National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Kidney Cancer

Version 1.2013

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Kidney Cancer

NCCN Guidelines Index
Kidney Cancer TOC
Discussion

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

Neeraj Agarwal, MD ‡
Huntsman Cancer Institute at the University of Utah

Clair Beard, MD §
Dana-Farber/Brigham and Women's Cancer Center

Sam Bhayani, MD ω
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

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

Mark K. Buyyounouski, MD, MS §
Fox Chase Cancer Center

Sam S. Chang, MD ω
Vanderbilt-Ingram Cancer Center

* **Toni K. Choueiri, MD † Þ**
Dana-Farber/Brigham and Women's Cancer Center

Shilpa Gupta, MD †
Moffitt Cancer Center

Steven L. Hancock, MD § Þ
Stanford Cancer Institute

Eric Jonasch, MD †
The University of Texas MD Anderson Cancer Center

Jenny J. Kim, MD †
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

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

Clayton Lau, MD ω
City of Hope Comprehensive Cancer Center

Ellis G. Levine, MD †
Roswell Park Cancer Institute

Daniel W. Lin, MD ω
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Kim A. Margolin, MD † ‡
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

M. Dror Michaelson, MD, PhD †
Massachusetts General Hospital Cancer Center

Thomas Olencki, DO †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Roberto Pili, MD †
Roswell Park Cancer Institute

Elizabeth R. Plimack, MD, MS †
Fox Chase Cancer Center

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

Cary N. Robertson, MD ω
Duke Cancer Institute

Charles J. Ryan, MD † ω
UCSF Helen Diller Family Comprehensive Cancer Center

Joel Sheinfeld, MD ω
Memorial Sloan-Kettering Cancer Center

Kanishka Sircar, MD ≠
The University of Texas MD Anderson Cancer Center

Brad Somer, MD †
St. Jude Children's Research Hospital/ University of Tennessee Cancer Institute

Jue Wang, MD †
UNMC Eppley Cancer Center at The Nebraska Medical Center

Richard B. Wilder, MD §
Moffitt Cancer Center

NCCN
Mary Dwyer, MS
Rashmi Kumar, PhD

Continue

† Medical oncology
‡ Hematology/hematology oncology
§ Radiotherapy/Radiation oncology
Þ Internal medicine
ω Urology
≠ Pathology
* Writing committee member

NCCN Guidelines Panel Disclosures

NCCN Guidelines Version 1.2013 Table of Contents
Kidney Cancer

NCCN Guidelines Index
Kidney Cancer TOC
Discussion

Clinical Trials: 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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013 Updates Kidney Cancer

NCCN Guidelines Index
Kidney Cancer TOC
Discussion

Updates in the 1.2013 version of the NCCN Guidelines for Kidney Cancer from the 2.2012 version include:

KID-1

- **Initial workup and follow-up, "including LDH" was removed from "comprehensive metabolic panel."**
- **Follow-up, imaging was modified: "Chest and abdominal ± *pelvic* imaging."**

KID-3

- **Predominant clear cell histology**
  - **Subsequent therapy, "interferon" was removed as a treatment option.**
- **Footnote "i" was added: "Chemotherapy (category 3) in clear cell and non-clear cell RCC with predominant sarcomatoid features has shown modest response to gemcitabine + doxorubicin or gemcitabine + capecitabine."**

KID-4

- **Systemic therapy**
  - **The treatment option of "Chemotherapy in sarcomatoid only (category 3): gemcitabine + doxorubicin" was modified and moved to footnote "i": "Chemotherapy (category 3) in clear cell and non-clear cell RCC with predominant sarcomatoid features has shown modest response to gemcitabine + doxorubicin or gemcitabine + capecitabine."**
- **Footnote "k" was added: "Partial responses have been observed to cytotoxic chemotherapy (carboplatin + gemcitabine or carboplatin + paclitaxel) with collecting duct or medullary subtypes."**

KID-B

- **The title of the page was clarified to read: "Predictors of Short Survival Used to Select Patients for Temsirolimus."**

