Overview

An estimated 58,240 Americans were diagnosed with renal cancer and 13,040 died of the disease in the United States in 2010.\(^1\) Renal cell carcinoma (RCC) constitutes 2% to 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 constitutes fewer than 1% of kidney cancer cases. Medullary renal carcinoma is a variant of collecting duct renal carcinoma and was described initially 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 an autosomal dominant constitutional mutation in the VHL gene that predisposes to clear cell carcinoma and other proliferative vascular lesions.3,4

The overall 5-year relative survival rate of patients with renal and pelvic cancers for the period between 1999 and 2005 from 17 SEER geographic areas was 69.4%.5 The most important prognostic determinants of 5-year survival are 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 CT scan. As the use of imaging methods (e.g., abdominal/pelvic CT or ultrasound) has become more widespread, the frequency of incidental detection of RCC has increased. 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

Text continues on p. 967
INITIAL WORKUP

Suspicous mass →

- H&P
- CBC, comprehensive metabolic panel
- 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 b

Stage Ia

Partial nephrectomy d (preferred) or Radical nephrectomy (if partial not feasible or central location) or Active surveillance in selected patients or Thermal ablation therapy for nonsurgical candidates

Stage Ib

Partial nephrectomy d or Radical nephrectomy

Stage II, III

Potentially surgically resectable solitary metastatic site → Nephrectomy + surgical metastasectomy e → Relapse See First-Line Therapy (facing page) or
Potentially surgically resectable primary f with multiple metastatic sites → Cytoreductive nephrectomy in select patients prior to systemic therapy → See First-Line Therapy (facing page) or
Medically or surgically unresectable f → See First-Line Therapy (facing page)

Stage IV

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

PRIMARY TREATMENT c

FOLLOW-UP e

(category 2B)

.category 2B

*Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies.

**Patients are encouraged to participate in clinical trials.

See Principles of Surgery (page 965).

Can be open or robotic/laparoscopic.

No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient and tumor characteristics. Alternate follow-up schemes have been proposed.

Individualized treatment based on symptoms and extent of metastatic disease.

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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**FIRST-LINE THERAPY**

- 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 Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Palliative Care*)

**NON-CLEAR CELL HISTOLOGY**

- See Systemic Therapy (page 964)

**PREDOMINANT CLEAR CELL HISTOLOGY**

- Relapse or Stage IV and medically or surgically unresectable

**SUBSEQUENT THERAPY**

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

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

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9 Category 1 recommendations are listed in order of FDA approval.

1 Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival (page 966).

1’ Patients with excellent performance status and normal organ function.

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

1 Tyrosine kinase inhibitors with a category 1 designation are listed in order of FDA approval.

1 Currently available tyrosine kinase inhibitors include sorafenib, sunitinib, and pazopanib.
SYSTEMIC THERAPY

Relapse or Stage IV and medically or surgically unresectable → Non-clear cell histology

Clinical trial (preferred)
or Temsirolimus (category 1 for poor-prognosis patients,\textsuperscript{m} category 2A for other risk groups)
or Sorafenib
or Sunitinib
or Pazopanib (category 3)
or Erlotinib (category 3)
or Chemotherapy in sarcomatoid only (category 3):
gemcitabine + doxorubicin
and Best supportive care\textsuperscript{i} (see NCCN Guidelines for Palliative Care*)

\textsuperscript{*}To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

\textsuperscript{i}Best supportive care can include palliative RT, metastasectomy, or bisphosphonates for bony metastases.
\textsuperscript{m}Poor-prognosis patients, defined as those with \geq 3 predictors of short survival. See Predictors of Short Survival (page 966).
PRINCIPLES OF SURGERY

