

**Invited Review Article**

Contemporary management of locally advanced and metastatic renal cell carcinoma: An update of current evidence

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Abstract

Management of renal cell carcinoma (RCC), particularly locally advanced (laRCC) and metastatic disease (mRCC), has evolved rapidly with the integration of immune checkpoint inhibitors, targeted therapies, and multimodal strategies. The aim of this review is to provide an updated, evidence-based overview of current treatment paradigms and emerging concepts.

A comprehensive literature review was conducted focusing on pivotal phase III trials, contemporary guidelines (EAU, NCCN), and recent advances in systemic therapy, surgery, and metastasis-directed approaches. Key domains included: (i) management of locally advanced RCC; (ii) first-line systemic therapy in clear cell mRCC; (iii) second- and later-line treatment; (iv) non-clear cell and sarcomatoid variants; and (v) oligometastatic and oligoprogressive disease.

Adjuvant immunotherapy, particularly in regard to pembrolizumab, has become standard in selected high-risk laRCC following nephrectomy. In mRCC immune checkpoint inhibitor-based combination therapies (IO-IO or IO-TKI) have demonstrated superior survival outcomes in comparison to monotherapy. Novel agents such as HIF-2 α inhibitors (e.g., belzutifan) are expanding treatment options in later lines. Increasing emphasis is placed on individualized strategies, including active surveillance in favorable-risk patients and metastasis-directed therapy in oligometastatic disease.

The management of la/mRCC is increasingly personalized and multidisciplinary. While immunotherapy-based combinations dominate current practice, ongoing trials and biomarker development will further refine treatment sequencing and patient selection.

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Introduction

Kidney cancer, predominantly renal cell carcinoma (RCC), remains a significant global health burden. The incidence of RCC has gradually increased worldwide over the past two decades, particularly in developed regions, likely reflecting greater use of diagnostic imaging, improved healthcare access, and changes in lifestyle-related risk factors.¹

Given the increasing global burden of RCC, optimizing management strategies for locally advanced and metastatic disease has become increasingly important. Prognosis remains strongly stage-dependent; with approximately 80% of patients presenting with localized disease and excellent outcomes being achieved following partial or radical nephrectomy, with 5-year survival rates exceeding 90%.² Despite these encouraging results, disease recurrence occurs in approximately 20–40% of patients following curative-intent surgery.³ In contrast, patients with locally advanced (laRCC) or metastatic disease (mRCC) have substantially poorer outcomes, with reported 5-year cancer-specific survival rates ranging from 30% to 80%, depending on disease burden and risk stratification.²

The aggressive nature of locally advanced and metastatic renal cell carcinoma (la/mRCC) underscores a persistent unmet clinical need, necessitating ongoing efforts to refine therapeutic strategies and improve patient outcomes. In recent years, the treatment landscape of la/mRCC has undergone rapid transformation, driven by the accumulation of evidence supporting several novel approaches. These include the adoption of adjuvant immunotherapy following nephrectomy in high-risk laRCC^{4,5} the introduction of hypoxia-inducible factor 2 alpha (HIF-2 α) inhibitors such as belzutifan for advanced clear cell mRCC⁵, and the expanding role of immune checkpoint inhibitor-based combination regimens, including immunotherapy plus tyrosine kinase inhibitors (TKI), across both clear cell and non-clear cell histologies.^{6,7}

In parallel, increasing attention has been directed towards the management of oligometastatic disease, where multimodal strategies incorporating metastasis-directed therapy (MDT) and systemic treatment have demonstrated promising outcomes.^{8–11} Collectively, these advances highlight the need for an updated, evidence-based

synthesis to guide contemporary clinical practice in la/mRCC.

Materials and Methods

This literature review was conducted to summarize contemporary evidence on the management of la/mRCC. The focus of the review was on perioperative management, first- and later-line systemic therapies, sarcomatoid and non-clear cell RCC, and the management of oligometastatic and oligoprogressive disease.

Relevant studies were identified through a PubMed search of articles published between January 2021 and June 2026 using terms related to RCC, cytoreductive nephrectomy (CN), perioperative therapy, immunotherapy, targeted therapy, sarcomatoid differentiation, non-clear cell histology, and oligometastatic disease. Eligible publications included randomized controlled trials, observational studies, systematic reviews, and contemporary clinical guidelines. Titles, abstracts, and full texts were reviewed for relevance. Evidence was synthesized narratively, with emphasis on pivotal clinical trials and guideline-defining studies that have shaped current treatment paradigms.