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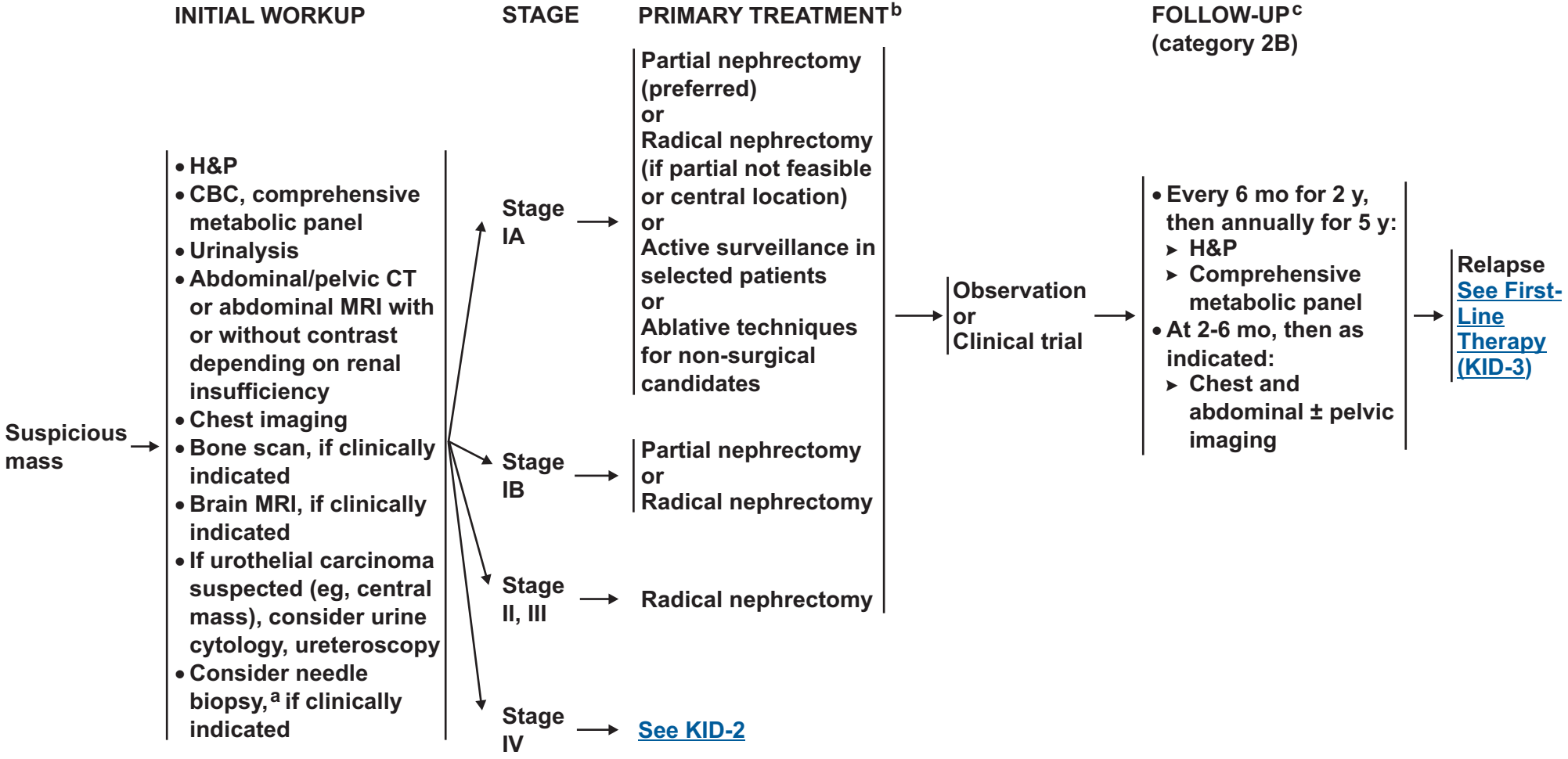
NCCN Guidelines Version 1.2013
Kidney Cancer

NCCN Guidelines Index
Kidney Cancer TOC
Discussion



[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] See Principles of Surgery (KID-A).

[c] 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.

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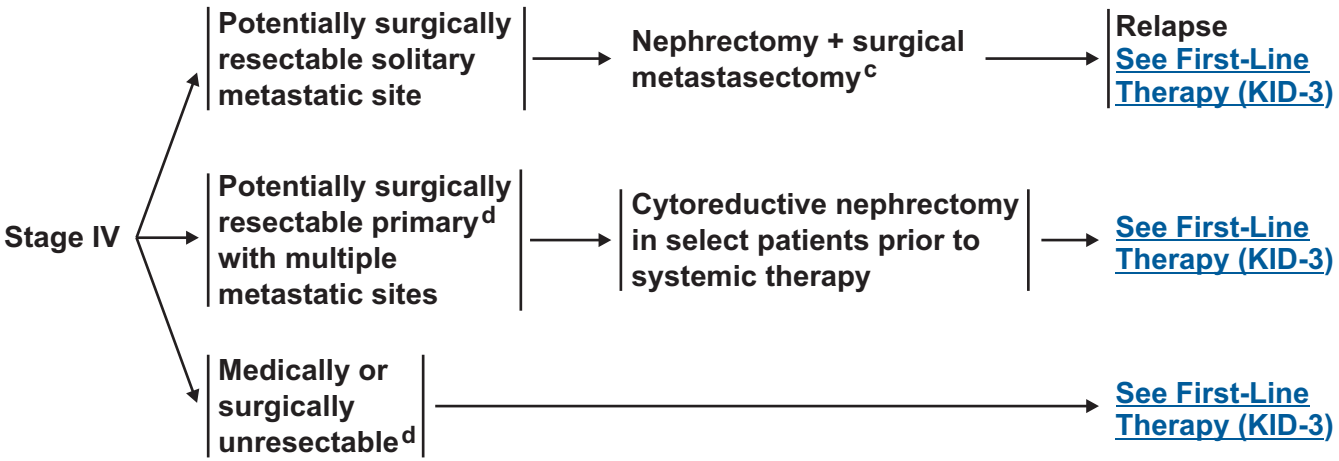
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



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

[c] 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.

[d] Individualize treatment based on symptoms and extent of metastatic disease.