- Nephron-sparing surgery is appropriate in selected patients, for example:
  - Small unilateral tumors (T1a and selected patients T1b)
  - Uninephric state, renal insufficiency, bilateral renal masses, familial renal cell cancer
- Nephron-sparing surgery should be performed by a surgeon proficient in the procedure.
- Regional lymph node dissection is optional but is recommended for patients with adenopathy on preoperative imaging or palpable/visible adenopathy at time of surgery.
- Adrenal gland resection may be omitted if adrenal is uninvolved and tumor is not high-risk based on size and location.
- Special teams may be required for extensive inferior vena cava involvement.
- Observation or ablative techniques (e.g., cryosurgery or radiofrequency ablation):
  - Can be considered for patients with clinical stage T1 renal lesions who are not surgical candidates
  - Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies
  - Rigorous comparison with surgical resection (i.e., total or partial nephrectomy using open or laparoscopic techniques) has not been performed
  - Thermal ablative techniques are associated with a higher local recurrence rate than conventional surgery

- Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have:
  - Excellent performance status (ECOG PS < 2)
  - No brain metastasis

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Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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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/L)
- Interval of < 1 year from original diagnosis to the start of systemic therapy
- Karnofsky performance score ≤ 70
- ≥ 2 sites of organ metastasis

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Treatment of Localized Disease

Surgical resection remains an effective therapy for clinically localized RCC, with options including radical nephrectomy and nephron-sparing surgery. Each of these modalities is associated with its own benefits and risks, the balance of which should optimize long-term renal function and expected cancer-free survival.

A radical nephrectomy includes a perifascial resection of the kidney, perirenal fat, regional lymph nodes, and ipsilateral adrenal gland. 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.

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. The updated EORTC phase III trial compared radical nephrectomy with a complete lymph node dissection and radical nephrectomy alone. The results showed no significant differences in overall survival, time to progression of disease, or progression-free survival between the study groups. However, primary tumor pathologic features such as nuclear grade, sarcomatoid component, tumor size, stage, and presence of tumor necrosis all influence the likelihood of regional lymph node involvement at the time of radical nephrectomy.

The panel recommends lymph node dissection for patients with palpable or CT-detected enlarged lymph nodes, and for those with normal-appearing nodes to obtain adequate staging information.

Ipsilateral adrenal gland resection should be considered for patients with large upper-pole tumors or abnormal-appearing adrenal glands seen on CT. Adrenalectomy is not indicated when imaging shows a normal adrenal gland or if the tumor is not high-risk based on size and location.

Originally, partial nephrectomy (nephron-sparing surgery) was indicated only in clinical settings in which a radical nephrectomy would render the patient functionally anephric, necessitating dialysis. 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. Radical nephrectomy should not be used when nephron sparing is possible.

Patients with a hereditary form of RCC, such as VHL syndrome, should also be considered for nephron-sparing therapy. Partial nephrectomy has well-established oncologic outcomes data comparable to radical nephrectomy, which can lead to an increased risk of chronic kidney disease that is associated with increased risks of cardiovascular morbidity and mortality, according to population-based studies. Compared with radical nephrectomy, partial nephrectomy can preserve renal function, decrease overall mortality, and reduce frequency of cardiovascular events.

The goals of nephron-sparing surgery should be optimal locoregional tumor control while minimizing ischemia time to ideally less than 30 minutes.
Laparoscopic, robotic, and open partial nephrectomy all offer comparable outcomes in the hands of skilled surgeons. Patients in satisfactory medical condition should undergo surgical excision of stage I through III tumors. Active surveillance (with delayed intervention if indicated) or thermal ablation techniques such as cryo- or radiofrequency ablation are alternative strategies for selected patients, particularly elderly patients and those with competing health risks. The panel has addressed the efficacy of each treatment modality in the context of tumor stages IA, IB, II, and III.

Management of Stage IA Disease
The panel members prefer surgical excision through partial nephrectomy for the management of clinical stage IA renal masses. Adequate expertise and careful patient selection are important. Partial nephrectomy is most appropriate in patients with small unilateral tumors or whenever preservation of renal function is a primary issue, such as in uninephric patients or those with renal insufficiency, bilateral renal masses, or familial RCC. Both open and laparoscopic approaches to partial nephrectomy can be considered, depending on tumor size, location, and surgeon expertise.

