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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Kidney Cancer

Version 1.2011

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Kidney Cancer

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Discussion

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

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

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

See NCCN Categories of Evidence and Consensus

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NCCN Guidelines™ Version 1.2011 Updates Kidney Cancer

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Updates in Version 1.2011 of the NCCN Kidney Cancer Guidelines from Version 1.2010 include:

General
- **UCLA Integrated Staging System (UISS) surveillance protocol was removed from the guidelines.**

KID-1:
- **For stage I-III, the primary treatment was separated into Stage IA and IB and Stage II, III and the corresponding treatment options were added.**
- **Footnote c, "See Principle of Surgery (KID-A)" was added to the page.**
- **Footnote d, "Can be open or robotic/laparoscopic" was added to the page.**
- **Footnote e was modified by adding, "Alternate follow-up schemes have been proposed".**

KID-3:
- **For predominant clear cell histology:**
  - **First-line therapy, footnote i, "Patients with excellent performance status and normal organ function" was added.**
  - **Subsequent therapy, the category for bevacizumab was changed from a category 2B to category 2A following cytokine therapy and category 2B following tyrosine kinase inhibitor.**

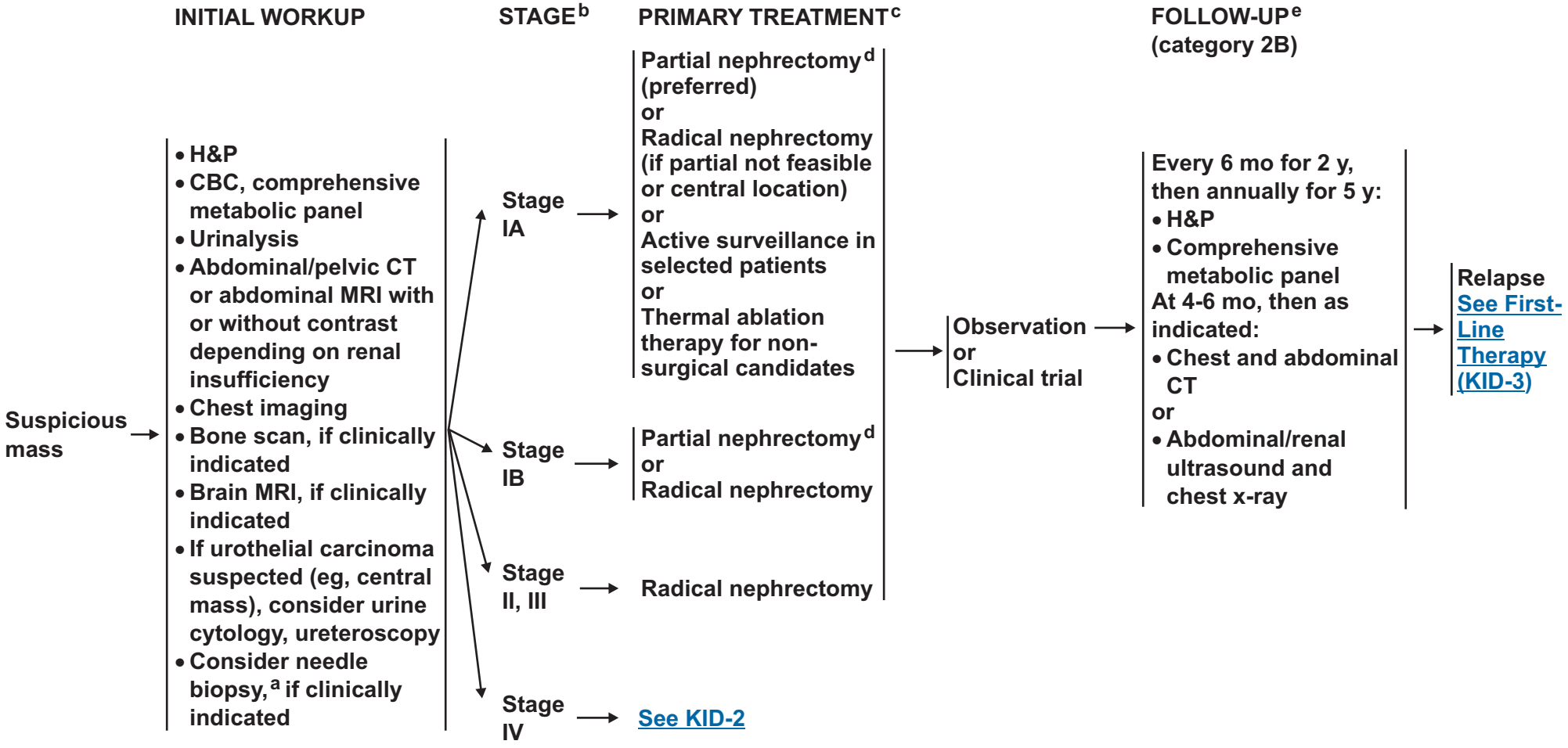
KID-4:
- **For non-clear cell histology, systemic therapy:**
  - **"Erlotinib" was added with a category 3 designation.**
  - **Chemotherapy for sarcomatoid only (category 3) was revised to include combination therapy with gemcitabine + doxorubicin and single-agent capecitabine, floxuridine, fluorouracil, and doxorubicin were removed.**