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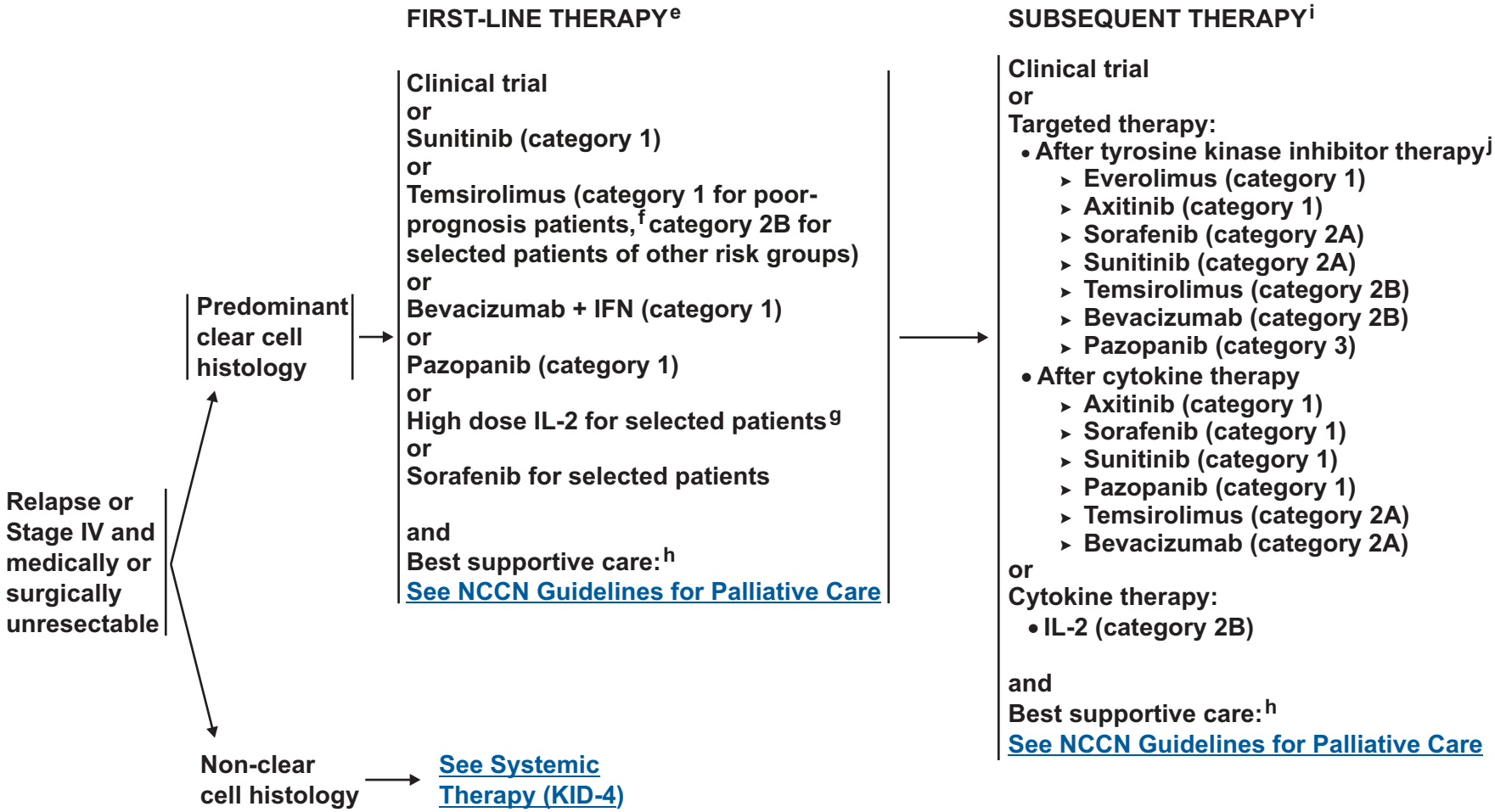

[e] Category 1 recommendations are listed in order of FDA approval.

[f] Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-B).

[g] Patients with excellent performance status and normal organ function.

[h] Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.

[i] Chemotherapy (category 3) in clear cell and non-clear cell RCC with predominant sarcomatoid features has shown modest response to gemcitabine + doxorubicin or gemcitabine + capecitabine.

[j] Currently available tyrosine kinase inhibitors include: axitinib, pazopanib, sorafenib, or sunitinib.

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SYSTEMIC THERAPY[i,k]

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

Clinical trial (preferred)
or
Temsirolimus (category 1 for poor-prognosis patients;[f] category 2A for other risk groups)
or
Sorafenib
or
Sunitinib
or
Pazopanib (category 3)
or
Erlotinib (category 3)
or
Axitinib (category 3)

and
Best supportive care:[h] **See NCCN Guidelines for Palliative Care**

[f]Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-B).
[h]Best supportive care can include palliative RT, metastasectomy, bisphosphonates, or RANK ligand inhibitors for bony metastases.
[i]Chemotherapy (category 3) in clear cell and non-clear cell RCC with predominant sarcomatoid features has shown modest response to gemcitabine + doxorubicin or gemcitabine + capecitabine.
[k]Partial responses have been observed to cytotoxic chemotherapy (carboplatin + gemcitabine or carboplatin + paclitaxel) with collecting duct or medullary subtypes.

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PRINCIPLES OF SURGERY

- **Nephron-sparing surgery (partial nephrectomy) is appropriate in selected patients, for example:**
  - **Small unilateral tumors (T1a and selected patients T1b)**
  - **Uninephric state, renal insufficiency, bilateral renal masses, and familial renal cell cancer**

- **Open, laparoscopic, or robotic surgical techniques may be used to perform radical and partial nephrectomies.**

- **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, 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.**
  - **Randomized phase III comparison with surgical resection (ie, radical or partial nephrectomy by open or laparoscopic techniques) has not been done.**
  - **Ablative techniques are associated with a 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.

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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 USED TO SELECT PATIENTS FOR TEMSIROLIMUS[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;356:2271-2281.

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.