Some localized renal tumors may not be amenable to partial nephrectomy, in which case radical nephrectomy is recommended. These NCCN Guidelines also list radical nephrectomy as an alternative for patients with stage IA RCC if the urologic surgeon determines that a partial nephrectomy is not feasible technically.

Other options in selected patients with stage IA RCC include active surveillance and thermal ablation. Active surveillance is an option for the management of localized renal masses and should be a primary consideration for patients with decreased life expectancy or extensive comorbidities that would place them at excessive risk for more invasive intervention. Short- and intermediate-term oncologic outcomes indicate that an appropriate strategy is to initially monitor small renal masses, and then to treat for progression if required.55

Although distant recurrence-free survival rates are comparable, thermal ablation has been associated with an increased risk of local recurrence compared with conventional surgery.26,27 Judicious patient selection and counseling remain of paramount importance for these less-invasive technologies.

Management of Stage IB Disease
Surgery involving either radical or partial nephrectomy (whenever feasible) is the standard of care for clinical T1b tumors.

Management of Stage II and III Disease
Radical nephrectomy is the preferred treatment if the tumor extends into the inferior vena cava, and is the standard of care for patients with stage II and III renal tumors. 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 may reach 10%, depending on the local extent of the primary tumor and the level of vena caval extension.

Management After Surgical Excision of Stages I to 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.

Adjuvant treatment after nephrectomy currently has no established role in patients who have undergone a complete resection of their tumor. No systemic therapy has yet 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 no delay in time to relapse or improvement in survival with adjuvant therapy.28–30 Observation remains standard care after nephrectomy, and eligible patients should be offered enrollment in randomized clinical trials. Several ongoing and recently completed clinical trials have explored the role of targeted therapy in the adjuvant setting. Adjuvant radiation therapy after nephrectomy has not shown benefit, even in patients with nodal involvement or 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 and then as clinically indicated. Chest radiograph and
ultrasound may also be performed to assess patients, especially those with small tumors and low risk of recurrence.

No single follow-up plan is appropriate for all patients; therefore, individual follow-up plans should be developed that take into account the size of the primary tumor, extent of extrarenal spread, tumor 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).

Alternate surveillance programs have been proposed, such as the surveillance protocol based on the University of California Los Angeles (UCLA) Integrated Scoring System (UISS).\(^{31}\) The UISS is an evidence-based system in which patients are stratified based on the 1997 TNM stage, grade, and ECOG performance status into low-, intermediate-, or high-risk groups for developing recurrence or metastases after surgical treatment of localized or locally advanced RCC.\(^{31}\) This protocol enables selective use of imaging and appropriate targeting of patients most in need of intensive surveillance.

**Management of Advanced or Stage IV Disease**

Patients with stage IV disease also may benefit from surgery. For example, lymph nodes suspicious for metastatic disease on CT may be hyperplastic and not involved with tumor, and thus the presence of minimal regional adenopathy does not preclude surgery. 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. 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 metastasis experience recurrence at the primary or metastatic site, but long-term progression-free survival has been reported in a subset of patients after radiotherapy for solitary bone metastases.\(^{32}\)

**Primary Treatment of Advanced or Stage IV Disease**

Cytoreductive nephrectomy before systemic therapy is recommended generally in patients with a potentially surgically resectable primary and multiple resectable metastases. Randomized trials showed a benefit of cytoreductive nephrectomy in patients who received IFN-α therapy after surgery. In similar phase III trials, the SWOG and EORTC randomized patients with metastatic disease to undergo either nephrectomy followed by IFN-α therapy or treatment with IFN-α alone.\(^{33–35}\) A combined analysis of these trials showed that median survival favored the surgery plus IFN-α group (13.6 vs. 7.8 months for IFN-α alone).\(^{33–36}\)

