National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Kidney Cancer

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NCCN Guidelines Panel Disclosures

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§ Radiotherapy/Radiation oncology
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ω Urology
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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

Summary of the Guidelines updates

Summary of changes in the 1.2009 version of the Kidney Cancer Guidelines from the 1.2008 version include:

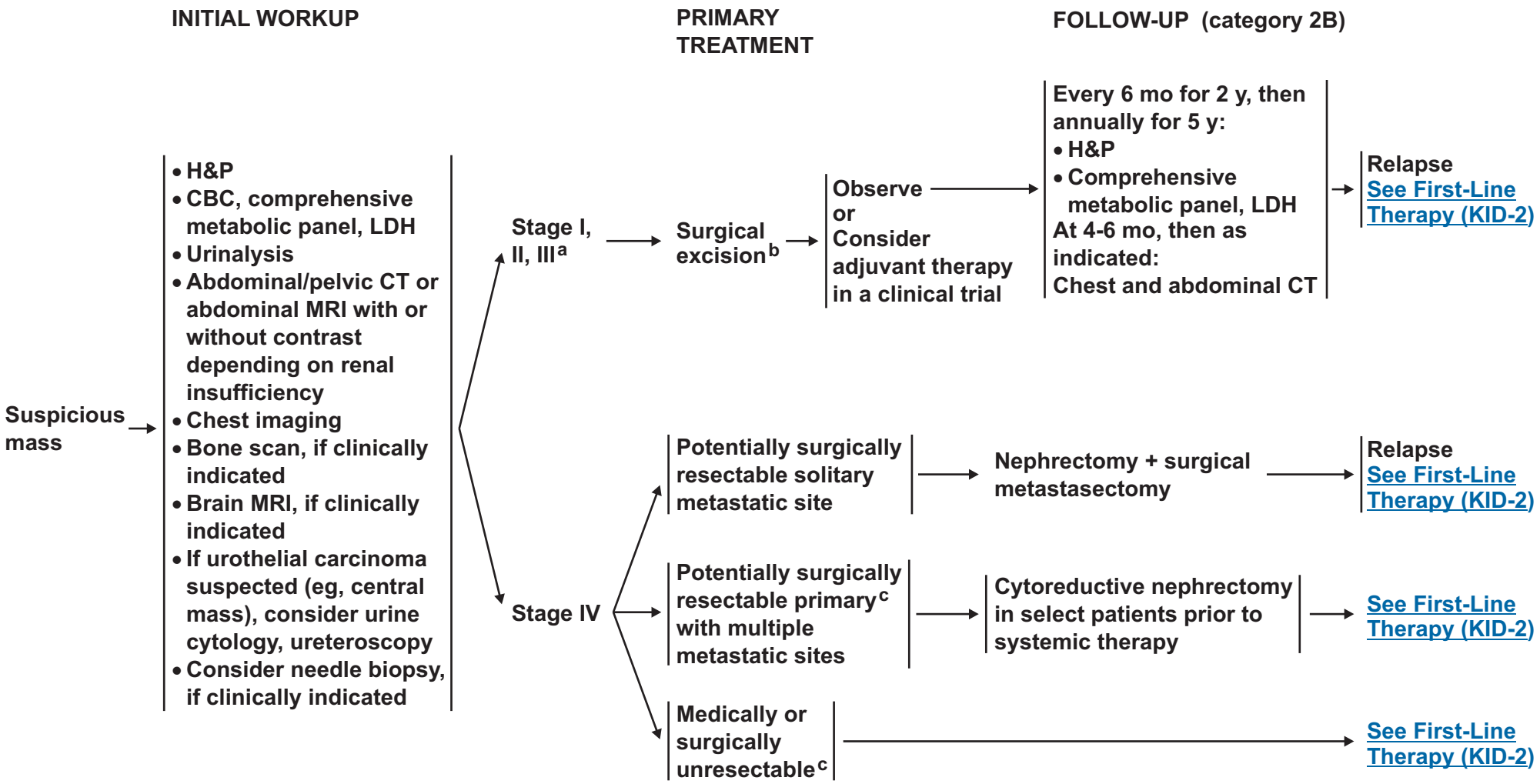
KID-1:
- **Initial workup: "Consider needle biopsy, if clinically indicated" was added as an option.**
- **Initial workup: "Transitional cell carcinoma" was clarified as "urothelial carcinoma"**