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 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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010), published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

An estimated 64,770 Americans will be diagnosed with renal cancer and 13,570 will die of the disease in the United States in 2012.[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, translocation, 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 described initially as occurring in patients who are sickle-cell trait positive.

Smoking and obesity are established 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]

Analysis of the Surveillance, Epidemiology, and End Results (SEER) database indicates that the five-year survival rate for kidney cancer has increased over time for localized disease (from 88.4% during 1992-1995 to 91.1% during 2002-2008) and for advanced disease (from 7.3% during 1992-1995 to 11.1% during 2002-2008).[1, 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, lymph nodes, 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. 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 these patients should be referred to a hereditary cancer clinic for further evaluation.

A thorough physical examination should be performed along with obtaining a complete medical history of the patient. Laboratory evaluation includes a complete blood cell count, comprehensive metabolic panel (may include serum corrected calcium, serum creatinine, liver function studies, 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.[6]

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.[7, 8]

A central renal mass may suggest the presence of urothelial carcinoma; if so, urine cytology or uteroscopy should be considered.

Most bone and brain metastases are symptomatic at diagnosis. Therefore, a bone scan is not routinely performed unless the patient has an elevated serum alkaline phosphatase or complains of bone pain.[9] CT or MRI of the brain can be performed if clinical signs, presentation, and symptoms suggest brain metastases.

Needle-biopsy may be considered to establish diagnosis of RCC and guide active surveillance strategies.[10]

The value of positron emission tomography (PET) in RCC remains to be determined. Currently, PET alone is not a tool that is standardly used to diagnose kidney cancer or follow for evidence of relapse after nephrectomy.[11]

Treatment of Localized Disease

Surgical resection remains an effective therapy for clinically localized RCC; with options including radical nephrectomy and nephron-sparing surgery, each detailed below. 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. Open, laparoscopic, or robotic surgical techniques may be used to perform radical nephrectomies. Long-term outcome data indicate that laparoscopic and open radical nephrectomies have equivalent cancer-free survival rates.[12-19]

The lymph node dissection has not been consistently shown to provide therapeutic benefit but does provide prognostic information, because virtually all patients with nodal involvement subsequently relapse with distant metastases despite lymphadenectomy. The updated European Organization for the Research and Treatment of Cancer (EORTC) phase III trial compared radical nephrectomy with a complete lymph-node dissection to radical nephrectomy alone. The results showed no significant differences in OS, time to progression of disease, or PFS between the two study groups.[20] However, primary tumor pathological features such as nuclear grade, sarcomatoid component, tumor size, stage and presence of tumor necrosis are all factors that influence the likelihood of regional lymph node involvement at the time of radical nephrectomy.[21]

The NCCN Kidney Cancer Panel recommends lymph node dissection for patients with palpable or CT detected enlarged lymph nodes and to obtain adequate staging information in those with nodes that appear normal.

Ipsilateral adrenal gland resection should be considered for patients with large upper pole tumors or abnormal appearing adrenal glands appearing on CT.[22-24] Adrenalectomy is not indicated when imaging shows a normal adrenal gland or if the tumor is not high-risk, based on size and location.[25]

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.

Partial nephrectomy has well established oncologic outcomes data comparable to radical nephrectomy.[26-29] Radical nephrectomy can lead to an increased risk of chronic kidney disease[30, 31] and is associated with increased risks of cardiovascular morbidity and mortality according to population based studies.[32] When compared with radical nephrectomy, partial nephrectomy can achieve preserved renal function, decreased overall mortality and reduced frequency of cardiovascular events.[32-36] Patients with a hereditary form of RCC, such as VHL syndrome, should also be considered for nephron-sparing therapy. 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.[29, 37-39] Radical nephrectomies should not be employed when nephron sparing can be achieved. A more recent study showed that among Medicare beneficiaries with early stage kidney cancer, treatment with partial rather than radical nephrectomy was associated with improved survival.[40]

The oncological outcome for laparoscopic versus open nephron sparing surgery appears to be similar based on studies with limited follow-up.[41,42] The goals of nephron sparing surgery should be optimal locoregional tumor control while minimizing ischemia time to ideally less than 30 minutes.[43] However, in some patients with localized RCC, nephron–sparing surgery may not be suitable because of locally advanced tumor growth or because tumor is in an unfavorable location. 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[44, 45] (with delayed intervention if indicated) or ablative techniques such as cryo- or radiofrequency ablation are alternative strategies for selected patients, particularly the elderly and those with competing health risks. Randomized phase III comparison of ablative techniques with surgical resection (ie, radical or partial nephrectomy by open or laparoscopic techniques) has not been done.

The NCCN Kidney Cancer Panel has addressed the utility of each treatment modality in the context of tumor stages: Stage IA, Stage IB, and Stages II & III.

Management of Stage IA Disease

The NCCN Panel prefers surgical excision by 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 patients having one kidney 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 the surgeon's expertise.

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

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 if required, to treat for progression.[44]

Although distant recurrence-free survival rates of ablative techniques and conventional surgery are comparable, ablative techniques have been associated with an increased risk of local recurrence.[46-49] Judicious patient selection and counseling remain of paramount importance for these less invasive technologies.

Management of Stage IB Disease

Partial nephrectomy for localized RCC has an oncologic outcome similar to that of radical surgery for T1b tumors.[50, 51] Surgery by either radical nephrectomy or partial nephrectomy (whenever feasible) is the standard of care for clinical T1b tumors according to the NCCN Kidney Cancer Panel.