Patient selection is important for identifying those who might benefit from cytoreductive therapy. Patients most likely to benefit from cytoreductive nephrectomy before systemic therapy are those with lung-only metastases, good prognostic features, and good performance status.\(^{37}\) Although similar data are not available for patients who are candidates for high-dose IL-2 (see later discussion), data from the UCLA renal cancer database and from a variety of publications by other groups suggest that nephrectomy also provides benefit to patients who undergo other forms of immunotherapy.\(^{38}\) As for the role of nephrectomy for patients presenting with metastatic disease and considered for targeted therapies (detailed later), randomized trials are ongoing. Patients with metastatic disease who present with hematuria or other symptoms related to the primary tumor should be offered palliative nephrectomy if they are surgical candidates.

**First-Line Therapy for Patients With Predominantly Clear Cell Carcinoma**

**Cytokine 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, various combinations and dosages of IL-2 and IFN-α were studied in randomized trials. IL-2 was shown to have potent antitumor activity first in several murine tumor models,\(^{39}\) and subsequently in patients with RCC.\(^{40–42}\) With both IFN-α and IL-2, objective response rates of 5% to 27% have been reported.\(^{42–44}\) Although these agents have been helpful
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for some patients, the clinical benefit is modest in most cases and is achieved at the expense of significant toxicity.

**High-Dose IL-2 as First-Line Therapy for Predominantly Clear Cell Carcinoma:** IL-2–based immunotherapy is reported to produce long-lasting complete or partial remissions in a small subset of patients. In patients treated with IFN-α, durable complete responses are rare. Although IFN-α and high-dose intravenous bolus IL-2 as approved by the FDA and used in United States centers have not been directly compared, data from a French multicenter study suggested similar outcomes from aggressive IFN-α or infusional IL-2, with superior responses at the cost of much higher toxicity reported in the combination therapy group. High-dose IL-2 is associated with substantial toxicity, and attempts to characterize tumor or patient factors for best response to this therapy have been unsuccessful.39,41,45 Thus, the best criteria to select patients for IL-2 therapy are based largely on safety and include performance status, medical comorbidities, tumor histology (predominantly clear cell), Memorial Sloan-Kettering Cancer Center (MSKCC)46 or UCLA Survival After Nephrectomy and Immunotherapy (SANI) risk scores,38,47 and the patient’s attitude toward risk.

According to the panel, high-dose IL-2 is listed as a first-line treatment option with a category 2A designation for selected patients with relapsed or medically unresectable stage IV clear cell renal carcinoma.

**Targeted Therapy**

Targeted therapy using tyrosine kinase inhibitors are used widely in first- and second-line treatments. To date, 6 of these agents have been approved by the FDA for the treatment of advanced RCC: sunitinib, sorafenib, pazopanib, temsirolimus, everolimus, and bevacizumab in combination with interferon.

Tumor histology and risk stratification of patients is important in targeted therapy selection. The most widely used model for risk stratification is the MSKCC model,48 which classifies patients according to the presence or absence of 5 adverse prognostic factors: Karnofsky performance status of 70 or less, serum LDH level greater than 1.5 times the upper limit of normal (ULN), hemoglobin level below normal, corrected serum calcium level above the ULN, and time from diagnosis and nephrectomy to therapy of less than 1 year. Patients with none of these factors are considered low-risk or good prognosis, those with 1 or 2 factors are considered intermediate-risk, and those with 3 or more of the factors are considered poor-risk based on shorter survival compared with the good- and intermediate-risk patients.

**Sunitinib as First-Line Therapy for Predominantly Clear Cell Carcinoma:** Sunitinib is a multikinase inhibitor targeting several receptor tyrosine kinases, including platelet-derived growth factor receptors (PDGFR-α and -β), vascular endothelial growth factor receptors (VEGFR-1, -2, and -3), stem cell factor receptor (c-KIT), FMS-like tyrosine kinase (FLT-3), colony stimulating factor (CSF-1R), and neurotrophic factor receptor (RET).48,49

