NCCN Guidelines® Insights

Kidney Cancer, Version 3.2015

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Kidney Cancer provide multidisciplinary recommendations for the clinical management of patients with clear cell and non-clear cell renal carcinoma. These NCCN Guidelines Insights highlight the recent updates/changes in these guidelines, and updates include axitinib as first-line treatment option for patients with clear cell renal carcinoma, new data to support pazopanib as subsequent therapy for patients with clear cell carcinoma after first-line treatment with another tyrosine kinase inhibitor, and guidelines for follow-up of patients with renal cell carcinoma. (J Natl Compr Canc Netw 2015;13:151–159)

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Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes to the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the NCCN Guideline Panel discussion, including the literature reviewed.**

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Release date: February 18, 2015; Expiration date: February 18, 2016

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Kidney Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Kidney Cancer

Disclosure of Relevant Financial Relationships

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Eric Jonasch, MD, Panel Vice-Chair, has disclosed the following relationships with commercial interests: consultant fees/honoraria from AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, and Pfizer Inc.; and grant/research support from Exelixis Inc., GlaxoSmithKline, Novartis Pharmaceuticals Corporation, and Pfizer Inc.

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Supported by an educational grant from Eisai; a contribution from Exelixis Inc.; educational grants from Bristol-Myers Squibb, Genentech BioOncology, Merck, Novartis Oncology, Novocure; and by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

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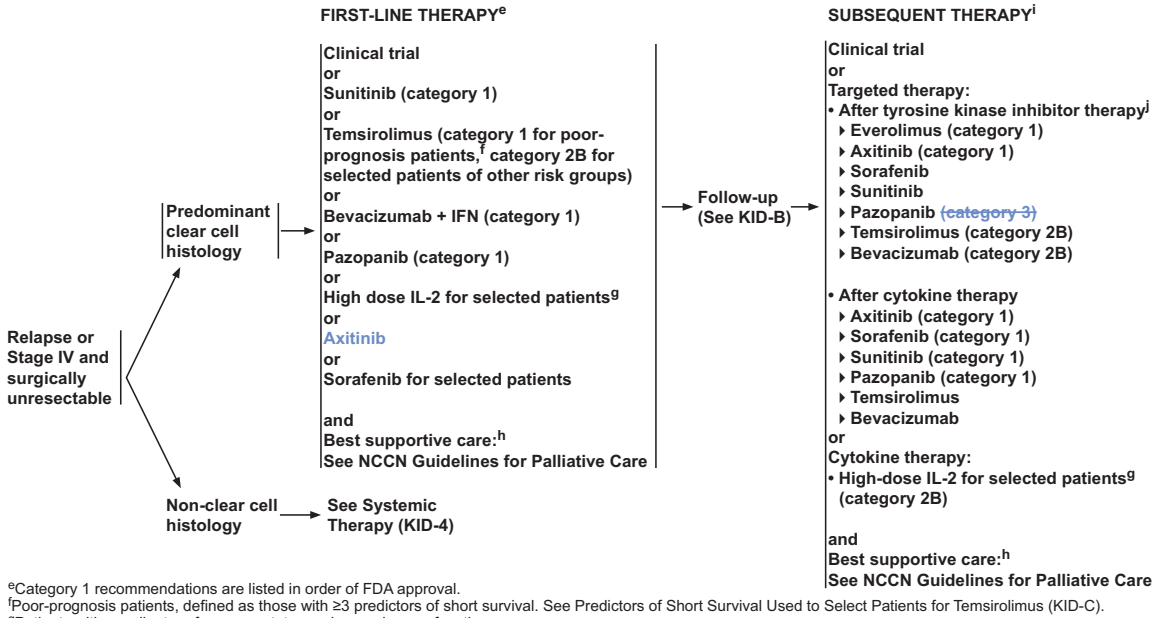

[e]Category 1 recommendations are listed in order of FDA approval.
[f]Poor-prognosis patients, defined as those with ≥3 predictors of short survival. See Predictors of Short Survival Used to Select Patients for Temsirolimus (KID-C).
[g]Patients with excellent performance status and normal organ function.
[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.

KID-3

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.

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

Overview

Renal cell carcinoma (RCC) constitutes approximately 3.9% of new cancers, with a median age of 64 years at diagnosis. The American Cancer Society estimated that 63,920 Americans would be diagnosed with and 13,860 would die of RCC in the United States in 2014.[1] The rate of RCC has increased by 1.6% per year for the past 10 years (2002–2011).[2] Analysis of the SEER database, however, indicates that the 5-year survival rate for kidney cancer has increased over time for localized disease (from 88.4% during 1992–1995 to 91.8% during 2004–2010) and advanced disease (from 7.3% during 1992–1995 to 12.3% during 2004–2010).[2] This improvement in survival may be attributed to the recent advances in treatment options for patients with RCC.