Management of Stage II and III Disease

Partial nephrectomy is generally not suitable in patients with locally advanced tumors. In these situations, the curative therapy remains radical nephrectomy.[18] Radical nephrectomy is the preferred treatment for the tumors that extend into the inferior vena cava. It 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.

The NCCN Panel lists radical nephrectomy as the only option for Stage II and III tumors.

Followup 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.[52]

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 alpha (IFN-α) or high-dose interleukin (IL-2) or cytokines combinations 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.[53] Observation remains standard care after nephrectomy, and eligible patients should be offered enrolled in randomized clinical trials. There are several ongoing clinical trials and trials completed recently exploring 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.

No single follow-up plan is appropriate for all patients; therefore, individual follow-up plans should be developed that take into account the size, stage and grade to estimate a relative risk of relapse. The NCCN Kidney Cancer Panel recommends that patients be seen every 6 months for the first 2 years after surgery and annually thereafter and each visit should include a history, physical examination, comprehensive metabolic panel (e.g., blood urea nitrogen, serum

creatinine, calcium levels, and liver function tests) and imaging. In terms of imaging, the Panel recommends abdominal (+/- pelvic) and chest imaging.

Alternate surveillance programs have been proposed, such as the surveillance protocol based on the University of California Los Angeles (UCLA) Integrated Scoring System (UISS).[54] The UISS is an evidence-based system in which patients are stratified based on the 1997 TNM stage, grade, and Eastern Cooperative Oncology Group (ECOG) performance status into low, intermediate, or high risk groups for developing recurrence or metastases post-surgical treatment of localized or locally advanced RCC.[54] The use of this protocol may allow selective use of imaging and appropriately targeting those 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 a prolonged disease-free interval from 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 but long-term progression-free survival (PFS) has been reported in these patients.

Prognostic models

Prognostic scoring systems have been developed to define risk groups of patients by combining independent prognostic factors for survival in patients with metastatic RCC.

The most widely used prognostic factor model is from the Memorial Sloan-Kettering Cancer Center (MSKCC). The model was derived from examining prognostic factors in patients (n = 463) with metastatic RCC enrolled on clinical trials and treated with IFN.[55] Prognostic factors on multivariable analysis included five variables - interval from diagnosis to treatment of less than 1 year, Karnofsky performance status less than 80%, serum LDH greater than 1.5 times the upper limit of normal (ULN), corrected serum calcium greater than the ULN, and serum hemoglobin less than the lower limit of normal (LLN). Patients with none of these factors are considered low risk or with good prognosis, those with 1 or 2 factors present are considered intermediate risk, and patients with 3 or more of the factors are considered poor risk. The MSKCC criteria have been additionally elaborated by an independent group at the Cleveland Clinic. The Cleveland group used a data set of 353 patients enrolled on clinical trials involving immunotherapy to validate the MSKCC prognostic model.[56]

The MSKCC prognostic risk profiles are derived from the era of immunotherapy and limited to a population of patients eligible for participation in immunotherapy clinical trials. A prognostic model applicable to the population of patients with metastatic RCC treated with VEGF-targeted therapy has recently been developed popularly known as the International mRCC Database Consortium (IMRDC) or Heng's model.[57] This model was derived from a retrospective study of 645 patients with metastatic RCC treated with sunitinib, sorafenib, or bevacizumab plus interferon. Patients who received prior immunotherapy (ie, received their targeted therapy as second-line

treatment) also were included in the analysis. The analysis identified six clinical parameters to stratify patients into favorable, intermediate, and poor prognosis groups. Four of the five adverse prognostic factors are those previously identified by MSKCC as independent predictors of short survival: hemoglobin less than the LLN, serum corrected calcium greater than the ULN, Karnofsky performance status less than 80% and time from initial diagnosis to initiation of therapy of less than 1 year. Additional independent adverse prognostic factors validated in this model are, absolute neutrophil count greater than ULN and platelets greater than ULN.[57]

Patients with none of the identified six adverse factors were in the favorable-risk category (n = 133; 22.7%) in which a median overall survival (OS) was not reached and a 2-year OS was 75% (95% CI, 65% to 82%). Patients with one or two adverse factors were in the intermediate-risk category (n = 301; 51.4%), in which a median OS was 27 months and a 2-year OS was 53% (95% CI, 46% to 59%). Finally, those patients with three to six adverse factors were in the poor-risk category (n = 152; 25.9%), in which a median OS was 8.8 months and a 2-year OS was 7% (95% CI, 2% to 16%).[57] This model was recently validated in an independent dataset.[58]

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 Southwest Oncology Group (SWOG) and the EORTC randomized patients with metastatic disease to undergo either nephrectomy followed by IFN-α therapy or treatment with IFN-α alone.[59-61] 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).[59-62]

Patient selection is important to identify 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.[63] While similar data are not available for patients who are candidates for high-dose IL-2 (see below), data from the UCLA renal cancer database and from a variety of publications by other groups suggests that nephrectomy also provides benefit to patients who undergo other forms of immunotherapy.[64] As for the role of nephrectomy for patients presenting with metastatic disease and considered for targeted therapies (detailed below), randomized trials are ongoing at this time, but data from the IMRDC suggests that cytoreductive nephrectomy continues to play a role in patients treated with VEGF-targeted agents.[65] 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 were studied in randomized trials. IL-2 was shown to have potent antitumor activity first in several murine tumor models[66] and subsequently in patients with RCC.[67-69] With both IFN- α and IL-2, objective response rates of 5-27% have been reported.[69-71] Although these agents have been helpful for

some patients, in most cases the clinical benefit is modest at best 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 achieve long-lasting complete or partial remissions in a small subset of patients. In patients treated with IFN-α, durable complete responses are rare. While direct comparison of IFN-α and high-dose intravenous bolus IL-2 as approved by the FDA and used in U.S. centers has not been performed, 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 to date attempts to characterize tumor or patient factors for best response to this therapy have been unsuccessful.[66, 70, 72] Thus, the best criteria to select patients for IL-2 therapy are based in large part on safety and include the patient's performance status, medical co-morbidities, tumor histology (predominantly clear cell), MSKCC or Survival After Nephrectomy and Immunotherapy (SANI) risk scores, [55,64, 73] and the patient's attitude toward risk.