Preclinical data suggested that sunitinib has antitumor activity that may result from both inhibition of angiogenesis and inhibition of cell proliferation.50,51 After promising phase I and II data, the efficacy of sunitinib in previously untreated patients with metastatic RCC was studied in a large multinational phase III trial in which 750 patients with metastatic (all risk) clear cell histology RCC were randomized 1:1 to receive either sunitinib or IFN-α.44 The patients selected for the trial had no prior treatment with systemic therapy, good performance status, and measurable disease. The primary end point was progression-free survival, and secondary end points were patient-related outcomes, overall survival, response rate, and safety. 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 progression-free survival was 11 months for the sunitinib arm and 5 months for the IFN-α arm. The objective response rate assessed through independent review was 31% for the sunitinib arm versus 6% for the IFN-α 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-α (12% vs. 7%). Updated results show an overall survival advantage of sunitinib over IFN-α in the first-line setting (26.4 vs. 21.81 months).44 Recent data from an expanded access trial that was performed before the drug became commercially available show that sunitinib possesses an acceptable safety profile and has activity in subgroups...
of patients with brain metastases, non–clear cell histology, and poor performance status.\textsuperscript{32}

Based on these studies and its tolerability, the panel has listed sunitinib as a category 1 option for the first-line treatment of patients with relapsed or medically unresectable, predominantly clear cell, stage IV renal carcinoma.

**Bevacizumab Along With IFN as First-Line Therapy for Predominantly Clear Cell Carcinoma:**

Bevacizumab is a recombinant humanized monoclonal antibody that binds and neutralizes circulating VEGF-A. The FDA approved bevacizumab in combination with IFN-\(\alpha\) for the treatment of advanced RCC on August 3, 2009. A multicenter double-blind phase III trial (AVOREN) randomized 649 patients (641 treated) to either bevacizumab plus IFN-\(\alpha\) or placebo plus IFN-\(\alpha\).\textsuperscript{53} The addition of bevacizumab to IFN-\(\alpha\) significantly increased progression-free survival (10.2 vs. 5.4 months) and objective tumor response rate (30.6% vs. 12.4%). No significant increase or novel adverse effects were observed with the combination compared with IFN-\(\alpha\) alone. A trend toward improved overall survival was also observed (23.3 months with bevacizumab plus IFN-\(\alpha\) vs. 21.3 months for IFN-\(\alpha\)), although the difference did not reach statistical significance.\textsuperscript{53}

In the United States, a similar trial was performed by CALGB, with 732 previously untreated patients randomized 1:1 to receive either IFN-\(\alpha\) or the combination of bevacizumab plus IFN-\(\alpha\). Bevacizumab plus IFN-\(\alpha\) produced a superior progression-free survival (8.5 vs. 5.2 months) and higher objective response rate (25.5% vs. 13.1%) than IFN-\(\alpha\) alone. However toxicity was greater in the combination therapy arm.\textsuperscript{54} The survival data for this trial were recently updated, showing no significant differences in median survival between the groups (18.3 months for bevacizumab plus IFN-\(\alpha\) vs. 17.4 months for IFN-\(\alpha\) alone).\textsuperscript{55}

The panel recommends bevacizumab in combination with IFN-\(\alpha\) as a category 1 option for first-line treatment of patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