Results

The evidence-based findings were identified and synthesized (Table 1), forming the basis of the following thematic review.

Surgical and (neo)adjuvant treatment in locally advanced RCC

Role of cytoreductive nephrectomy (CN)

The role of CN in the management of advanced RCC has evolved considerably in the era of targeted therapy and immunotherapy. Contemporary evidence suggests that upfront CN may be selectively considered in carefully chosen patients, particularly those with limited metastatic burden, symptomatic primary tumors (e.g., significant hematuria), or favorable clinical characteristics.

However, data from pivotal phase III trials, including CARMENA¹² and SURTIME¹³, demonstrated no overall survival (OS) advantage for immediate CN followed by systemic therapy in comparison with systemic therapy alone in the targeted therapy era. Importantly, these trials predominantly enrolled patients with high metastatic burden and poor-risk disease according to

**Table 1.** Update statements

Part / Topic	Statements
1.1 Cytoreductive nephrectomy	Upfront CN can be considered in selected patients with good performance status, symptomatic primary tumor, oligometastases, or low metastatic burden. Deferred CN can be considered after IO-based combination therapy or TKI-based therapy.
1.2 Neoadjuvant therapy	Routine neoadjuvant systemic therapy for locally advanced RCC is not recommended.
1.3 Adjuvant therapy	Urologists should coordinate care and refer intermediate-to-high-risk recurrence or M1 NED patients to oncologists. Adjuvant therapy should start within 16 weeks after nephrectomy in eligible patients.
1.4 Monitoring adjuvant therapy	Contrast-enhanced CT chest/abdomen/pelvis is recommended before adjuvant therapy. CBC, liver function, creatinine, and TSH should be monitored regularly. CT every 3–6 months in years 1–2 and every 6 months in years 3–5 is recommended. Follow-up after year 5 should be individualized. PET-CT or MRI may be used for equivocal CT findings. MRI may be used if CT is contraindicated. Bone and brain imaging are recommended only when clinically indicated.
2.1 Genomic testing	Routine genomic testing to guide treatment selection for metastatic clear-cell RCC is not recommended.
2.2 Prior adjuvant pembrolizumab	For recurrence during adjuvant pembrolizumab, TKI monotherapy is an option. IO+TKI rechallenge may be considered if recurrence occurs ≥ 12 months after completion of adjuvant pembrolizumab.
2.3 First-line systemic therapy	Active surveillance is feasible in selected patients. TKI monotherapy is an option for IMDC very-favourable risk. IO+TKI is standard for favourable-risk disease. TKI monotherapy may be an alternative in selected favourable-risk patients. IMDC intermediate/poor-risk patients should receive IO+IO or IO+TKI. IO+TKI is preferred for rapidly progressing or extensive disease. Treatment discontinuation may be considered after 2 years of IO+IO.
2.4 Treatment monitoring	Contrast-enhanced CT thorax/abdomen/pelvis should be performed regularly. Imaging outside these areas should be done only when clinically indicated.
3.1 Second-line treatment	IO rechallenge is not recommended after progression on first-line IO+IO or IO+TKI. Options include unused TKI, lenvatinib + everolimus, lenvatinib + belzutifan, and belzutifan after TKI and IO exposure. After first-line TKI, options include cabozantinib, nivolumab, lenvatinib + everolimus, or IO+TKI.
3.2 Third-line and beyond	After exposure to IO, TKI, and belzutifan, lenvatinib + everolimus may be considered.
4.1 Sarcomatoid features	IO+IO or IO+TKI is recommended for IMDC intermediate/poor-risk mRCC with sarcomatoid dedifferentiation. In favourable-risk disease, IO+IO or IO+TKI are treatment options.
4.2 Non-clear-cell RCC	Preferred first-line options include pembrolizumab + lenvatinib, nivolumab + cabozantinib, nivolumab + ipilimumab, or cabozantinib.
5.1 Oligometastatic definitions	Synchronous oligometastatic RCC: ≤ 3 metastatic lesions at diagnosis. Metachronous oligometastatic RCC: ≤ 3 metastatic lesions >1 year after primary diagnosis. Oligoprogressive RCC: ≤ 3 new/progressive lesions after systemic therapy or enlargement of known metastatic lesions by RECIST.
5.2 Oligometastatic RCC management	Upfront systemic therapy is preferred in patients with IMDC poor risk, brain metastases, non-clear-cell RCC, sarcomatoid features, or rapidly progressive disease. Selected options include nephrectomy + complete MDT followed by surveillance, adjuvant pembrolizumab, IO combinations, or IO-based therapy followed by consolidative nephrectomy and MDT. SBRT may delay progression and systemic therapy.
5.3 Oligorecurrent / oligoprogressive RCC	In oligorecurrent disease after nephrectomy, IO-based combinations should be first-line, and MDT/SBRT may delay progression. In oligoprogression after nephrectomy and IO-based therapy, SBRT to new lesions with continuation of current therapy may be considered, and IO/TKI may need temporary withholding during MDT.