KID-2:
- **For predominant clear cell histology, first-line therapy, "category 2B for selected patients of other risk groups" was added to temsirolimus.**
- **For predominant clear cell histology, first-line therapy, "Bevacizumab + IFN" was changed from a category 2A to category 1 designation.**
- **For predominant clear cell histology, subsequent therapy, "Low dose IL-2 ± IFN" was changed from a category 2B to a category 3 designation.**

KID-A:
- **Principles of Surgery, "Emerging energy ablative techniques (eg, cryosurgery or radiofrequency ablation) are currently considered an option by some experts for selected small tumors. Though a rigorous comparison with surgical resection (ie, total or partial nephrectomy by open or laparoscopic techniques) has not been done. " is a new bullet.**

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.

Kidney Cancer



[a] Patients are encouraged to participate in clinical trials.
[b] See Principles of Surgery (KID-A).
[c] Individualized treatment based upon symptoms and extent of metastatic disease.

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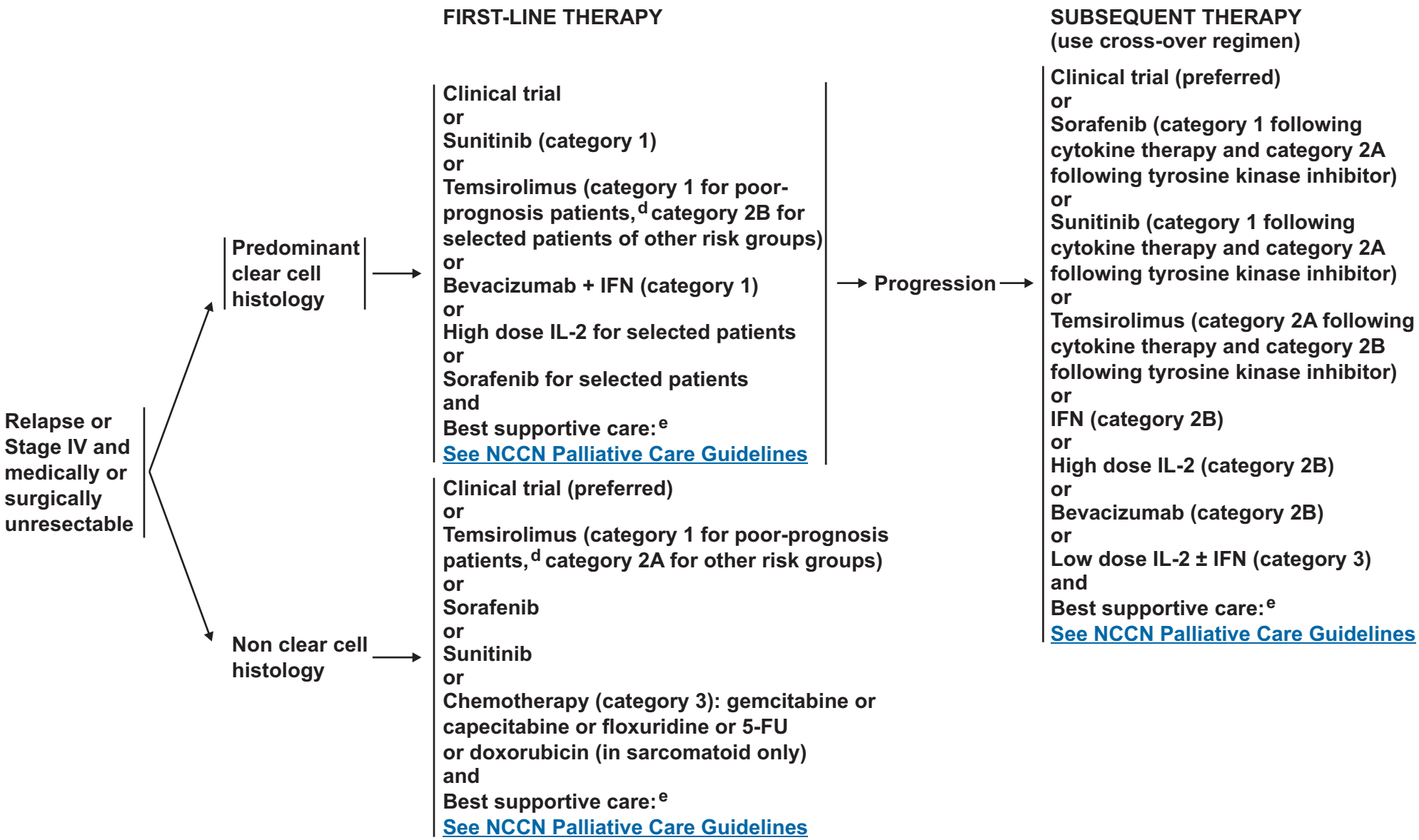
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Kidney Cancer