**Pazopanib as First-Line Therapy for Predominantly Clear Cell Carcinoma:**

Pazopanib is an oral angiogenesis inhibitor that targets VEGFR-1, -2, and -3, PDGFR-\(\alpha\) and -\(\beta\), and c-KIT. Pazopanib received FDA approval on October 19, 2009, for the treatment of patients with advanced RCC. The safety and effectiveness of pazopanib was evaluated in a phase III, open-label, international, multicenter trial, in which 435 patients with clear cell advanced RCC and measurable disease with no prior treatment or 1 prior cytokine-based treatment were randomized 2:1 to pazopanib or placebo. Progression-free survival was prolonged significantly with pazopanib in the overall study population, averaging 9.2 versus 4.2 months for patients assigned to placebo.\textsuperscript{56} The treatment-naïve subpopulation of 233 patients, randomized 2:1 to pazopanib versus placebo, had a median progression-free survival of 11.1 months on pazopanib versus 2.8 months on placebo.\textsuperscript{56} The objective response rate was 30% with pazopanib and 3% with placebo (all results statistically significant). Common adverse reactions to pazopanib (any grade) included diarrhea (52%), hypertension (40%), hair color changes, nausea (26%), anorexia (22%), vomiting (21%), fatigue (19%), weakness (14%), abdominal pain (11%), and headache (10%). A notable grade 3 toxicity was hepatotoxicity, indicated by elevated levels of alanine (30%) and aspartate (21%) transaminase. Therefore liver function must be monitored before and during treatment with the drug. Pazopanib also has been associated with heart rhythm irregularities.

The panel includes pazopanib as a category 1 option for the first-line treatment of patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

**Temsirolimus as First-Line Therapy for Predominantly Clear Cell Carcinoma:**

Temsirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) protein and was approved for treatment of RCC by the FDA on May 30, 2007. mTOR regulates micronutrients, cell growth, apoptosis, and angiogenesis through its downstream effects on a variety of proteins. Efficacy and safety of temsirolimus was demonstrated at a second interim analysis of the Global Advanced Renal Cell Carcinoma (ARCC) trial, which was a phase III, multicenter, randomized, open-label study in previously untreated patients with advanced RCC who had at least 3 of 6 unfavorable prognostic factors.\textsuperscript{57} The prognostic factors included less than 1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score of 60 to 70, hemoglobin less than the lower limit of normal, corrected cal-
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cium of greater than 10 mg/dL, LDH greater than 1.5 times the ULN, and metastasis to one or more than one organ site. This trial equally randomized 626 patients to receive either IFN-α alone, temsirolimus alone, or a combination. Patients in both temsirolimus-containing groups were recommended to undergo premedication with an antihistamine to prevent infusion reactions. Patients were stratified for prior nephrectomy and geographic region; 70% were younger than 65 years and 69% were men. The group of patients who received temsirolimus alone showed a significant improvement in overall survival compared with those receiving either IFN-α alone or both drugs. The median overall survival was 10.9 months for patients on temsirolimus alone versus 7.3 months for those treated with IFN-α alone. The median progression-free survival (the study’s secondary end point) was increased from 3.1 months with IFN-α alone to 5.5 months with temsirolimus alone. The combination of temsirolimus and IFN-α not only failed to improve overall or progression-free survival but also led to an increase in multiple adverse reactions, including grade 3 or 4 rash, stomatitis, pain, infection, peripheral edema, thrombocytopenia and neutropenia, hyperlipidemia, hypercholesteremia, and hyperglycemia.

Based on this data, the panel included temsirolimus as a category 1 recommendation for the first-line treatment of patients with a poor prognosis and relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma. Sorafenib as First-Line Therapy for Predominantly Clear Cell Carcinoma: Sorafenib is a small molecule that inhibits multiple isoforms of the intracellular serine/threonine kinase, RAF, and other receptor tyrosine kinases, including VEGFR-1, -2, and -3; PDGFR-β; FLT-3; c-KIT; and RET."

A randomized phase II trial investigated the efficacy and safety of sorafenib versus IFN-α in previously untreated patients with clear cell RCC. This trial randomized 189 patients to continuous oral sorafenib (400 mg, twice daily) or IFN-α, with an option of dose escalation of sorafenib to 600 mg twice daily or crossover from IFN-α to sorafenib (400 mg, twice daily) for those experiencing disease progression. The primary end point was progression-free survival. In the IFN-α arm, 90 patients received treatment and 56 experienced disease progression, 50 of whom crossed over to sorafenib (400 mg, twice daily). Ninety-seven patients in the sorafenib arm received treatment and had a median progression-free survival of 5.7 months compared with 5.6 months for IFN-α. The results showed that more sorafenib-treated (68.2% vs. 39.0%) patients experienced tumor regression. Progression-free rates for sorafenib versus IFN-α were 90.0% vs. 70.4%, 45.9% vs. 46.5%, and 11.5% vs. 30.4% at 3, 6, and 12 months, 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-α group. Sorafenib-treated patients reported fewer symptoms and better quality of life than those treated with IFN-α. Both dose escalation of sorafenib after progression and a switch to sorafenib after progression on IFN-α resulted in progression-free intervals that suggested a clinical benefit with sorafenib (as second-line therapy) in patients for whom IFN-α treatment failed and those who had been treated with sorafenib upfront.