the International mRCC Database Consortium (IMDC) criteria.

Immediate CN is no longer routinely recommended in metastatic RCC. A deferred approach after initial systemic therapy is increasingly adopted to optimize patient selection. Although prospective evidence is lacking, retrospective data suggest that CN may improve outcomes in selected patients. In a pooled analysis of five phase III IO+TKI trials (N = 981), upfront CN was associated with longer progression-free survival (PFS) (15 vs. 11 months), OS (46 vs. 28 months), and higher response rates (60% vs. 46%).¹⁴

Similarly, data from the IMDC cohort, which included patients treated with IO-based combination therapy with either delayed CN (n = 24), upfront CN (n = 182), or no CN (n = 179), suggested that the performance of CN, whether upfront or deferred, was independently associated with improved OS (HR, 0.45; 95% CI, 0.26–0.78; p = 0.005).¹⁵ Additional smaller retrospective studies have also reported encouraging oncological outcomes and acceptable safety profiles for deferment of CN following initial systemic therapy.^{16–18}

Although current evidence is largely retrospective and subject to selection bias, upfront CN may be considered in selected patients with symptomatic primary tumors or oligometastatic disease. In contrast, patients with poor-risk features or aggressive disease are generally better managed with initial systemic therapy. A deferred CN approach following favorable response or disease stabilization with systemic treatment may further optimize patient selection and outcomes.¹⁹

Role of neoadjuvant therapy

Locally advanced renal cell carcinoma (laRCC) is often characterized by complex anatomical features. These may include venous tumor thrombus involving the renal vein and/or inferior vena cava (levels I–IV), extension beyond Gerota's fascia (T4 disease), and/or bulky regional lymphadenopathy (N1/2 disease), all or any of which may render surgical resection technically challenging.²⁰

Neoadjuvant systemic therapy has been investigated as a means of reducing tumor burden, facilitating complete surgical resection, and targeting occult micrometastatic disease prior to definitive surgery. Furthermore, the response to

preoperative therapy may provide valuable insight into tumor biology and treatment sensitivity, potentially informing subsequent therapeutic decision-making.²¹

Several studies evaluating TKIs and immune checkpoint inhibitors, either as a monotherapy or in combination, have reported modest tumor shrinkage and partial response rates in the neoadjuvant setting.^{21,22} Although neoadjuvant systemic therapy offers a compelling biological rationale, current evidence does not support its routine use in locally advanced RCC. The negative results of the phase III PROSPER trial underscore the need for further prospective evaluation, and neoadjuvant immunotherapy should presently be regarded as investigational.²³

No clear clinical benefit has been shown by perioperative single-agent immunotherapy in locally advanced RCC. Although several ongoing trials are evaluating the efficacy of neoadjuvant combinations of immune checkpoint inhibitors and TKIs, robust evidence supporting routine neoadjuvant therapy remains lacking. Given concerns regarding treatment-related toxicity, potential disease progression during treatment, and delayed surgery, neoadjuvant systemic therapy should currently be considered investigational and reserved for clinical trial settings.²¹

Role of adjuvant therapy

Adjuvant pembrolizumab has become the standard of care for patients with high-risk RCC following nephrectomy. In the phase III KEYNOTE-564 trial, pembrolizumab significantly improved both DFS (HR 0.72) and OS (HR 0.62) compared with placebo, with consistent benefit observed across all clinically relevant subgroups.^{4,24}

Based on current evidence, adjuvant pembrolizumab is generally recommended for eligible patients within an appropriate postoperative window, typically within 16 weeks after CN. Careful assessment of recurrence risk and patient fitness is required to balance the potential survival benefit against treatment-related toxicity, reinforcing the importance of individualized decision-making in this setting.

