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## **Preface: Current Landscape of Advanced and Metastatic Renal Cell Carcinoma Management**

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Anil Kapoor, Jaehoon Kim, George Goucher, and Jen Hoogenes

Advanced renal cell carcinoma is not uncommon, but necessitates a multidisciplinary approach for optimal treatment. Targeted therapy has increased the likelihood of urologists managing patients in all disease stages. Neoadjuvant therapy is currently experimental. Systemic therapy for metastatic disease demonstrates survival benefits. The role of cytoreductive nephrectomy and adjuvant therapy is dependent on patient selection. Management of advanced renal cell carcinoma involves continued optimization of available agents and biomarker development. This article reviews the role of the urologist in medical and surgical therapies, including prognostication, management of locally advanced and metastatic disease, and provides the most recent clinical trial data.

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Soumya V.L. Vig, Elcin Zan, and Stella K. Kang

Patients with renal cell carcinoma may develop metastases after radical nephrectomy, and therefore monitoring with imaging for recurrent or metastatic disease is critical. Imaging varies with specific suspected site of disease. Computed tomography/MRI of the abdomen and pelvis are mainstay modalities. Osseous and central nervous system imaging is reserved for symptomatic patients. Radiologic reporting is evolving to reflect effects of systemic therapy on lesion morphology. Nuclear medicine studies compliment routine imaging as newer agents are evaluated for more accurate tumor staging. Imaging research aims to fill gaps in treatment selection and monitoring of treatment response in metastatic renal cell carcinoma.

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Kyrollis Attalla, Stanley Weng, Martin H. Voss, and A Ari Hakimi

In the preceding two decades, several milestones have been reached in the management of patients with metastatic renal cell carcinoma (mRCC), including the development of novel targeted agents paralleling an increased understanding of the molecular biology of this disease process. Recently, a renewed enthusiasm for immunotherapy in the form of immune checkpoint blockade has resulted in significant strides in the treatment of mRCC. Despite these advances, treatment remains challenging for clinicians, and only modest survival benefits are observed with current treatment paradigms. The risk-stratification tools and investigated predictive and prognostic biomarkers in patients with mRCC are detailed in this review.

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Nazli Dizman, Zeynep E. Arslan, Matthew Feng, and Sumanta K. Pal

In an era of several therapeutic options available, optimal treatment sequencing is crucial to providing patients the most effective therapy and promoting quality of life. In clear cell renal cell carcinoma, a combination approach with an immunotherapy backbone, such as nivolumab/ipilimumab or axitinib/pembrolizumab, has a key role in the first-line setting. Safety and activity data support the transition to single-agent targeted therapies in the second-line setting. Nivolumab monotherapy possesses clinical and mechanistic rationale as a second-line therapeutic option for patients treated with targeted therapies in the first-line setting. Gene expression models are being generated from large prospective clinical trial data sets.

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Ronan Flippot, Vijay Damarla, and Bradley A. McGregor

Variant histology renal cell carcinoma (vRCC) encompasses rare non-clear cell subtypes that have long been associated with poor prognosis and minimal response to therapies targeting vascular endothelial growth factor and its receptor. Molecular advances have helped classify vRCC into distinct entities and identify putative targetable driver alterations, such as MET in papillary subtypes. More have since been identified in other vRCC subtypes, including alterations of tumor metabolism, chromatin remodeling genes, cell-cycle genes, and inactivation of tumor suppressors such as TP53 or NF2. New targeted therapies, as well as immune checkpoint inhibitors, have been in development and yielded encouraging results. Collaborative clinical trials will be an essential step toward better implementation of these regimens in clinical practice.

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Mary E. Westerman, Daniel D. Shapiro, Christopher G. Wood, and Jose A. Karam

There has been strong interest in using neoadjuvant therapy to decrease recurrence rates and facilitate surgical resection in locally advanced renal cell carcinoma. To date, no evidence exists to support improvement in oncologic outcomes with neoadjuvant therapy. Likewise, although targeted therapies have shown efficacy in tumor downsizing, this does not often translate to downstaging. Use of presurgical therapy for the purpose of downstaging inferior vena cava tumor thrombi is currently not supported. Future studies evaluating the benefit of newer immune checkpoint inhibitors will determine if there is a larger role for neoadjuvant therapy in locally advanced renal cell carcinoma.