KID-A:
- **Principles of surgery:**
  - **First bullet was modified by adding, "Small unilateral tumors *(T1a and selected patients T1b)*" and "uninephric state, renal insufficiency, *bilateral renal masses, familial renal cell cancer*".**
  - **Second bullet, "Nephron-sparing surgery should be performed by a surgeon proficient in the procedure" is new to the page.**
  - **Third bullet was modified by adding, "but is recommended for patients with adenopathy on preoperative imaging or palpable/visible-adenopathy at time of surgery.**
  - **Sixth bullet was modified by adding, "Thermal ablative techniques are associated with higher local recurrence rate than conventional surgery" with two corresponding references.**
  - **Last bullet, "Generally, patients who would be candidates for cytoreductive nephrectomy prior to systemic therapy have: excellent performance status (ECOG PS < 2), no brain metastasis" is new to the guidelines.**

ST-1:
- **The staging has been updated to the 2010 American Joint Committee on Cancer (AJCC) TNM Staging System for Kidney Cancer.**

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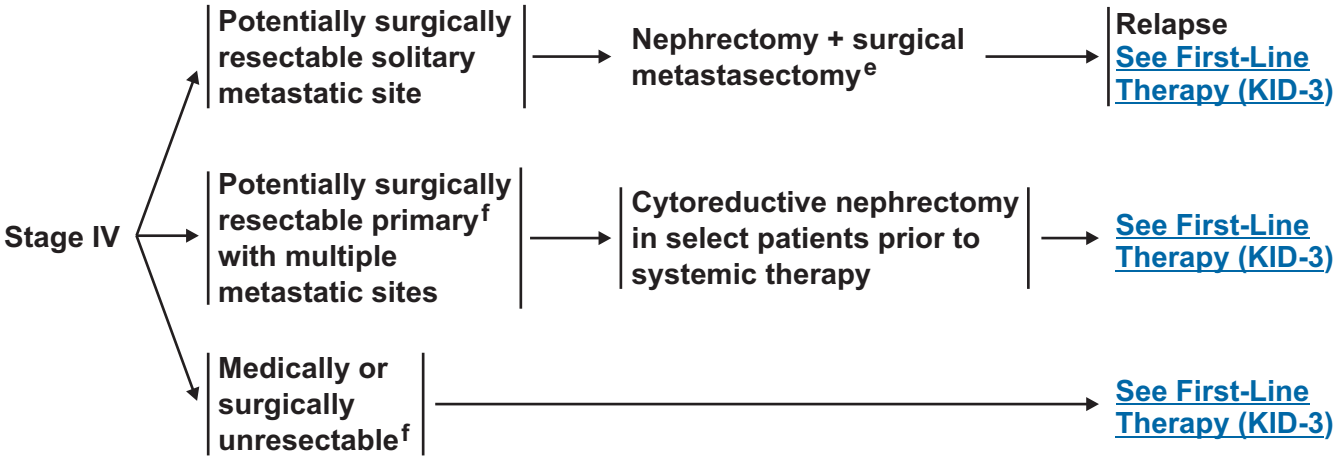
[a] Biopsy of small lesions may be considered to obtain or confirm a diagnosis of malignancy and guide surveillance, cryosurgery, and radiofrequency ablation strategies.
[b] Patients are encouraged to participate in clinical trials.
[c] See Principle of Surgery (KID-A).
[d] Can be open or robotic/laparoscopic.
[e] 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.

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.

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PRIMARY TREATMENT[c]



[c] See Principle of Surgery (KID-A).