The NCCN Kidney Cancer Panel is a multidisciplinary panel of leading experts from NCCN Member Institutions consisting of medical oncol-

FOLLOW-UP[a,b]
(category 2B)

Stage I (pT1a)

Follow-up During Active Surveillance

- H & P every 6 mo for 2 y, then annually up to 5 y after diagnosis
- Comprehensive metabolic panel and other tests as indicated every 6 mo for first 2 y, then annually up to 5 y after diagnosis
- Abdominal imaging:
  - Abdominal CT or MRI within 6 mo of surveillance initiation, then CT, MRI or US at least annually
- Chest imaging:
  - Chest x-ray or CT annually to assess for pulmonary metastases, if biopsy positive for RCC
- Pelvic imaging, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

Follow-up After Ablative Techniques

- H & P every 6 mo for 2 y, then annually up to 5 y after diagnosis
- Comprehensive metabolic panel and other tests as indicated every 6 mo for first 2 y, then annually up to 5 y after diagnosis
- Abdominal imaging:
  - Abdominal CT or MRI with and without contrast at 3-6 mo following ablative therapy unless otherwise contraindicated then CT, MRI or US, annually for 5 y
- Chest imaging:
  - Chest x-ray or CT annually for 5 y for patients who have biopsy proven low risk RCC, nondiagnostic biopsies or no prior biopsy
- Repeat biopsy:
  - New enhancement, a progressive increase in size of an ablated neoplasm with or without contrast enhancement, new nodularity in or around the treated zone, failure of the treated lesion to regress over time, satellite or port site lesions
- Pelvic imaging, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

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[a]Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
[b]No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years at the discretion of the physician. Further study is required to define optimal follow up duration.

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ogists, hematologists and hematologic oncologists, radiation oncologists, urologists, and pathologists. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Kidney Cancer are developed by the NCCN Kidney Cancer Panel and updated by the panel continually. The most recent and complete version of these guidelines, is available on the NCCN Web site (NCCN.org).

These NCCN Guidelines Insights highlight recent updates/changes in the NCCN Guidelines for Kidney Cancer, including the addition of axitinib as a first-line treatment option for patients with clear cell RCC, the inclusion of new data supporting pazopanib as subsequent therapy for patients with clear cell carcinoma after first-line treatment with another tyrosine kinase inhibitor, and guidelines for follow-up of patients with RCC during or after primary treatment.

Axitinib as First-Line Therapy for Patients With Predominantly Clear Cell RCC

Patients with predominantly clear cell RCC treated with axitinib, 5 mg orally twice daily in the second-line setting demonstrated greater objective response and longer median progression-free survival (PFS) compared with those treated with sorafenib, 400 mg orally twice daily. To determine whether this held true in the first-line setting, a randomized, open-label, phase III trial was performed in newly diagnosed patients randomized (2:1) to receive axitinib (5 mg, twice daily) or sorafenib (400 mg, twice daily).[3] The median PFS in patients treated with axitinib was 10.1 months (95% CI, 7.2–12.1) versus 6.5 months with sorafenib (95% CI, 4.7–8.3), a difference that was not statistically significant.[3] The adverse events more commonly seen with axitinib (≥10% difference) than with sorafenib included diarrhea, hypertension, weight loss, decreased appetite, dysphonia, hypothyroidism, and upper abdom-

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FOLLOW-UP[a,b]
(category 2B)

Stage I (pT1a) and (pT1b)

Follow-up After a Partial or Radical Nephrectomy

- H & P every 6 mo for 2 y, then annually up to 5 y after nephrectomy
- Comprehensive metabolic panel and other tests as indicated every 6 mo for 2 y, then annually up to 5 y after nephrectomy
- Abdominal imaging:
  - After Partial Nephrectomy:
    - Baseline abdominal CT, MRI, or US within 3-12 mo of surgery
    - If the initial postoperative scan is negative, abdominal CT, MRI, or US may be considered annually for 3 y based on individual risk factors
  - After Radical Nephrectomy:
    - Patients should undergo abdominal CT, MRI or US within 3-12 mo of surgery
    - If the initial postoperative imaging is negative, abdominal imaging beyond 12 mo may be performed at the discretion of the physician
- Chest imaging: Chest x-ray or CT annually for 3 y, then as clinically indicated
- Pelvic imaging, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

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[a]Donat SM, Diaz M, Bishoff JT, et al. Follow-up for clinically localized renal neoplasms: AUA Guideline. J Urol 2013;190:407-416.
[b]No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years at the discretion of the physician. Further study is required to define optimal follow up duration.