In addition to KEYNOTE-564, several other phase III randomized trials have evaluated adjuvant immunotherapy in patients with locally advanced RCC, including PROSPER (perioperative nivolumab)²³, IMmotion010 (atezolizumab)²⁵,



and CheckMate 914 (nivolumab plus ipilimumab)²⁶. However, none of these studies demonstrated a significant improvement in disease-free survival (DFS), highlighting the variability in outcomes across different immunotherapeutic strategies in the adjuvant setting.

Several factors may account for the positive findings observed in KEYNOTE-564 compared with other trials.²⁷ The positive results of KEYNOTE-564 may reflect differences in patient selection, trial design, and the biological activity of PD-1 inhibition. Notably, the study enrolled patients with high-risk disease who may derive greater benefit from immunotherapy. Based on these findings, adjuvant pembrolizumab has been incorporated into major international guidelines as the standard of care for selected patients with high-risk RCC following CN.²⁸

Patients with high-risk RCC or M1 NED status should be considered for adjuvant pembrolizumab following multidisciplinary evaluation, with treatment typically initiated within 16 weeks after CN.²⁴ Careful assessment of postoperative recovery, pathological risk stratification, and patient fitness is essential to optimize treatment outcomes.

Monitoring during and after adjuvant therapy

Patients receiving adjuvant pembrolizumab should undergo baseline staging with contrast-enhanced CT before initiation of treatment, followed by regular clinical, laboratory, and radiologic surveillance to monitor for recurrence and treatment-related toxicities. Follow-up schedules should be individualized according to recurrence risk and clinical status.

The recommended surveillance strategies following adjuvant pembrolizumab are largely reliant on the design of KEYNOTE-564 and contemporary guideline recommendations.²⁴ Most RCC recurrences occur within the first five years after curative-intent surgery, with the lungs and regional lymph nodes representing the most common sites of relapse.^{3,29} Consequently, routine imaging of these regions is essential, most commonly performed using contrast-enhanced CT, with MRI or positron emission tomography (PET)-CT serving as alternative modalities in selected clinical scenarios.

In addition to imaging, periodic laboratory evaluation is important for the early detection of treatment-related adverse events associated with pembrolizumab. Surveillance strategies should

be tailored according to the individual risk of recurrence. In patients with lower-risk disease who remain recurrence-free for 2-3 years, a reduction in imaging frequency may be appropriate.³⁰ Conversely, extended follow-up beyond five years may be warranted in patients with high-risk features, with some evidence supporting surveillance durations of up to 10 years in those with aggressive histopathological characteristics.³¹

Contemporary role of robot-assisted surgery in RCC

Surgery remains an important component of multidisciplinary management in selected patients with locally advanced and metastatic RCC. Advances in minimally invasive surgery, particularly robot-assisted techniques, have expanded the feasibility of complex renal procedures while reducing perioperative morbidity. Robot-assisted partial nephrectomy (RAPN) provides excellent oncological and functional outcomes and can be safely performed in selected patients with highly complex renal tumors.³²⁻³⁴

Robot-assisted approaches, including RAPN, may facilitate nephron-sparing surgery in selected complex renal tumors when performed in experienced centers. However, their role in locally advanced or metastatic RCC should be individualized within a multidisciplinary framework. Recent publications from Fujita Health University and other leading robotic centers have contributed substantially to the understanding of advanced robotic kidney surgery, highlighting the importance of selective arterial clamping, ischemia-sparing techniques, three-dimensional image-guided surgical planning, and functional outcome optimization after partial nephrectomy.^{32,33} Furthermore, the increasing integration of robotic surgery into the management of complex RCC, including locally advanced tumors, inferior vena cava thrombus, and selected metastatic settings, reflects an ongoing paradigm shift toward individualized and precision-based surgical care.