The panel has listed sorafenib as a first-line treatment option with a category 2A designation for selected patients with relapsed or medically unresectable stage IV predominantly clear cell RCC.

Subsequent Therapy for Patients With Predominantly Clear Cell Carcinoma

Everolimus as Subsequent Therapy

Everolimus (RAD001) is an orally administered inhibitor of mTOR. It received FDA approval on March 30, 2009, for patients with advanced RCC after treatment failure with sorafenib or sunitinib. In the international, multicenter, double-blind, randomized phase III RECORD-1 trial, everolimus was compared with placebo for the treatment of metastatic RCC in patients whose disease had progressed on treatment with sunitinib or sorafenib. This trial randomized 410 patients in a 2:1 fashion to receive either everolimus or placebo, with progression-free survival as the primary end point. The median progression-free survival assessed by an independent review committee favored everolimus (4.0 vs. 1.9 months). The most common adverse events reported in patients on everolimus (mostly of mild or moderate severity) were stomatitis (40% vs. 8% in the placebo group), rash (25% vs. 4%), and fatigue (20% vs. 16%).
According to the updated results of this trial, median progression-free survival determined through independent central review was 4.9 months for everolimus versus 1.9 months (95% CI, 1.8–1.9) for placebo. Serious adverse events (in ≥ 5% of patients) with everolimus, independent of causality, included infections (all types, 10%), dyspnea (7%), and fatigue (5%).

Based on these data, the panel listed everolimus as a category 1 recommendation after tyrosine kinase therapy.

**Tyrosine Kinase Inhibitors as Subsequent Therapy**

A phase III placebo-controlled randomized TARGET (Treatment Approaches in RCC Global Evaluation Trial) studied the efficacy of sorafenib in 903 patients who experienced progression on a prior therapy (mostly cytokines). The patients selected had measurable disease, clear cell histology, had experienced failure of one prior systemic therapy in the past 8 months, had an ECOG performance status of 0 to 1, and a good or intermediate prognosis. Almost all patients had undergone nephrectomy. The primary end point of the trial was overall survival, and the secondary end point was progression-free survival. Sorafenib significantly prolonged median progression-free survival compared with placebo (5.9 vs. 2.8 months), and median overall survival in the preliminary analysis (19.3 vs. 15.9 months) for all patient subsets. Because of the large difference in progression-free survival, crossover to the sorafenib treatment arm was permitted, which likely resulted in the failure of this trial to show an overall survival benefit for sorafenib in the final analysis. With censoring of crossover data, the median overall survival was 19.3 months for sorafenib versus 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. This study showed the effectiveness of sorafenib in a clinical setting consisting primarily of patients who experienced progression on prior cytokine therapy.

Sunitinib also has shown substantial antitumor activity in the second-line therapy of metastatic RCC in patients experiencing progression after cytokine therapy. Studies investigating the sequential use of sunitinib and sorafenib are mostly retrospective. Prospective data, although limited, suggest a lack of total cross-resistance between tyrosine kinase inhibitors—either sorafenib followed by sunitinib failures, or vice versa—an observation that is consistent with their differences in target specificities and slightly different toxicity spectra that sometimes permit tolerance of one agent over another. Sorafenib and sunitinib are considered category 1 by the panel when used after cytokine therapy and category 2A when used after a prior tyrosine kinase inhibitor therapy.