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Erika Wood, Nicholas Donin, and Brian Shuch

This article reviews the use of adjuvant therapies for prevention of recurrence following resection of clinically localized renal cell carcinoma (RCC). Clinical trials evaluating adjuvant therapy for RCC have focused primarily on the use of tyrosine kinase inhibitors and mammalian target of rapamycin inhibitors, which had improved outcome in patients with metastatic disease. However, all but 1 trial found no difference in disease-free survival in the adjuvant setting and none improved overall survival.

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Michael J. Biles, Hiten D. Patel, and Mohamad E. Allaf

The role for cytoreductive nephrectomy (CN) in the treatment of metastatic renal cell carcinoma (mRCC) has evolved with advancements in systemic therapy. During the cytokine-based immunotherapy era, CN provided a clear survival benefit and was considered standard of care in management of mRCC. The development of targeted systemic therapy directed at the vascular endothelial growth factor pathway altered the treatment paradigm and accentuated the importance of risk stratification in treatment selection. This article reviews the literature evaluating the benefit of CN during the evolution of systemic therapy and provides clinical recommendations for current utilization of CN in patients with mRCC.

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Pooja Unadkat, Aria F. Olumi, and Boris Gershman

The role of lymph node dissection (LND) in the management of renal cell carcinoma (RCC) is controversial. LND serves an indisputable staging role by providing pathologic nodal stage. However, while earlier observational studies had suggested a survival benefit to LND, more recent observational evidence and a randomized trial do not support a survival benefit. The majority of patients with isolated lymph node involvement appear to harbor occult metastatic disease. Still, LND is not associated with increased perioperative morbidity when performed in experienced centers. LND may therefore play a predominantly staging role in patients at increased risk of lymph node metastases.

**The Evolving Role of Metastasectomy for Patients with Metastatic Renal Cell Carcinoma** 379

Bryan DR Hall and Edwin Jason Abel

Surgical metastasectomy continues to be utilized for patients with solitary or low-volume metastatic renal cell carcinoma (mRCC). Although few high-quality data are available to evaluate outcomes, local treatment is recommended when feasible because it may allow a subset of patients to delay or avoid systemic treatments. With the development of improved mRCC therapies, utilization of metastasectomy has increased because most patients have incomplete responses to systemic treatment of their metastases. This review discusses the rationale and history of metastasectomy, trends in utilization, prognostic factors for patient selection, site-specific considerations, alternatives for nonsurgical local treatment, and risk of morbidity associated with metastasectomy.

**Minimally Invasive Surgery for Patients with Locally Advanced and/or Metastatic Renal Cell Carcinoma** 389

Ezequiel Becher, Dora Jericevic, and William C. Huang

Despite advances in systemic therapy and immunotherapy, surgery continues to have a role in management of advanced renal cell carcinoma (aRCC). Minimally invasive surgery (MIS) is considered standard of care for smaller, localized tumors due to faster recovery without compromising oncologic outcomes. There are concerns about MIS for aRCC due to a potential risk of inferior oncologic outcomes and unusual patterns of disease recurrence. Recent studies, however, suggest that in properly selected patients with aRCC, MIS can provide improved peri-operative outcomes without compromising oncologic control.

**Radiation Therapy for Patients with Advanced Renal Cell Carcinoma****399**

Joseph A. Miccio, Oluwadamilola T. Oladeru, Sung Jun Ma, and Kimberly L. Johung

Stereotactic radiosurgery and stereotactic body radiation therapy (SBRT) have led to a resurgence of the use of radiotherapy in the management of advanced renal cell carcinoma (RCC). These techniques provide excellent local control and palliation of metastatic sites of disease with minimal toxicity. Additionally, SBRT to the primary tumor may be efficacious and well tolerated in select patients that are not surgical candidates. Emerging data suggest that SBRT may potentiate the immune response, and current and future study will evaluate if SBRT can improve survival outcomes in patients with metastatic RCC.