First-line management of clear cell mRCC

Role of genomic testing

Despite increasing interest in biomarker-driven treatment selection, no genomic or molecular biomarker has been reliably validated for routine clinical use in clear cell mRCC. Although higher expression of PD-L1 may be associated with improved outcomes in some studies, its pre-

dictive value remains inconsistent and insufficient to guide therapeutic decision-making.³⁵

Beyond PD-L1, several molecular and immune-related biomarkers, including angiogenesis signatures, CD8⁺ T-cell infiltration, myeloid inflammation-related gene expression profiles, PD-1, T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and lymphocyte activation gene-3 (LAG-3), have demonstrated an association with PFS outcomes in patients treated with immunotherapy.^{36,37} Nevertheless, their predictive value for long-term survival outcomes remains unclear, and none have been validated for routine clinical decision-making. Tumor mutational burden and neoantigen load, which are predictive in other malignancies, do not appear to significantly influence treatment response in RCC.³⁶

Ongoing research is evaluating the role of genomic alterations and novel molecular technologies, including circulating tumor DNA, single-cell RNA sequencing, and spatial profiling, as potential biomarkers for treatment selection in mRCC. Despite promising preliminary findings, these approaches remain investigational and are not currently recommended for routine clinical practice.³⁸

Management of patients with prior exposure to adjuvant pembrolizumab

As the use of adjuvant pembrolizumab increases, the management of metastatic recurrence following prior immunotherapy exposure has emerged as an important clinical challenge. However, evidence guiding treatment selection in this setting remains limited, with current recommendations largely based on retrospective data and extrapolation from studies in immunotherapy-naïve patients. Available retrospective data suggest that outcomes following metastatic recurrence after adjuvant immunotherapy are broadly similar across currently used first-line treatment approaches, with no clear differences in progression-free or OS observed. These findings underscore the lack of an established standard of care in this setting.³⁹

Current evidence suggests that both TKI monotherapy and immunotherapy-based combinations remain reasonable treatment options for patients who develop metastatic recurrence after adjuvant pembrolizumab. Treatment selection should be individualized according to disease burden, prior treatment tolerance, and timing

of recurrence, with immunotherapy rechallenge generally considered more appropriate in patients with a longer disease-free interval following adjuvant therapy.⁴⁰

Prospective evidence in this setting remains limited, although several ongoing randomized studies are evaluating novel treatment strategies in patients previously exposed to immunotherapy. These include combinations incorporating the HIF-2 α inhibitor belzutifan with agents such as pembrolizumab⁴¹, cabozantinib⁴², and lenvatinib⁴³. The results of these trials are expected to provide important insights into optimal treatment sequencing and therapeutic selection for this increasingly common clinical scenario.

Selection of first-line systemic therapy

The selection of first-line systemic therapy in clear cell mRCC has become increasingly individualized, taking into account clinical risk stratification, disease burden, and patient-specific factors. In selected patients with indolent disease biology, for example those with low metastatic volume, oligometastatic presentation, or excellent performance status, active surveillance may represent a reasonable initial management strategy, provided that close monitoring can be ensured as shown in table 2.

Considerable heterogeneity exists within the IMDC favorable-risk population. A subset of patients with “very favorable-risk” disease, characterized by a prolonged interval from diagnosis to systemic therapy, absence of critical visceral metastases, and excellent performance status, may exhibit a more indolent disease course and require individualized treatment strategies.^{44,45}

Emerging retrospective evidence suggests that treatment intensification with dual immune checkpoint blockade may not improve outcomes in very favorable-risk patients and could be associated with inferior survival in comparison with TKI monotherapy. These findings highlight the importance of individualized treatment selection within the IMDC favorable-risk population.^{44,45} These findings underscore the importance of individualizing treatment in accordance with the disease biology. In selected patients with very favorable-risk disease, TKI monotherapy remains a reasonable first-line option, while active surveillance may be considered for those with indolent disease characteristics, limited metastatic burden, and minimal symptoms.⁴⁶



Table 2. Proposed first-line systemic therapies for patients with clear cell metastatic renal cell carcinoma across different risk categories

Risk category	IMDC very-favorable risk	IMDC favorable risk	IMDC intermediate/poor risk
Preferred regimens	Undetermined	<ul style="list-style-type: none"> • Pembrolizumab + lenvatinib • Pembrolizumab + axitinib • Nivolumab + cabozantinib 	<ul style="list-style-type: none"> • Pembrolizumab + lenvatinib* • Pembrolizumab + axitinib* • Nivolumab + cabozantinib* • Nivolumab + ipilimumab
Possible regimens	<ul style="list-style-type: none"> • Active surveillance • TKI monotherapy 	<ul style="list-style-type: none"> • TKI monotherapy (e.g. for patients with a low metastatic burden and no symptoms) 	As above

*Immunotherapy plus tyrosine kinase inhibitor (TKI) is the preferred regimen for International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate/poor-risk patients with rapidly progressive or extensive disease.