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

Targeted Therapy

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

Tumor histology and risk stratification of patients is important in targeted therapy selection. The histological diagnosis in RCC is established after surgical removal of renal tumors or after biopsy. According to the World Health Organization (WHO),[74] there are three major histologic RCC types: clear cell RCC (80–90%), papillary RCC (10–15%), and chromophobe RCC (4–5%). Prognostic systems are used for risk stratification in the metastatic setting.[55, 57]

Sunitinib as first-line therapy for predominantly clear cell carcinoma

Sunitinib is a multi-kinase 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).[75, 76]

Preclinical data suggested that sunitinib has anti-tumor activity that may result from both inhibition of angiogenesis and inhibition of cell proliferation.[77, 78] 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.[75] The patients selected for the trial had no prior treatment with systemic therapy, good performance status and measurable disease. The primary endpoint was PFS and secondary endpoints were patient related outcomes, OS, 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 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 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 demonstrate a strong trend towards OS advantage of sunitinib over IFN-α in the first-line setting (26.4 months vs. 21.81 months, $P = 0.051$).[71] Recent data from an expanded access trial that was performed before the drug became commercially available revealed 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.[79]

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

Bevacizumab along with Interferon as first-line therapy for predominantly clear cell carcinoma

Bevacizumab is a recombinant humanized monoclonal antibody that binds and neutralizes circulating VEGF-A. 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).[80] 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 significant increase or novel adverse effects were observed with the combination over IFN-α alone. A trend toward improved OS also was observed (23.3 months with bevacizumab plus IFN-α versus 21.3 months for IFN-α), although the difference did not reach statistical significance.[80]

In the United States, a similar trial was performed by the Cancer and Leukemia Group B, with 732 previously untreated patients randomized 1:1 to receive either IFN-α or the combination of bevacizumab plus IFN-α. 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 alone. However toxicity was greater in the combination therapy arm.[81] The survival data for this trial were recently updated, showing no significant differences in median survival between the two groups (18.3 vs 17.4 months for bevacizumab plus IFN-α vs. IFN-α alone).[82]

The NCCN Kidney Cancer Panel recommends bevacizumab in combination with IFN-α as a category 1 option for first line treatment of patients 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 targeting VEGFR-1, -2, and -3, PDGFR-α and -β, and c-KIT. The safety and effectiveness of pazopanib was evaluated in a phase III trial open-label, international, multi-center study. Four hundred thirty-five 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 months versus 4.2 months for patients assigned to placebo.[83] The treatment naive subpopulation of 233 patients, randomized 2:1 to pazopanib versus placebo had a median PFS 11.1 months on pazopanib versus 2.8

months on placebo.[83] 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%). Notable grade 3 toxicity was hepatotoxicity, indicated by elevated levels of alanine (30%) and aspartate (21%) transaminase. Therefore it is critical to monitor liver function before and during treatment with the drug. Recently reported results of a large non-inferiority study (COMPARZ) of sunitinib versus pazopanib suggests that these two drugs have a similar efficacy profile with better tolerability for pazopanib.[84]

The NCCN Kidney Cancer Panel has listed pazopanib as a category 1 option for 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. mTOR regulates micronutrients, cell growth, apoptosis and angiogenesis by 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, a phase III, multicenter, randomized, open-label study in previously untreated patients with advanced RCC who had 3 or more of 6 unfavorable prognostic factors.[85] The prognostic factors included: less than one year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60-70, hemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, LDH > 1.5 times the ULN, metastasis to one or more than one organ site. Six hundred and twenty six patients were randomized equally to receive IFN-α alone, or temsirolimus alone or the combination of temsirolimus and IFN-α. Patients in both temsirolimus-containing groups were recommended pre-medication with an antihistamine to prevent infusion reactions. Patients were stratified for prior nephrectomy and geographic region. Seventy percent were less than 65 years old and 69% were male. The group of patients who received temsirolimus alone showed a significant improvement in OS over those receiving IFN-α alone or both drugs. The median OS was 10.9 months for patients on temsirolimus alone versus 7.3 months for those treated with IFN-α alone. The median PFS (the study's secondary endpoint) 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 OS or PFS 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, or hyperglycemia.

Based on this data, the NCCN Kidney Cancer Panel has included temsirolimus as a category 1 recommendation for first-line treatment of poor risk patients with relapsed or medically unresectable predominantly clear cell stage IV renal carcinoma.