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inal pain, whereas those more commonly seen with sorafenib included palmar-plantar erythrodysesthesia, rash, alopecia, and erythema.[3] Even though the difference in PFS between patients treated with axitinib versus sorafenib was not statistically significant, these results showed that axitinib had clinical activity and an acceptable toxicity profile in the first-line setting.

Another randomized multicenter phase II trial evaluated the efficacy and safety of axitinib dose escalation in patients with newly diagnosed metastatic RCC.[4] In this study, all patients received axitinib, 5 mg twice daily for 4 weeks. They were then assigned (1:1) to undergo upward titration of axitinib or continuation of axitinib, 5 mg twice daily plus placebo titration. The axitinib dose was increased in the study arm to 7 mg orally twice per day, and if tolerated, was increased up to a maximum of 10 mg orally twice per day.[4] More patients in the axitinib titration group experienced an objective response than those treated with axitinib, 5 mg orally twice daily (54% vs 34%), although PFS was not different between groups.[4]

Based on the findings from the studies described, the NCCN Kidney Cancer Panel included axitinib as an option for the first-line treatment of patients with predominantly clear cell carcinoma (category 2A; see KID-3, page 153).

Pazopanib as Subsequent Therapy for Predominantly Clear Cell Carcinoma

The safety and effectiveness of pazopanib in patients who received first-line cytokines was evaluated in a phase III, open-label, international, multicenter study, which randomized patients to either pazopanib, 800 mg orally daily, or placebo. Of the 435 patients with advanced clear cell RCC, 202 had received prior cytokine therapy. The average PFS in cytokine pretreated patients was 7.4 months in pazopanib-treated patients versus 4.2 months in

FOLLOW-UP[a,b]
(category 2B)

Stage II or III

Follow-up After a Radical Nephrectomy

- H & P every 3-6 mo for 3 y, then annually up to 5 y after radical nephrectomy and then as clinically indicated thereafter
- Comprehensive metabolic panel and other tests as indicated every 6 mo for 2 y, then annually up to 5 y after radical nephrectomy, then as clinically indicated thereafter
- Abdominal imaging:
  - Baseline abdominal CT or MRI within 3-6 mo, then CT, MRI or US (US is category 2B for Stage III), every 3-6 mo for at least 3 y and then annually up to 5 y
  - Imaging beyond 5 y: as clinically indicated
  - Site specific imaging: as symptoms warrant
- Chest imaging:
  - Baseline chest CT within 3-6 mo after radical nephrectomy with continued imaging (CT or chest x-ray) every 3-6 mo for at least 3 y and then annually up to 5 y
  - Imaging beyond 5 y: as clinically indicated based on individual patient characteristics and tumor risk factors
- Pelvic imaging, as clinically indicated
- CT or MRI of head or MRI of spine, as clinically indicated
- Bone scan, as clinically indicated

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[b]No single follow-up plan is appropriate for all patients. Follow-up frequency and duration should be individualized based on patient requirements, and may be extended beyond 5 years at the discretion of the physician. Further study is required to define optimal follow up duration.

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placebo-treated patients.[5] Based on the results of this trial, the NCCN Kidney Cancer Panel included pazopanib as a category 1 option after cytokine therapy.

Until now, the use of pazopanib after progression on a first-line tyrosine kinase inhibitor was listed as a category 3 recommendation because of lack of data in this setting. Recently, a prospective phase II trial examined the activity and toxicity of second-line treatment with pazopanib (800 mg, orally daily) in 56 patients with advanced metastatic RCC.[6] The patients enrolled in this trial had received first-line treatment with sunitinib (n=39) or bevacizumab (n=16). Responses were evaluated after 8 weeks of treatment using RECIST. The trial showed that 27% of patients (n=15) had an objective response to pazopanib and 49% (n=27) had stable disease.[6] After a median follow-up of 16.7 months, the median PFS was 7.5 months (95% CI, 5.4–9.4 months).[6] The PFS was similar whether previous treatment was with sunitinib or bevacizumab. The estimated overall survival rate at 24 months was 43%.[6]

A retrospective analysis reported data on 93 patients with metastatic RCC treated with multiple lines of prior targeted therapies and who were subsequently treated with pazopanib.[7] Among 85 evaluable patients, 15% (n=3) had a partial response and the observed median PFS was 6.5 months (95% CI, 4.5–9.7).