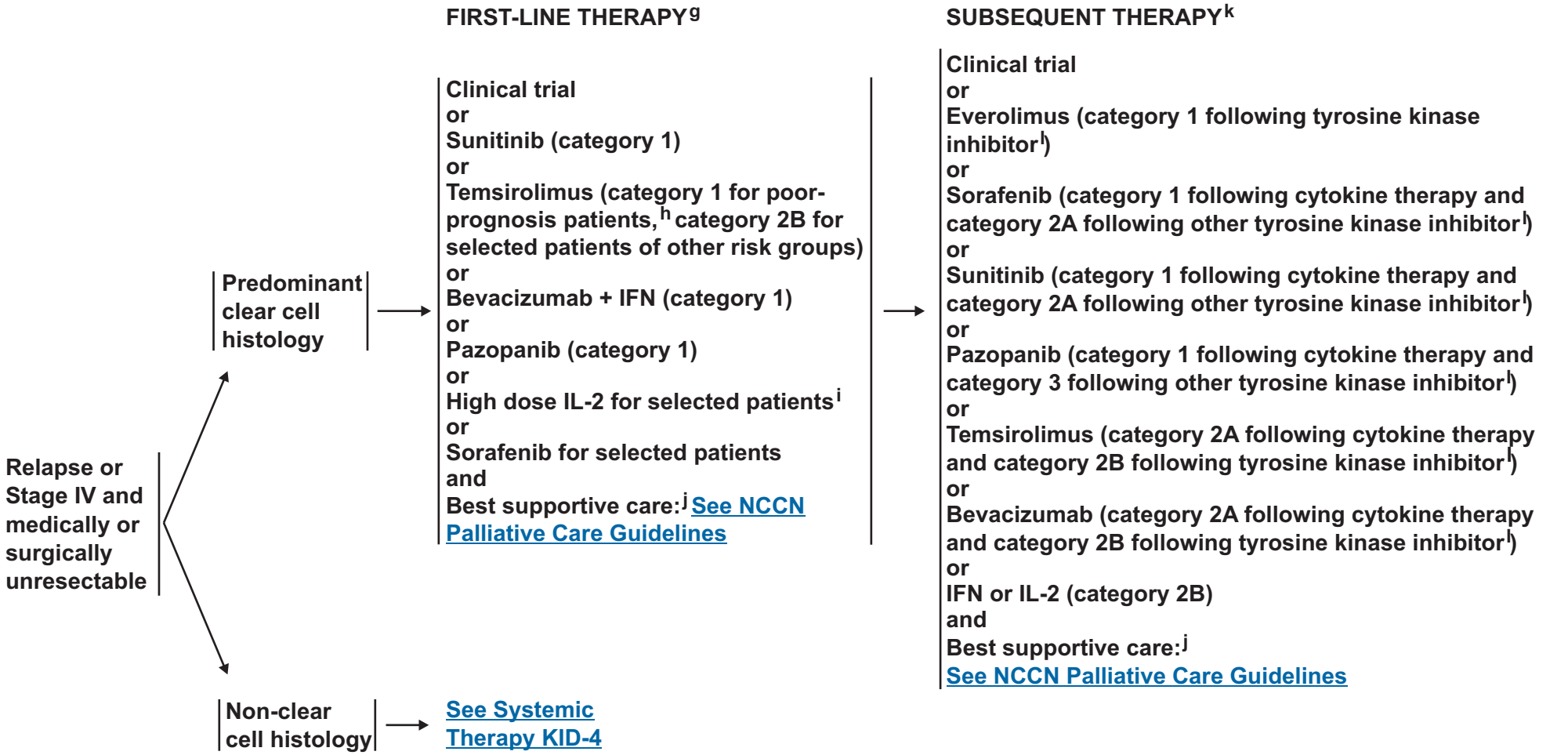
[e] No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on patient and tumor characteristics. Alternate follow-up schemes have been proposed.

[f] Individualized treatment based upon symptoms and extent of metastatic disease.

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[g] Category 1 recommendations are listed in order of FDA approval.
[h] Poor-prognosis patients, defined as those with ≥ 3 predictors of short survival. See Predictors of Short Survival (KID-B).
[i] Patients with excellent performance status and normal organ function.
[j] Best supportive care can include palliative RT, metastasectomy, or bisphosphonates for bony metastases.
[k] Tyrosine kinase inhibitors with a category 1 designation are listed in order of FDA approval.
[l] Currently available tyrosine kinase inhibitors include: sorafenib, sunitinib, or pazopanib.

Note: All recommendations are category 2A unless otherwise indicated.
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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,[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:[j] See NCCN Palliative Care Guidelines

[j] Best supportive care can include palliative RT, metastasectomy, or bisphosphonates for bony metastases.
[m] Poor-prognosis patients, defined as those with ≥ 3 predictors of short survival. See Predictors of Short Survival (KID-B).