Sorafenib as first-line therapy for predominantly clear cell carcinoma

Sorafenib tosylate is a small molecule that inhibits multiple isoforms of the intracellular serine/threonine kinase, RAF, and also other receptor tyrosine kinases, including VEGFR-1, -2, and -3, PDGFR-β, FLT-3, c-KIT, and RET.[86-90]

A randomized phase II trial investigated the efficacy and safety of sorafenib versus IFN-α in previously untreated patients with clear cell RCC.[91] One hundred and eighty nine patients were randomized to

continuous oral sorafenib (400 mg bid) or IFN-α, with an option of dose escalation of sorafenib to 600 mg bid or crossover from IFN-α to sorafenib (400 mg bid) upon disease progression. The primary endpoint was PFS. In the IFN-α arm, 90 patients received treatment; 56 had disease progression, 50 of whom crossed to sorafenib (400 mg bid). Ninety-seven patients in the sorafenib arm received treatment and had median 5.7 months PFS versus 5.6 months for IFN-α. The results showed that more sorafenib treated (68.2% vs. 39.0%) patients had tumor regression.[91] 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 for sorafenib (as second-line therapy) in patients who failed IFN-α treatment and those who had been treated with sorafenib up-front.

Sorafenib is listed as a category 2A option as first-line treatment, for selected patients with relapsed or medically unresectable stage IV predominantly clear cell stage IV renal carcinoma by the NCCN Kidney Cancer Panel.

Subsequent Therapy for Patients with Predominantly Clear Cell Carcinoma

Everolimus as subsequent therapy

Everolimus (RAD001) is an orally administered inhibitor of mTOR. 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.[92] Four hundred ten were randomly assigned 2:1 to receive either everolimus or placebo, and the primary end point was PFS. The median PFS assessed by an independent review committee was in favor of everolimus, 4.0 versus1.9 months.[92] The most common adverse events reported in patients on everolimus (mostly of mild or moderate severity) were stomatitis in 40% versus 8% in the placebo group, rash 25% versus 4%, and fatigue 20% versus16%.[92] According to the updated results of this trial, median PFS determined by independent central review was 4.9 months for everolimus versus 1.9 months (95% CI, 1.8-1.9) for placebo.[93]

Everolimus is a category 1 recommendation after tyrosine kinase therapy according to the NCCN Kidney Cancer Panel.

Axitinib as subsequent therapy

Axitinib is a selective, second generation inhibitor of VEGFR -1, -2, and -3.[94] A multicenter, randomized phase III study compared axitinib versus sorafenib as second-line therapy after 1 prior systemic therapy (with mostly cytokines or sunitinib).[95] The patients (n = 723) were stratified for performance status and type of prior therapy, and randomized 1:1 to axitinib 5 mg orally twice daily or sorafenib 400 mg twice daily.[95] The overall median PFS was 6.7 months for axitinib versus 4.7 months for sorafenib (HR 0.665, $P < .0001$) and the response rate was 19% is axitinib versus 9% in sorafenib treated patients ($P = .0001$). The PFS favored axitinib in the both the groups treated with a prior cytokine (12.1 vs. 6.5 months; $P < .0001$) and with prior sunitinib (4.8 vs. 3.4 months; $P = .01$).[95] Adverse events of all grades more frequent with axitinib were hypertension, fatigue, dysphonia and hypothyroidism. Adverse events more frequent with

sorafenib were hand-foot syndrome, rash, alopecia and anemia. Axitinib is considered a category 1 recommendation by the NCCN Kidney Cancer Panel in patients who have failed at least one prior systemic therapy.

Sorafenib as subsequent therapy

Efficacy of sorafenib was studied in patients who progressed on a prior therapy (mostly cytokines) in a phase III placebo controlled randomized trial, TARGET (Treatment Approaches in RCC Global Evaluation Trial).[96] Nine hundred and three 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 OS, and the secondary endpoint was PFS. Sorafenib significantly prolonged median PFS compared with placebo (5.9 months vs. 2.8 months) and median OS in the preliminary analysis (19.3 vs. 15.9 months) for all patient subsets; with the large difference in PFS, crossover to the sorafenib treatment arm was permitted, which likely resulted in the failure of this trial to demonstrate an OS benefit for sorafenib in the final analysis. With censoring of crossover data, the median OS was 19.3 months for sorafenib versus 14.3 months for placebo.[97] Adverse effects were grade 3 to 4 hand-foot syndrome, fatigue, and hypertension observed in 5%, 2%, and 1% of patients, respectively.[98] This study showed the effectiveness of sorafenib in a clinical setting comprising primarily of patients who progressed on prior cytokine therapy. Sorafenib has also been studied in as second-line therapy in patients treated with sunitinib or bevacizumab and found to be safe, feasible, and effective.[99, 100] Sorafenib is considered category 1 by the NCCN Kidney Cancer Panel when used after cytokine therapy and category 2A when used after a prior tyrosine kinase inhibitor therapy.

Sunitinib as subsequent therapy

Sunitinib also has demonstrated substantial anti-tumor activity in the second-line therapy of metastatic RCC after progression on cytokine therapy.[76, 101] Studies investigating the sequential use of sunitinib and sorafenib mostly are retrospective. There are prospective data, although limited, suggest a lack of total cross resistance between TKIs, 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.[102-108] Sunitinib is considered category 1 by the NCCN Kidney Cancer Panel when used after cytokine therapy and category 2A when used after a prior tyrosine kinase inhibitor therapy.

Pazopanib as subsequent therapy

The phase III trial comparing pazopanib with placebo, detailed earlier under the section titled "*Pazopanib as first-line therapy for predominantly clear cell carcinoma"*, included 202 patients who received prior cytokine therapy. The average PFS in cytokine pre-treated patients was 7.4 versus 4.2 months.[83] Based on the results from this trial, the NCCN Kidney Cancer Panel considers pazopanib as a category 1 option after cytokine therapy. However after tyrosine kinase failure, the use of pazopanib is listed as category 3, because there no data are available in this setting.