Although the concept of a very favorable-risk subgroup remains exploratory and requires prospective validation, it highlights the heterogeneity within the IMDC favorable-risk population. For most favorable-risk patients, IO+TKI combinations remain the preferred first-line treatment based on demonstrable survival benefits, although TKI monotherapy may be appropriate in selected patients with indolent, low-volume disease. In contrast, patients with IMDC intermediate- or poor-risk disease derive substantial benefit from combination therapy, including IO+IO or IO+TKI regimens, with the latter often favored when rapid disease control is required. The optimal duration of immunotherapy remains uncertain, and treatment discontinuation after prolonged disease control should be individualized.

In comparison with TKI monotherapy, combinations of immune checkpoint inhibitors with TKIs (IO+TKI) have consistently demonstrated superior efficacy in pivotal phase III trials, with significant improvements in progression-free survival (PFS; hazard ratios ranging from 0.47 to 0.69) and overall survival (OS; hazard ratios approximately 0.70) in intention-to-treat populations during extended follow-up.⁴⁷⁻⁴⁹ However, it is noteworthy that the magnitude of OS benefit, typically a secondary endpoint in these studies, may attenuate over longer follow-up durations, particularly beyond five years.

Indirect comparisons among IO+TKI regimens suggest variability in efficacy across com-

binations. In patients with IMDC favorable-risk disease, pembrolizumab plus lenvatinib appears to confer the greatest PFS advantage (HR, 0.50; 95% CI, 0.35–0.71), compared with pembrolizumab plus axitinib (HR, 0.76; 95% CI, 0.57–1.02) and nivolumab plus cabozantinib (HR, 0.69; 95% CI, 0.48–1.00). These differences, although derived from cross-trial comparisons, highlight potential distinctions in treatment efficacy that may inform clinical decision-making.

Dual immune checkpoint blockade with nivolumab plus ipilimumab has also demonstrated durable clinical benefit, particularly in patients with IMDC intermediate- or poor-risk disease. Long-term follow-up from the phase III CheckMate 214 trial confirmed sustained improvements in both PFS and OS compared with TKI monotherapy in this population.⁵⁰ While IO+TKI combinations generally achieve higher objective response rates (ORR) (approximately 55–69%) and lower rates of primary progressive disease (6–11%) based on indirect comparisons, IO+IO regimens remain significant for their capacity to induce long-lasting responses and durable survival benefits in selected patients.

Real-world evidence has further informed treatment selection in metastatic RCC. In the multinational ARON-1 study, IO+TKI combinations were associated with improved OS and higher clinical benefit rates in comparison with IO+IO among patients with IMDC intermediate- or poor-risk disease, supporting the growing pref-

erence for IO+TKI regimens in patients requiring rapid and durable disease control.⁵¹

In a separate analysis focusing on IMDC favorable-risk patients (N = 524), IO+TKI was associated with improved PFS compared with sunitinib monotherapy (30.7 vs. 22.9 months; $p = 0.007$), although no significant difference in OS was observed at a median follow-up of 37 months.⁵² These findings suggest that while IO+TKI regimens may offer improved disease control, their long-term survival advantage in favorable-risk populations remains less clearly defined.

Consistent with these data, multiple international guidelines recommend immunotherapy-based combination regimens as first-line treatment for patients with clear cell mRCC across all IMDC risk categories, while acknowledging that TKI monotherapy remains a reasonable alternative in selected favorable-risk patients.^{40,53} In clinical practice, IO+TKI combinations are generally favored for most patients, given their higher response rates and broader applicability. However, TKI monotherapy may still be appropriate for asymptomatic individuals with low metastatic burden or in cases where treatment tolerability is a concern.

In patients with IMDC intermediate- or poor-risk disease, both IO+IO and IO+TKI regimens have been supported by high-level evidence. IO+TKI combinations are often preferred in patients with rapidly progressive or high-volume disease due to their ability to achieve faster and more pronounced tumor responses. In contrast, IO+IO regimens may be considered in selected patients where durable responses are prioritized.

