Management of Metastatic Clear Cell Renal Cell Carcinoma: ASCO Guideline

Rathmell et al.
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Background & Methodology
Introduction

• Kidney cancer will be diagnosed in 79,000 U.S. patients in 2022 and will account for 13,920 deaths.¹

• Clear cell renal cell carcinoma, ccRCC, is the most common subtype of RCC, and it continues to be a major source of morbidity and mortality.¹,²

• An acceleration in reported phase III studies has created a seismic shift in available treatment options.

• Opportunities for extended survival and even durable disease control in the metastatic setting are reshaping the trajectory of this cancer and raising the stakes in providing optimal treatment planning.

• This rapid evolution has paved the way for the first creation of a comprehensive set of guidelines to guide therapeutic selection and future translational development to continue to advance the treatment of metastatic ccRCC.
ASCO Guideline Development Methodology

• The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  ▪ a systematic literature review by ASCO guidelines staff
  ▪ an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  ▪ final guideline approval by ASCO EBMC

• The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology
Clinical Questions

This clinical practice guideline addresses six overarching clinical questions:

1. How is metastatic clear cell renal cell carcinoma defined and how is it diagnosed?
2. What is the role of cytoreductive nephrectomy in metastatic clear cell renal cell carcinoma?
3. What are the preferred options for first line systemic treatment of metastatic clear cell renal cell carcinoma?
4. What is the optimal second or later line systemic treatment for metastatic clear cell renal cell carcinoma?
5. What is the optimal application of metastasis directed therapy for metastatic clear cell renal cell carcinoma?
6. What considerations should be applied to treatment of special subsets of metastatic clear cell renal cell carcinoma? (e.g., bone metastases, brain metastases, sarcomatoid carcinomas).
Target Population and Audience

Target Population

• Patients with metastatic clear cell renal cell carcinoma

Target Audience

• Medical oncologists, radiation oncologists, urologists, nurses, other healthcare practitioners, social workers, patients, and caregivers.
Summary of Recommendations
Summary of Recommendations

Clinical Question 1

• How is metastatic clear cell renal cell carcinoma defined and how is it diagnosed?

Recommendation 1.1

• The diagnosis of metastatic clear cell renal cell carcinoma should ideally involve comparison of tissue acquired outside the site of primary disease to the primary histology. Histologic evaluation should include common markers of clear cell renal cell carcinoma including paired box gene 8 (PAX8) and Carbonic anhydrase IX (CAIX).
Summary of Recommendations

Recommendation 1.2

• Radiographic diagnosis of metastatic clear cell renal cell carcinoma may be applied in selected circumstances, such as settings in which a prior diagnosis of renal cell carcinoma has been established, when metastatic tissue is not readily accessible by biopsy, or when RECIST 1.1 measurable disease is evident, especially within a year of the initial diagnosis.
Summary of Recommendations

Clinical Question 2

• What is the role of cytoreductive nephrectomy in metastatic clear cell renal cell carcinoma?

Recommendation 2.1

• Select patients (see Practical Information) with metastatic clear cell renal cell carcinoma may be offered cytoreductive nephrectomy.

• Practical Information: Select patients include those with optimally 1 IMDC risk factor who can have a significant majority of their tumor burden removed at the time of surgery.
Summary of Recommendations

Clinical Question 3

• What are the preferred options for first line systemic treatment of metastatic clear cell renal cell carcinoma?

Recommendation 3.1

• Select patients with metastatic clear cell renal cell carcinoma (see Practical Information) may be offered an initial active surveillance strategy.