Based on these data, the use of pazopanib is now listed as a category 2A recommendation after tyrosine kinase failure in the updated NCCN Guidelines for Kidney Cancer (see KID-3, page 153).

Follow-up of Patients With Kidney Cancer

The updated NCCN Guidelines provide a framework for follow-up of patients undergoing surveillance of a small renal mass, those who underwent surgery or ablative therapy of a primary RCC, and those under-

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FOLLOW-UP[c]
(category 2B)

Follow-up for Relapsed or Stage IV and Surgically Unresectable Disease

- H & P every 6-16 weeks for patients receiving systemic therapy, or more frequently as clinically indicated and adjusted for type of systemic therapy patient is receiving
- Laboratory evaluation as per requirements for therapeutic agent being used
- Chest, abdominal and pelvic imaging:
  - CT or MRI imaging to assess baseline pretreatment or prior to observation
  - Follow up imaging every 6-16 weeks as per physician discretion and per patient clinical status. Imaging interval to be adjusted upward and downward according to rate of disease change and sites of active disease.
- Consider CT or MRI of head at baseline and as clinically indicated. Annual surveillance scans at physician discretion.
- MRI of spine as clinically indicated.
- Bone scan as clinically indicated.

[c]No single follow-up plan is appropriate for all patients. Follow-up should be individualized based on treatment schedules, side effects, comorbidities, and symptoms.

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going systemic therapy for advanced disease. These NCCN Guidelines incorporate a risk-stratified use of imaging that may target the patients most in need of intensive surveillance and/or imaging tests during follow-up.

The panel has reiterated in a footnote that no single follow-up plan is appropriate for everyone, and follow-up should be modified for the individual patient using clinical judgement. Because uniform consensus is lacking among the panel members regarding the most appropriate follow-up plan, these recommendations are listed as category 2B (see KID-B, 1–4 of 4; pages 154–157). Additionally, the NCCN Guidelines include follow-up for the first 5 years after nephrectomy, with follow-up evaluation to be extended beyond 5 years at the discretion of the physician. Results from a retrospective analysis indicate that in a subset of patients, relapses occur more than 5 years after surgery for their primary RCC.[8] This report suggests that continued follow-up/surveillance after 5 years may be of potential value in some patients. Identification of subsets of patients with higher risk that require longer follow-up has not been defined, and further research is required to refine follow-up strategies for patients with RCC.

Follow-up During Active Surveillance for Stage pT1a RCC

For follow-up during active surveillance, the NCCN Guidelines recommend a history and physical examination, comprehensive metabolic panel, and other tests every 6 months for the first 2 years and then annually up to 5 years after diagnosis. To study the growth rate of the tumor, the panel recommends abdominal imaging (with CT or MRI) within 6 months from initiation of active surveillance, and subsequent imaging (with CT, MRI, or ultrasound) may be performed annually thereafter. All 3 modalities (ultrasound, CT, and MRI) have been found to

accurately predict pathologic tumor size in a retrospective analysis.[9] Therefore, best clinical judgement should be used in choosing the imaging modality. For patients with biopsy-proven RCC, the recommendation is to assess annually for pulmonary metastases using chest imaging techniques (radiograph or CT). The panel recommends imaging of the pelvis; CT or MRI of the head or MRI of the spine in the presence of neurologic symptoms; or bone scan in cases of elevated alkaline phosphatase (ALP), bone pain, or abnormal radiologic findings.

Follow-up After Ablative Therapy for Stage pT1a RCC

Most follow-up tests recommended by the panel after ablative therapy are similar to those included during active surveillance. For imaging tests after ablative therapy, the panel recommends abdominal CT or MRI with or without intravenous contrast unless otherwise contraindicated at 3 and 6 months to assess treatment response, followed by annual abdominal CT or MRI scans for 5 years. The panel recommends annual chest radiograph or chest CT for 5 years to assess for pulmonary metastases in patients who have biopsy-proven low-risk RCC, nondiagnostic biopsies, or no prior biopsy to assess for liver metastases. The panel suggests repeat biopsy if radiographic evidence shows progressive increase in size of an ablated neoplasm with or without contrast enhancement, new nodularity in or around the treated zone, failure of the treated lesion to regress over time, or the presence of satellite or port site lesions.