[d] Poor-prognosis patients, defined as those with ≥ 3 predictors of short survival. See Predictors of Short Survival (KID-B).

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

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.

PRINCIPLES OF SURGERY

- Nephron-sparing surgery may be indicated in selected patients, for example:
  - Multiple primaries
  - Uninephric state
  - Renal insufficiency
  - Selected patients with small unilateral tumors
- Lymph node dissection is optional.
- Adrenal gland may be left if uninvolved and tumor is not high risk, on the basis of size and location.
- Special teams may be required for extensive inferior vena cava involvement.
- Observation or emerging energy ablative techniques (eg, cryosurgery or radiofrequency ablation) can be considered for patients who are not surgical candidates.
- Emerging energy ablative techniques (eg, cryosurgery or radiofrequency ablation) are currently considered an option by some experts for selected small tumors. Though a rigorous comparison with surgical resection (ie, total or partial nephrectomy by open or laparoscopic techniques) has not been done.

Back to Primary Treatment (KID-1)

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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.

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

Staging (2002 AJCC 6th Edition)

Table 1

AJCC Staging of Renal Cell Carcinoma

Primary Tumor (T)

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

Regional Lymph Nodes (N)*

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

* *Note:* Laterality does not affect the N classification
Note: If a lymph node dissection is performed, then pathologic evaluation would ordinarily include at least eight nodes.

Distant Metastasis (M)

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

Stage Grouping

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

Discussion

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 54,390 Americans will be diagnosed with kidney cancer and 13,010 will die of the disease in the United States in 2008.[1] Renal cell carcinoma (RCC) comprises approximately 2% of all malignancies, with a median age at diagnosis of 65 years. The rate of RCC has increased by 2% per year for the past 65 years. The reason for this increase is unknown. Approximately 90% of renal tumors are 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 for the period between 1996-2003 from 17 SEER geographic areas was 65.5%.[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.[3]

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 von Hippel-Lindau disease, and these patients should be referred to a hereditary cancer clinic for further evaluation.

Renal tumors may also be identified on an imaging study (e.g., CT or ultrasound) performed to evaluate other conditions (KID-1). As the use of imaging methods has become more widespread, the frequency of incidental detection of RCC has increased. These small low-stage carcinomas may be treated with more conservative surgical approaches, such as nephron-sparing techniques, discussed in later sections.