Other agents as subsequent therapy

The NCCN Panel considers temsirolimus a category 2A recommendation after cytokine therapy and category 2B after tyrosine kinase inhibitor. Bevacizumab is a category 2A recommendation after

cytokine therapy and category 2B after tyrosine kinase inhibitor. IL-2 is a category 2A recommendation.

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

Subset analysis of the global ARCC trial demonstrated benefit of temsirolimus not only in clear cell renal carcinoma but also in non-clear cell histology.[85, 109] Temsirolimus is a category 1 recommendation for non-clear cell carcinoma patients with poor prognosis features (according to MSKCC risk criteria) and category 2A for patients belonging to other prognostic risk groups.

Tyrosine kinase inhibitors for predominantly non-clear cell carcinoma

Data from expanded-access trials and phase II trials support clinical activity of sunitinib[79, 110-115] and sorafenib[116-118] in patients with non–clear cell histologies. However, the data indicate that compared with clear cell type RCC, clinical activity of these drugs expressed seems to be reduced in patients with non-clear cell histologies. Additional prospective studies are needed to further clarify the role of sunitinib and sorafenib in non-clear cell carcinoma. There are ongoing[119 120] or recently completed[121] phase II studies investigating the role of sunitinib in non-clear cell carcinoma. Sunitinib and sorafenib are category 2A recommendations for treatment naïve patients with stage IV non-clear cell carcinoma.

The efficacy of pazopanib or axitinib has not yet been studied in patients with non-clear carcinoma. Therefore based on extrapolation, the NCCN Kidney Cancer Panel has included these therapies as a first line therapy for patients with relapsed or medically unresectable stage IV disease with non-clear cell histology (category 3).

The efficacy of erlotinib, an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, was studied in patients with advanced papillary RCC.[122] Fifty two patients were treated with erlotinib given orally once daily. The overall response rate was 11% (five of 45 patients; 95% CI, 3% to 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 OS was 27 months.[122] This study demonstrated disease control and survival outcomes of interest with an expected toxicity profile with single agent erlotinib. The NCCN Kidney Cancer Panel has included erlotinib as an option for first-line therapy for patients with relapsed or medically unresectable stage IV non-clear cell carcinoma (category 3).

Chemotherapy for metastatic renal cell carcinoma

Treatment of RCC with sarcomatoid features and non-clear cell histologies and remains a challenge.

Sarcomatoid variant is an aggressive form of RCC that can occur in any histology subtype.[123] Sarcomatoid RCC is associated with a poor prognosis.[124-127] Chemotherapy plays a role in the management of a variety of sarcomas therefore its use in sarcomatoid RCC patients has been explored. Gemcitabine in combination with doxorubicin or in combination with capecitabine has shown some activity in patients with non-clear cell or clear cell tumors with sarcomatoid features.[128-135]

Among the non-clear cell histologies, renal medullary carcinoma is extremely rare; comprising approximately 2% of all primary renal tumors in young people and metastatic disease is seen at presentation

in 95% of the patients.[136, 137] Chemotherapy remains the focus of treatment for this subtype, although the prognosis remains dismal.

Collecting-duct carcinoma is also a very rare type of non-clear cell RCC, often presenting at an advanced stage of disease. Up to 40% of patients have metastatic spread at initial presentation and most patients die within 1–3 years from the time of primary diagnosis.[138-141] Collecting duct carcinoma shares biologic features with urothelial carcinoma. In a multicenter prospective study, 23 patients with no prior therapy were treated with a combination of gemcitabine and either cisplatin or carboplatin.[142] The results showed a response rate of 26% and an OS of 10.5 months.[142]

The NCCN Kidney Cancer Panel has noted in a footnote that chemotherapy is a category 3 option for treatment of clear cell and non clear cell RCC with predominant sarcomatoid features. The chemotherapy regimens that have shown some benefit for patients with predominant sarcomatoid features include: gemcitabine in combination with doxorubicin or capecitabine. In addition, the Panel has noted that partial responses to cytotoxic chemotherapy have been observed (gemcitabine in combination with carboplatin; or paclitaxel with carboplatin) in patients with other non-clear cell subtypes such as collecting duct or medullary subtypes.

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 those 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 or patients remain symptomatic. 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.

While the role of bone modifying agents such as bisphosphonates (eg. zoledronic acid) has been established in this setting[143, 144] the role of novel therapies such as inhibitors of RANK ligand (eg. denosumab) is emerging. A recent phase III randomized trial directly compared the development of skeletal-related events (SREs) on either denosumab or zoledronic acid in patients with multiple myeloma or bone metastases with a solid tumor (excluding breast or prostate cancer). The study enrolled 1,776 patients with bone metastases from a wide range of cancer types, including patients with renal cell carcinoma (6%) not treated previously with a bisphosphonate.[145] Denosumab was reported non-inferior to zoledronic acid in delaying time to first on-study SRE (hazard ratio, 0.84; 95% CI, 0.71 to 0.98; P = .0007).[145]

The NCCN Kidney Cancer Panel recommends a bisphosphonate or a RANK ligand inhibitor for selected patients with bony metastases and creatinine clearance ≥ 30 mL/min. Daily supplemental calcium and vitamin D are strongly recommended. 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).

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