• Practical Information: Select patients include those with IMDC favorable and intermediate risk, patients with limited or no symptoms related to disease, a favorable histologic profile, a long interval between nephrectomy and the development of metastasis or with limited burden of metastatic disease.
Summary of Recommendations

Recommendation 3.2

- All patients with metastatic clear cell renal cell carcinoma who require systemic therapy in the first line setting should undergo risk stratification into IMDC favorable (0), intermediate (1-2), and poor (3+) risk groups. Patients with intermediate or poor risk disease should be offered combination treatment with two immune checkpoint inhibitors (i.e., ipilimumab and nivolumab) or an immune checkpoint inhibitor in combination with a VEGFR TKI.
Summary of Recommendations

Recommendation 3.3

- Patients with favorable risk disease who require systemic therapy may be offered an immune checkpoint inhibitor in combination with a VEGFR TKI.

Evidence based benefits outweigh harms

Evidence Quality
High

Strength of Recommendation
Strong

Recommendation 3.4

- Select patients with metastatic clear cell renal cell carcinoma receiving systemic therapy in the first-line setting including those with favorable risk disease or with certain co-existing medical problems may be offered monotherapy with either a VEGFR TKI or an immune checkpoint inhibitor.

Evidence based benefits outweigh harms

Evidence Quality
Moderate

Strength of Recommendation
Strong
Summary of Recommendations

Recommendation 3.5

- The use of high dose Interleukin-2 (HD-IL2) may be considered in the first-line systemic therapy setting for patients with metastatic clear cell renal cell carcinoma (see Practical Information). Attempts to develop criteria to predict those patients most likely to derive benefit from HD-IL2 have been unsuccessful.

- Practical Information: The significant toxicity of this regimen must be weighed in relation to the newer immunotherapy regimens which have largely replaced this treatment. The expert panel was not able to identify a patient population who should receive this treatment preferentially based on available data. The expert panel did agree that HD-IL2 should be administered in experienced high-volume centers, and that enrollment in clinical trials was preferred.
Summary of Recommendations

Clinical Question 4

• What is the optimal second or later line systemic treatment for metastatic clear cell renal cell carcinoma?

Recommendation 4.1

• Nivolumab or cabozantinib should be offered to patients who progressed on a VEGFR TKI alone.

Evidence based benefits outweigh harms

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<tr>
<th>Evidence Quality</th>
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Summary of Recommendations

Recommendation 4.2

• Patients progressing on combination immunotherapy (e.g. nivolumab, ipilimumab) should be offered a VEGFR TKI.

Recommendation 4.3

• Patients who progress after initial therapy combining VEGFR TKI with an immune checkpoint inhibitor may be offered an alternate VEGFR TKI as a single agent.
Summary of Recommendations

Recommendation 4.4

• For patients on immunotherapy who experience limited disease progression (e.g., one site of progression), local therapy (radiation, thermal ablation, excision) may be offered, and immunotherapy may be continued.
Summary of Recommendations

Clinical Question 5

• What is the optimal application of metastasis directed therapy for metastatic clear cell renal cell carcinoma?

Recommendation 4.1

• For patients with low volume metastatic renal cell carcinoma, definitive metastasis-directed therapies may be offered and include surgical resection (metastasectomy), ablative measures, or radiotherapy.

Evidence based benefits outweigh harms

Evidence Quality: Moderate

Strength of Recommendation: Strong
Summary of Recommendations

Recommendation 5.2

• For patients undergoing complete metastasectomy subsequent TKIs are not routinely recommended.
Summary of Recommendations

Clinical Question 6

• What considerations should be applied to treatment of special subsets of metastatic clear cell renal cell carcinoma? (e.g., bone metastases, brain metastases, sarcomatoid carcinomas)

Recommendation 6.1.1

• Patients with symptomatic bone metastases from metastatic clear cell renal cell carcinoma should receive bone-directed radiation.
Summary of Recommendations

Recommendation 6.1.2

• Patients with bone metastases from metastatic clear cell renal cell carcinoma should be offered a bone resorption inhibitor (either bisphosphonate or RANKL inhibitor) when clinical concern for fracture or skeletal related events is present.

Consensus based benefits outweigh harms

Evidence Quality Strength of Recommendation
Moderate Strong

Recommendation 6.1.3

• No recommendation regarding optimal systemic treatment for metastatic clear cell renal cell carcinoma patients with bone metastasis can be made; however, it is our expert opinion that cabozantinib-containing regimens may be preferred.