Note: All recommendations are category 2A unless otherwise indicated.
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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 on the basis of size and location.**

- **Special teams may be required for extensive inferior vena cava involvement.**

- **Observation or ablative techniques (eg, cryosurgery or radiofrequency ablation):**
  - **Can be considered for patients with clinical stage T1 renal lesions and 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 (ie, total or partial nephrectomy by open or laparoscopic techniques) has not been done.**
  - **Thermal ablative techniques are associated with higher local recurrence rate than conventional surgery.[1,2]**

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

[1]Campbell SC, Novick AC, Belldegrun A, et al. Practice Guidelines Committee of the American Urological Association. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1271-1279.
[2]Kunkle DA, Uzzo RG. Cryoablation or radiofrequency ablation of the small renal mass: A meta-analysis. Cancer 2008;113:2671-2680.

Note: All recommendations are category 2A unless otherwise indicated.
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PREDICTORS OF SHORT SURVIVAL[1]

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**

[1]Hudes G, Carducci M, Tomczak P et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007; 356(22):2271-2281.

Note: All recommendations are category 2A unless otherwise indicated.
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Table 1

American Joint Committee on Cancer (AJCC)

TNM Staging System for Kidney Cancer (7th ed., 2010)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney
T1b	Tumor more than 4 cm but not more than 7 cm in greatest dimension, limited to the kidney
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney
T2a	Tumor more than 7 cm but less than or equal to 10 cm in greatest dimension, limited to the kidney
T2b	Tumor more than 10 cm, limited to the kidney
T3	Tumor extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota's fascia
T3a	Tumor grossly extends into the renal vein or its segmental (muscle containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond Gerota's fascia
T3b	Tumor grossly extends into the vena cava below the diaphragm
T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4	Tumor invades beyond Gerota's fascia (including contiguous extension into the ipsilateral adrenal gland)

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single regional lymph node(s)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage/Prognostic Groups

Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1 or T2	N1	M0
	T3	N0 or N1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 10/30/09

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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.

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.

Discussion update in progress

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A thorough physical examination should be performed with special attention to detecting supraclavicular adenopathy, an abdominal mass, lower extremity edema, a varicocele, or subcutaneous nodules. Laboratory evaluation includes a complete blood cell count, comprehensive metabolic panel (including serum calcium, liver function studies, lactate dehydrogenase [LDH], and serum creatinine), coagulation profile, and urinalysis.

CT of the abdomen and pelvis with and without contrast and chest imaging (either chest radiograph or CT scan) are essential studies in the initial workup. Abdominal magnetic resonance imaging (MRI) is used to evaluate the inferior vena cava if tumor involvement is suspected, or it can be used instead of CT for detecting renal masses and for staging when contrast material cannot be administered because of allergy or renal insufficiency.[6,7] A central renal mass may suggest the presence of urothelial cell carcinoma; if so, urine cytology or uteroscopy should be considered. A bone scan is not routinely performed unless the patient has an elevated serum alkaline phosphatase or complains of bone pain. CT or MRI of the brain is performed if the history or physical examination suggests brain metastases. A positron emission tomography scan is not a routine part of the initial workup.

Fine-needle biopsy [8] 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. 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. 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.[9-11]

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. 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.[12-14] Nephron-sparing surgery is most appropriate for

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tumors located over the upper or lower pole or in a peripheral location.[15] 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[16,17] or cryoablation[18].

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.[4]

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.[19-21] 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).

As an alternate protocol, the NCCN Kidney Cancer panel members suggest the surveillance protocol based on UCLA Integrated Scoring System (UISS) [22]. It is an evidence based surveillance protocol in which patients are stratified 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.[22] 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,

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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.[23] In some instances, radiation therapy may be administered after bone metastases.[24]

Cytoreductive nephrectomy before systemic therapy is recommended in patients with a potentially surgically resectable primary and multiple metastases. 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).[25-27]

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 Adult 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 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.[28-30] High-dose IL-2 has been shown to produce high response rates including complete remission in some patients.[30] 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

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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).[31] The risk factors or predictors of short survival 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-α, PDGFR-β), 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 α. 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 α (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 α arm. The objective response rate assessed by independent review was 31% for the sunitinib arm vs. 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 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-β, 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

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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.

Temsirolimus 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.[43] 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 mn/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

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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).[44] 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]

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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 trial[44] 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 [51,52] or gemcitabine with or without 5-FU [53] for metastatic RCC or doxorubicin-based regimen[54] 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.[55] 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).[55] 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%.[55] 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.[56] 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.[57] 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

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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).[58] 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.[59] 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.[60] However, a planned secondary analysis carried out by adjusting for crossover by censoring the placebo control patients, has shown the OS benefit of sorafenib.[60]

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. [61,62] Sorafenib and sunitinib are considered category 1 when used after cytokine therapy and category 2A when used after a prior tyrosine kinase inhibitor therapy. 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.[48]. Based on the results from this trial, the NCCN panel considers pazopanib as a category 1 option following cytokine therapy. 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. 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[63,64] 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.

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