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

CT of the abdomen and pelvis with and without contrast and chest imaging (either chest radiograph or CT scan) are essential studies in the initial workup. Abdominal magnetic resonance imaging (MRI) is used to evaluate the inferior vena cava if tumor involvement is suspected, or it can be used instead of CT for detecting renal masses and for staging (ST-1) when contrast material cannot be administered because of allergy or renal insufficiency.[6-7] A central renal mass may suggest the presence of a 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 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.[9–11] Nephron-sparing surgery is most appropriate for tumors located over the upper or lower pole or in a peripheral location.

Patients with a hereditary form of RCC, such as VHL disease, also should be considered for nephron-sparing therapy.

Patients in satisfactory medical condition should undergo surgical excision of stage I through III tumors. However, a small set of elderly or infirm patients with small tumors may be offered surveillance alone or energy ablative, minimally invasive techniques, such as radiofrequency ablation[12,13] or cryoablation[14] (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.[3]

Management after Surgical Excision of Stages I–III Tumors

After surgical excision, 20% to 30% of patients with localized tumors experience relapse. Lung metastasis is the most common site of distant recurrence, occurring in 50% to 60% of patients.[15] The median time to relapse after surgery is 1 to 2 years, with most relapses occurring within 3 years. Longer disease-free intervals between diagnosis and recognition of metastatic disease are associated with longer projected survival.

Adjuvant treatment after nephrectomy has no established role in patients who have undergone a complete resection of their tumor. No systemic therapy has been shown to reduce the likelihood of relapse. Randomized trials comparing adjuvant interferon α (IFN α) or high-dose interleukin (IL-2) with observation alone in patients who had locally advanced, completely resected RCC showed that no delay in time to relapse or improvement in survival was associated with adjuvant therapy.[16-18] Observation remains standard care after nephrectomy, and eligible patients should be enrolled in randomized clinical trials, if available. 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. Patients are seen periodically and each visit should include a history, physical examination, and comprehensive metabolic panel (e.g., blood urea nitrogen, serum creatinine, calcium levels, LDH, liver function tests) (KID-1).

Management of Stage IV Disease

Patients with stage IV disease are also candidates for surgery. For example, lymph nodes suspected for disease on CT may be hyperplastic and not involved with the tumor; therefore, patients with minimal regional adenopathy can be surgical candidates. In addition, the small subset of patients with potentially surgically resectable primary RCC and a solitary resectable metastatic site are candidates for nephrectomy and surgical metastasectomy. Candidates include patients who 1) initially present with primary RCC and a solitary site of metastasis or 2) develop a solitary recurrence after nephrectomy. Sites of solitary metastases that are amenable to this approach include the lung, bone, and brain. Both the primary tumor and the metastasis may be resected during the same operation or at different times. Most patients who undergo resection of a solitary metastatic site experience recurrence at the primary or metastatic site. However, long-term survival has been seen in some patients.[19] In some instances, radiation therapy may be administered after bone metastases.[20]

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).[21–23]

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

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.[24–26] High-dose IL-2 has been shown to produce high response rates including complete remission in some patients.[25] 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, three such agents have been approved by the FDA for the treatment of advanced RCC: sunitinib malate, sorafenib tosylate, and temsirolimus. A fourth, bevacizumab, recently showed benefit in a pivotal phase 3 trial. 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).[27] The risk factors or predictors of short survival (KID-B) include, high blood lactate dehydrogenase (LDH) level (>1.5 times upper limit of nl), high blood calcium level (corrected Ca^{++} >10mg/dL or 2.5mmol/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 of a number receptor tyrosine kinases, platelet-derived growth factor (PDGFRα, PDGFR-β), vascular endothelial growth factor receptors (VEGFR1, VEGFR2, VEGFR3), 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.[28, 29] To further evaluate the efficacy of sunitinib in previously untreated patients with metastatic RCC; a large multinational phase III trial was conducted.[30] 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, Eastern Cooperative Oncology Group (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 study presented at the 2008 ASCO annual meeting demonstrate an overall survival advantage of sunitinib in the first-line setting.[31]The overall survival of patients treated with sunitinib was longer (26.4 months vs. 21.81 months).[31] Based on these studies and its tolerability, sunitinib has been given 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.