The phase III trial comparing pazopanib with placebo, detailed earlier, included 202 patients who received prior cytokine therapy. The average progression-free survival in cytokine pretreated patients was 7.4 versus 4.2 months. Based on the results from this trial, the panel members consider pazopanib a category 1 option after cytokine therapy. However, after tyrosine kinase failure, pazopanib use is listed as a category 3 recommendation, because no data are available in this setting.

**Other Agents as Subsequent Therapy**

Temsirolimus and bevacizumab are listed as category 2A recommendations after cytokine therapy, and category 2B recommendations after tyrosine kinase inhibitor therapy. IFN-α and IL-2 are category 2B recommendations.

**Systemic Therapy for Patients With Non–Clear Cell Carcinoma**

Enrollment in clinical trials is the preferred strategy for non–clear cell RCC.

**Temsirolimus for Predominantly Non–Clear Cell Carcinoma**

Temsirolimus is the only agent that has shown activity in patients with non–clear cell RCC. Subset analysis of the global ARCC trial showed it had benefit in not only clear cell RCC but also non–clear cell RCC. Activity occurred irrespective of age, and most benefit was seen in patients with poor-risk features. Based on these data, the panel has included temsirolimus as first-line treatment for patients with metastatic non–clear cell RCC. It is a category 1 recommendation for patients with non–clear cell RCC with poor prognosis features (according to MSKCC risk criteria) and a category 2A recommendation for those in other prognostic risk groups.

**Tyrosine Kinase Inhibitors for Predominantly Non–Clear Cell Carcinoma**

Sunitinib and sorafenib are category 2A recommendations for treatment-naïve patients with non–clear cell RCC.
cell carcinoma. Recent data from an expanded access trial showed that sunitinib is safe and efficacious in subgroups of patients with treated brain metastases, non–clear cell histology, and poor performance status. 52

The efficacy of pazopanib has not yet been studied in patients with non–clear carcinoma. Therefore, based on extrapolation, the panel has included pazopanib with a category 3 designation as a first-line therapy for patients with relapsed or medically unresectable stage IV disease with non–clear cell histology.

The efficacy of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, was studied in 52 patients with advanced papillary RCC (given in a once-daily dose). 78 The overall response rate was 11% (5 of 45 patients; 95% CI, 3%–24%), and the disease control rate (defined as stable disease for 6 weeks, or confirmed partial response or complete response using RECIST [Response Evaluation Criteria in Solid Tumors]) was 64%. The median overall survival was 27 months. 78 This study showed that single-agent erlotinib was associated with disease control and survival outcomes of interest, with an expected toxicity profile. The panel has now included erlotinib as a category 3 option for first-line therapy for patients with relapsed or medically unresectable stage IV with non–clear cell histology.

Chemotherapy for Predominantly Non–Clear Cell Carcinoma

Gemcitabine in combination with doxorubicin has shown moderate activity in patients with sarcomatoid tumors. 79–81 The panel has listed chemotherapy with gemcitabine and doxorubicin as a category 3 option for first-line therapy for patients with relapsed or medically unresectable stage IV disease with non–clear cell histology.

Supportive Care

Supportive care remains a mainstay of therapy for all patients with metastatic RCC. This includes surgery for patients with solitary brain metastasis whose disease is well controlled extracranially. Stereotactic radiotherapy, if available, is an alternative to surgery for limited-volume brain metastasis, and whole-brain irradiation is recommended for patients with multiple brain metastases. Surgery also may be appropriate for selected patients with malignant spinal cord compression, or impending or actual fractures in weight-bearing bones, if the rest of the disease burden is limited. Furthermore, radiation therapy along with bisphosphonates 82,83 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.

Treatment for the palliation of symptoms, especially in patients with marginal performance status and evidence of metastatic disease, includes optimal pain management (See NCCN Clinical Practice Guidelines in Oncology for Adult Cancer Pain; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

References

Kidney Cancer


# Individual Disclosures for the NCCN Guidelines for Kidney Cancer Panel Members

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<th>Panel Member</th>
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