The optimal duration of therapy remains an area of uncertainty. In the CheckMate 214 trial, treatment with nivolumab plus ipilimumab was typically administered for up to two years, particularly in patients achieving a complete response.⁵⁰ In trials evaluating IO+TKI combinations, immunotherapy components were generally discontinued after two years, whereas TKI therapy was continued until disease progression or unacceptable toxicity occurred.⁴⁷⁻⁴⁹ Whether treatment de-escalation, particularly discontinuation of TKI therapy in responding patients, is feasible remains an open question and is the subject of ongoing investigation.

Treatment monitoring

Regular assessment of treatment response is a critical component in the management of patients receiving systemic therapy for metastatic RCC. Cross-sectional imaging with contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis remains the standard modality for disease evaluation and is typically performed at intervals of approximately 2–4 months, in accordance with contemporary guideline recommendations.⁵³

Additional imaging beyond routine CT of the chest, abdomen, and pelvis should be performed only when clinically indicated. Regular clinical and laboratory monitoring is essential to assess treatment response and detect toxicities associated with immune checkpoint inhibitors and TKIs.^{54,55}

The optimal follow-up strategy after discontinuation of systemic therapy, including in patients achieving complete response, remains poorly defined. Given the limited available evidence, surveillance should be individualized based on disease characteristics, depth of response, and patient factors.

Second- and later-line treatment of clear cell mRCC

Second-line treatment

The selection of second-line therapy in metastatic RCC is largely determined by the type of systemic treatment received in the first-line setting. In patients who experience disease progression after initial immune checkpoint inhibitor-based combinations, the role of immunotherapy rechallenge remains uncertain and is not currently supported by robust evidence.

Recent phase III randomized trials have evaluated the efficacy of continuing or reintroducing immunotherapy beyond progression. The CONTACT-03 trial, which compared cabozantinib with or without atezolizumab⁵⁶, and the TiNivo-2 trial, which assessed tivozanib with or without nivolumab⁵⁷, both demonstrated no significant survival advantage with the addition of immunotherapy in patients previously treated with IO-based regimens. These findings suggest that routine rechallenge with immune checkpoint inhibitors is unlikely to provide additional benefit in this setting.



Following progression on first-line IO-based therapy, treatment typically involves alternative targeted agents, including previously unused TKIs, lenvatinib plus everolimus, and belzutifan. The HIF-2 α inhibitor belzutifan has demonstrated efficacy in patients previously exposed to both immunotherapy and TKIs and has become an important later-line treatment option.

Several prospective studies have provided further insights into optimal treatment strategies for patients with metastatic RCC who progress after immune checkpoint inhibitor-based therapy. In the phase II randomized LenCabo trial, the combination of lenvatinib plus everolimus demonstrated a significant improvement in PFS compared with cabozantinib (median 15.7 vs. 10.2 months; HR, 0.51; 95% CI, 0.29–0.89; $p = 0.02$), in a cohort where approximately 70% of patients had received prior dual immunotherapy in the first-line setting.⁵⁸

Ongoing phase III trials are further evaluating novel combination strategies in this population. The LITESPARK-011 study is comparing lenvatinib plus belzutifan with cabozantinib in patients previously treated with immunotherapy, either in the metastatic or adjuvant setting, with both PFS and OS as primary endpoints.⁵⁹

In addition, the phase III LITESPARK-005 trial evaluated belzutifan monotherapy in patients previously exposed to both immunotherapy and at least one TKI. Belzutifan significantly improved 18-month PFS rates compared with everolimus (24.0% vs. 8.3%; $p = 0.002$), although no statistically significant difference in OS was observed between the treatment arms (55.2% vs. 50.6%; HR, 0.88; 95% CI, 0.73–1.07; $p = 0.20$).⁵

Collectively, these findings support the use of alternative targeted therapies and novel agents following progression on first-line IO-based regimens. Treatment options in this setting include combinations such as lenvatinib plus everolimus, emerging regimens incorporating belzutifan, and belzutifan monotherapy. In addition, switching to a TKI not previously administered remains a reasonable strategy, particularly in patients who have received prior IO+TKI combinations, consistent with current international guideline recommendations.^{40,53,54} Treatment selection should also consider tolerability, as certain regimens, for example lenvatinib plus everolimus, may be associated with increased toxicity in some patients.

