meeting.50 Seventy enrolled placebo patients were analyzed. Of these, 34 patients (48%) were treatment-naïve and 37 (52%) were cytokine pretreated (at baseline in VEG105192 phase III). Median time from randomization to placebo in VEG105192 to start of pazopanib treatment on VEG107769 was 6.4 months (1-18 months). Median exposure to pazopanib was 5.7 months. The initial results are encouraging, showing that patients achieved clinical benefit from pazopanib treatment in this extension study. Median progression free survival was 8.3 months (95% CI: 6.1, 11.4 months).50

Adverse reactions to pazopanib (grade 1 or 2) included diarrhea, high blood pressure, hair color changes, nausea, loss of appetite, vomiting, fatigue, weakness, abdominal pain and headache. The most common grade 3 toxicity was hepatotoxicity indicated by elevated levels of alanine and aspartate transaminase. Therefore it is critical to monitor the liver function before and during treatment with the drug. Pazopanib has also been associated with heart rhythm irregularities.

The NCCN Kidney Cancer panel members recommend pazopanib as one of the first-line therapy options (category 1 recommendation).for patients with relapsed or medically unresectable stage IV disease with predominant clear cell histology.

Treatment for Non-clear cell carcinoma
Enrollment in clinical trails is the preferred strategy for non-clear cell RCC. Temsirolimus is the only agent that has shown activity in non-clear cell patients. Subset analysis of the global ARCC trial44
demonstrated benefit of temsirolimus not only in clear cell renal cell carcinoma but also in non-clear cell. There was activity irrespective of age and most benefit in, again, patients with poor risk features. Sunitinib and sorafenib are category 2A recommendations in this setting. The NCCN panel has included pazopanib and chemotherapy with a category 3 designation as options first line therapy for patients with relapsed or medically unresectable stage IV disease with non-clear cell histology. Results of clinical trials evaluating capecitabine or gemcitabine with or without 5-FU for metastatic RCC or doxorubicin-based regimen for sarcomatoid renal cell carcinoma suggest minor or modest activity in patients experiencing progression after treatment with immunotherapy.

Subsequent (Second-line) therapy
Everolimus (RAD001) is an orally administered inhibitor of mTOR. It received FDA approval on March 30, 2009, for patients with advanced RCC after failure of treatment with sorafenib or sunitinib. In the RECORD 1 trial, an international, multicenter, double-blind, randomized phase III trial, everolimus was compared with placebo for the treatment of metastatic renal cell carcinoma in patients whose disease had progressed on treatment with sunitinib or sorafenib. Patients (N = 410) were randomly assigned in a two to one ratio to everolimus (10 mg once daily) or placebo and the primary end point was progression free survival. The median PFS assessed by an independent review committee was in favor of everolimus, 4.0 [95% CI 3.7–5.5] vs. 1.9 [1.8–1.9] months. The most common adverse events reported in patients on everolimus (mostly of mild or moderate severity) were stomatitis in 40% vs. 8% in the placebo group, rash 25% vs. 4%, and fatigue 20% vs. 16%. The updated results of this trial were presented at the 2009 ASCO, Genitourinary Cancers Symposium. Median PFS by central review was 4.9 (95% CI 4.0–5.5) for everolimus vs. 1.9 months (95% CI 1.8–1.9) for placebo. Based on this data, everolimus is a category 1 recommendation following tyrosine kinase therapy according to the NCCN Kidney Cancer panel members.

A randomized phase II “discontinuation trial” evaluated effects of sorafenib treatment versus placebo on 202 patients with metastatic RCC. After 12 weeks, patients with changes in bi-dimensional tumor measurements < 25% were randomized to sorafenib or placebo for an additional 12 weeks. Patients with 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. These results led to a phase III placebo-controlled randomized trial, known as TARGET (Treatment Approaches in RCC Global Evaluation Trial). Nine hundred and five patients were enrolled in this trial. The patients selected had measurable disease, clear cell histology, failed one prior systemic therapy in the last 8 months and had an ECOG performance status of 0 to 1, and a good or intermediate prognosis. Almost all patients had undergone nephrectomy. The primary endpoint of the trial was to assess overall survival, and the secondary endpoint was PFS. In a preliminary report, tumor control (stable disease or partial response) with sorafenib was achieved in 80% of patients, although only 2% attained a partial response. Sorafenib significantly prolonged median PFS compared with placebo (24 vs. 12 weeks), and median survival improvement was preliminarily reported (19.3 vs. 15.9 months). Benefit was evident across all subsets evaluated. Crossover from the placebo to the sorafenib arm was permitted owing to the magnitude of effect on PFS. The patients who crossed over to sorafenib also demonstrated a 30% improvement in survival. In the placebo arm assessed at the time of crossover, the median survival was 19.3 months for sorafenib vs. 14.3 months for placebo. Adverse effects were grade 3 to 4 hand-foot
syndrome, fatigue, and hypertension observed in 5%, 2%, and 1% of patients, respectively. The final results of the trial clearly demonstrate the PFS benefit of sorafenib in patients with advanced RCC. The OS benefit was confounded due to the crossover. However, a planned secondary analysis carried out by adjusting for crossover by censoring the placebo control patients, has shown the OS benefit of sorafenib.

The two aforementioned phase II and III trials to evaluate the effectiveness of sorafenib were conducted primarily in patients after progression on prior cytokine therapy. Sunitinib has also demonstrated substantial anti-tumor activity in the second-line metastatic RCC following progression after cytokine therapy. Sorafenib and sunitinib are considered category 1 when used after cytokine therapy and category 2A when used after a prior tyrosine kinase inhibitor therapy (KID-3). The phase III trial by Sternberg et al included patients who received prior cytokine therapy. Progression free survival was significantly prolonged with pazopanib in the overall study population averaging to 9.2 months compared to 4.2 months for patients who did not receive the drug. The average progression free survival in cytokine-pretreated patients was 7.4 vs. 4.2 months. Based on the results from this trial, the NCCN panel considers pazopanib as a category 1 option following cytokine therapy (KID-3). However following tyrosine kinase failure, the use of pazopanib is listed as category 3 since there is no data available in this setting.

Temsirolimus is category 2A recommendation following cytokine therapy and category 2B following tyrosine kinase inhibitor. IFN α, IL-2, and bevacizumab are all considered category 2B recommendations (KID-3). Clinical trials are preferred for second-line and subsequent therapy for metastatic disease.

Supportive care remains a mainstay of therapy for all 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.
References