Consensus based benefits outweigh harms

Evidence Quality Strength of Recommendation
Low Moderate
Summary of Recommendations

Recommendation 6.2.1

• Patients with brain metastases from metastatic clear cell renal cell carcinoma should receive brain-directed local therapy with radiation therapy and/or surgery.

Recommendation 6.2.2

• No recommendation regarding optimal systemic therapy for patients with metastatic clear cell renal cell carcinoma and brain metastases can be made.
Summary of Recommendations

Recommendation 6.3

- Patients with metastatic clear cell renal cell carcinoma with sarcomatoid features should receive immune checkpoint inhibitor-based combination first-line treatment (ipilimumab plus nivolumab, or alternatively, an immune checkpoint inhibitor plus a TKI).
Patient and Clinician Communication

• Additional factors identified by the two patient representatives on the panel that both patients and clinicians should consider and address for patients with metastatic ccRCC include:
  ▪ This patient group faces daunting median survival odds. The first-line treatments outlined in these recommendations will likely provide a survival benefit to many patients. However, when disease is no longer being controlled, patients may benefit by focusing on quality of life and time spent with loved ones. Palliative care can provide important benefits for this patient group, even when active treatment plans are in play.
  ▪ The goal of this guideline has been to assist clinicians with insights on the latest data to help inform their treatment decisions.
  ▪ The current pace of developments and change places a burden on clinicians and patients to recognize the rapidly changing environment and the need to stay abreast. Second opinions with kidney cancer content experts should become an accepted practice for patients and case conferences or tumor boards should focus on collaborating on difficult cases to the greatest extent possible.
  ▪ The level of uncertainty associated with treatment is high, and this would indicate a substantially greater need for shared decision making between clinicians and patients, along with input from multidisciplinary team members.
  ▪ Patients and caregivers should be encouraged to reach out to family members, friends, and other patients to ensure they can avoid the loneliness, depression, and poor decision making that frequently occurs by those attempting to go it alone.
  ▪ There is great need to improve personalized treatment for patients with metastatic ccRCC.
Cost Implications

• Individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and co-insurance, and the costs of RCC treatment have been increasing.\textsuperscript{4-6}

• Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended treatments.\textsuperscript{7,8}

• Comparisons of ipilimumab + nivolumab vs sunitinib and ipilimumab + nivolumab vs axitinib + pembrolizumab vs sunitinib both found ipilimumab + nivolumab to be the most cost-effective combination treating mRCC.\textsuperscript{9,10}

  ▪ In the absence of widely agreed upon definitions for incremental cost-effectiveness ratios and willingness to pay thresholds per quality-adjusted life years gained, these analyses are limited.

  ▪ The number of potential treatments available and the nuanced clinical judgment used by providers to recommend one over the others makes comprehensive comparisons challenging.

• Discussions of treatment expense, especially out-of-pocket costs, in the context of overall financial toxicity with the assistance of financial counselors and social workers can help with shared decision making and bolster informed consent.
Additional Resources

• More information, including a supplement and clinical tools and resources, is available at www.asco.org/genitourinary-cancer-guidelines

• Patient information is available at www.cancer.net
## Guideline Panel Members

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<tr>
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Abbreviations

- ASCO, American Society of Clinical Oncology
- CAIX, carbonic anhydrase IX
- ccRCC, clear cell renal cell carcinoma
- EBMC, Evidence Based Medicine Committee
- HD-IL2, high dose interleukin-2
- IMDC, International Metastatic RCC Database Consortium
- PAX8, paired box gene 8
- RANKL, receptor activator of nuclear factor kappa-B ligand
- RCC, renal cell carcinoma
- RECIST, Response Evaluation Criteria in Solid Tumours
- TKI, tyrosine kinase inhibitor
- U.S., United States
- VEGFR, vascular endothelial growth factor receptor
References

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