Follow-up After Nephrectomy for Stage I–III RCC

For patients with stages pT1a and pT1b RCC after partial or radical nephrectomy, the panel recommends a history and physical examination, comprehensive metabolic panel, and other tests be performed every 6 months for 2 years, and then annually up to 5 years after nephrectomy. The panel recommends a baseline abdominal scan (CT, MRI, or ultrasound) for patients undergoing either partial or radical nephrectomy within 3 to 12 months after renal surgery. If the initial postoperative imaging shows negative results, abdominal imaging beyond 12 months for patients who have undergone radical nephrectomy may be performed at the discretion of the physician; for those who have undergone partial nephrectomy, abdominal scans (CT, MRI, or ultrasound) may be considered annually for 3 years based on individual risk factors. Local recurrence rates for smaller tumors after partial nephrectomy are 1.4% to 2.0% versus 10.0% for larger tumors.[10–12]

The panel recommends yearly chest imaging (chest radiograph or CT) for 3 years, and as clinically indicated thereafter. Imaging of the pelvis, CT or MRI of the head or MRI of the spine, or bone scan is recommended as clinically indicated.

Follow-up for Patients With Stage II–III RCC After Radical Nephrectomy

Larger tumors have a substantially higher risk of both local and metastatic recurrence; therefore, an increase in frequency of examinations is recommended compared with patients with stages pT1a or pT1b. The panel recommends a history and physical examination every 3 to 6 months for 3 years, then annually up to 5 years after radical nephrectomy, and thereafter as clinically indicated. Comprehensive metabolic panel tests and other tests as indicated every 6 months for 2 years, then annually up to 5 years after radical nephrectomy, and thereafter as clinically indicated.

The panel recommends baseline chest imaging (with CT) and abdominal scans (CT or MRI) within 3 to 6 months after radical nephrectomy, with continued imaging (CT or radiograph of the chest; CT, MRI, or ultrasound of the abdomen) every 3 to 6 months for at least 3 years, and then annually thereafter for up to 5 years.[13] Although the use of ultrasound imaging for follow-up is an option for low-risk patients, CT is the preferred modality for those with a high risk of recurrence. Disagreement exists among the panel members regarding the usefulness of ultrasound in patients with stage III disease; therefore, it is listed as a category 2B option specifically for patients with stage II disease. The panel has noted that imaging beyond 5 years may be performed as clinically indicated, and site-specific imaging performed as symptoms warrant. Other tests, such as imaging of the pelvis, CT or MRI of the head or MRI of the spine, or bone scan, are recommended as clinically indicated.

Follow-up for Relapsed or Stage IV and Surgically Unresectable RCC

Patients with relapsed or stage IV and unresectable disease often receive systemic therapy. For these patients, the panel recommends a history and physical examination every 6 to 16 weeks, or more frequently as clinically indicated, adjusting according to the type of systemic therapy the patient is receiving. The panel

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recommends laboratory tests as per requirements for the therapeutic agent being used. For the chest, abdomen, and pelvis, the panel recommends pretreatment CT or MRI imaging to obtain a baseline evaluation. The panel suggests follow-up imaging every 6 to 16 weeks as per physician discretion and patient clinical status, adjusting the imaging intervals according to the rate of disease change and sites of active disease. The panel also suggests considering CT or MRI of the brain at baseline and as clinically indicated. Annual surveillance brain MRI or CT scans can be performed according to physician discretion. Other imaging tests, such as MRI of the spine and bone scan, can be performed as clinically indicated.

Conclusions

The NCCN Guidelines are in continuous evolution. They are updated annually, and sometimes more often if new high-quality clinical data become available in the interim. The recommendations in the NCCN Guidelines, with few exceptions, are based on evidence from clinical trials. Expert medical clinical judgment is required to apply these guidelines in the context of an individual patient to provide optimal care. The physician and the patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials. To view the full and most recent version of the NCCN Guidelines for Kidney Cancer, visit NCCN.org

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Posttest Questions

1. In the recently updated NCCN Guidelines for Kidney Cancer (Version 3.2015), which of the following agents is a new first-line treatment option for patients with predominantly clear cell carcinoma?
   a. Pazopanib
   b. Axitinib
   c. Everolimus
2. For patients with predominantly clear cell carcinoma, in which of the following instances does pazopanib have a lower level of evidence (phase II data) supporting its use?
   a. As first-line therapy
   b. As subsequent therapy after initial therapy with a tyrosine kinase inhibitor
   c. As subsequent therapy after initial therapy with a cytokine
3. True or False: Data show that relapses may occur after 5 years of surgical removal of primary RCC in a subset of patients.