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.[32-36]

A randomized phase II trial investigated the efficacy and safety of sorafenib vs. interferon (IFN) in previously untreated patients with clear-cell renal cell carcinoma (RCC).[37] 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 progression-free survival (PFS). In the IFN arm, 90 out of 92 patients received treatment; 56 had disease progression, of which 50 crossed to sorafenib (400 mb 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, including HIF-1.[38] 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.[39] 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: Interferon (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 overall survival (OS). OS was the primary end-point of the study. 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. Progression-free survival (PFS) was a secondary end-point and the median PFS showed increased 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, stomitis, 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. In a phase II randomized trial, 116 patients with metastatic RCC refractory to IL-2 therapy were randomized receive low-dose bevacizumab (n=37), or high-dose bevacizumab (n=39), or placebo (n=40).[40] There was a significant prolongation of the time to progression of disease in the high-dose–bevacizumab group as compared with the placebo group. There was not a significant difference between the time to progression of disease in the low-dose–antibody group and that in the placebo group. The probability of being progression-free for patients given high-dose bevacizumab, low-dose– bevacizumab, and placebo was 64%, 39%, and 20%, respectively, at four months and 30%, 14%, and 5% at eight months. Bevacizumab yielded a 10% response rate (with several patients having prolonged periods of stability or minor responses) and led to a PFS of 4.8 months vs. 2.5 months with placebo. Tumor progression was prolonged by a factor of 2.55 in patients given high-dose bevacizumab, as compared with patients in the placebo group. There were no significant differences in overall survival between the groups. Adverse effects of all grades included hypertension (36%), asymptomatic proteinuria (64%), hematuria (13%) and epistaxis (20%) were also significantly higher in the high-dose bevacizumab group.

Subsequently, 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).[41] 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%). A trend toward improved OS was

also observed. No new side-effects were observed with the combination, compared to that anticipated with each agent.

In the United States, a similarly conducted trial was performed by the Cancer and Leukemia Group B (CALGB).[42] This was a trial that randomized patients previously untreated to receive either interferon-alfa or the combination of bevacizumab plus interferon. Bevacizumab plus interferon produced a superior progression free survival (8.5 months vs 5.2 months) and higher objective response rate (25% vs 13.5%) versus interferon monotherapy. Toxicity however was greater in the combination therapy arm. The final survival analysis for this study is awaited.

The NCCN Kidney Cancer panel members recommend bevacizumab in combination with IFN α as first-line therapy for patients with relapsed or medically unresectable stage IV disease with predominant clear cell histology and this combination is a category 1 recommendation.

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[39] 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. Chemotherapy is a category 3 recommendation as first line therapy for patients with relapsed or medically unresectable stage IV disease with non-clear cell histology. Results of clinical trials evaluating capecitabine[43, 44] or gemcitabine with or without 5-FU[45] for metastatic RCC or doxorubicin-based regimen[46] for sarcomatoid renal cell carcinoma suggest minor or modest activity in patients experiencing progression after treatment with immunotherapy.

Second-line therapy

Clinical trials are preferred for second-line and subsequent therapy for metastatic disease.

A randomized phase II "discontinuation trial" evaluated effects of sorafenib treatment versus placebo on 202 patients with metastatic RCC.[47] After 12 weeks, patients with changes in bidimentional 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).[48] 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 progression-free survival (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. [49] 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.[50] However, a planned secondary analysis carried out by adjusting for crossover by censoring the placebo control patients, has shown the OS benefit of sorafenib.[50]

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 mRCC [51] Sorafenib and sunitinib are considered category 1 when used after cytokine therapy and category 2A when used after a prior tyrosine kinase inhibitor therapy.

Temsirolimus is category 2A recommendation following cytokine therapy and category 2B following tyrosine kinase inhibitor. IFN α, high dose IL-2, and bevacizumab are also considered category 2B recommendations and low dose IL-2 with or without IFN α is a category 3 (KID-2).

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.

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