In patients who experience disease progression after first-line TKI monotherapy, several second-line treatment options are available, reflecting the expanding therapeutic landscape in metastatic RCC. Historically, agents such as nivolumab and cabozantinib have been widely used in this setting based on evidence demonstrating survival benefits.

More recently, additional therapeutic strategies have been incorporated into clinical practice. The combination of lenvatinib plus everolimus has shown significant efficacy, supported by a randomized phase II trial demonstrating improved PFS compared with everolimus alone (median 14.6 vs. 5.5 months; HR, 0.40; 95% CI, 0.24–0.68; $p = 0.0005$) in patients previously treated with TKI monotherapy.⁶⁰

In addition, there is emerging evidence to suggest that immunotherapy-based combinations may retain activity in the post-TKI setting. Retrospective real-world data indicate that second-line treatment with immune checkpoint inhibitor plus TKI (IO+TKI) may achieve OS outcomes comparable to those observed with first-line IO+TKI in patients with IMDC intermediate- or poor-risk disease.⁶¹

Taken together, these findings support a range of treatment options following progression on TKI monotherapy, including alternative TKIs, immune checkpoint inhibitors, combination regimens such as lenvatinib plus everolimus, and IO-based combinations. Treatment selection should be individualized, taking prior therapy, disease characteristics, patient comorbidities, and potential treatment-related toxicities into consideration.

Third-line treatment and beyond

Therapeutic options in the third-line and later-line setting for metastatic RCC remain limited and are often guided by prior treatment exposure. In patients who have already received both immune checkpoint inhibitors and TKIs, belzutifan has emerged as a clinically relevant option, supported by evidence from the phase III LITESPARK-005 trial, which demonstrated activity in this heavily pretreated population.⁵

Despite these advances, the optimal management of patients who have progressed after sequential exposure to immunotherapy, TKIs, and newer agents such as belzutifan remains unclear due to the paucity of prospective data.

In this context, treatment decisions are largely individualized, and options become increasingly constrained.

The combination of lenvatinib plus everolimus may be considered in later lines, particularly in patients who have exhausted standard therapies, given its previously demonstrated efficacy in earlier treatment settings. However, evidence supporting its use specifically after prior exposure to immunotherapy, TKIs, and HIF-2 α inhibitors is limited, underscoring the need for further clinical investigation in this area.

Management of mRCC with sarcomatoid features or non-clear cell histology

Management of patients with sarcomatoid features

Sarcomatoid differentiation in RCC represents a dedifferentiated phenotype that can arise across various histological subtypes, rather than a distinct entity. This transformation is thought to be driven, in part, by processes such as epithelial–mesenchymal transition, which contribute to increased tumor invasiveness and aggressive clinical behavior.^{62,63} Although relatively uncommon, occurring in approximately 5% of RCC cases, sarcomatoid features are most frequently observed in tumors with underlying clear cell histology.⁶⁴

From a molecular perspective, sarcomatoid RCC is often associated with alterations in key oncogenic and tumor suppressor pathways, including mutations involving TP53, BAP1, CDKN2A, and MYC, in addition to increased expression of immune-related markers such as PD-1 and PD-L1.⁶³ These biological characteristics are thought to contribute to both the aggressive nature of the disease and its relative sensitivity to immunotherapy.

Immune checkpoint inhibitor–based combination therapies are the preferred first-line treatment for metastatic RCC with sarcomatoid differentiation. Although prospective trials dedicated to this subgroup are lacking, multiple phase III trial subgroup analyses have consistently demonstrated superior overall survival, PFS, and response rates with both IO+IO and IO+TKI regimens in comparison with TKI monotherapy.^{65–69}

Real-world data further corroborate these findings. In the multicenter retrospective ARON-1 study, which evaluated outcomes in patients

with metastatic RCC treated with first-line immunotherapy-based combinations, in those with sarcomatoid features (n = 226) comparable clinical outcomes were achieved with dual immunotherapy (IO+IO) and immunotherapy plus TKI (IO+TKI). Median OS (26.4 vs. 34.4 months; p = 0.729), PFS (12.3 vs. 12.4 months; p = 0.606), and ORR (48% in both groups) were similar between the two treatment strategies.⁷⁰

Taken together, these data suggest that both IO+IO and IO+TKI regimens are effective first-line options in patients with sarcomatoid differentiation, with treatment selection guided by clinical factors such as disease burden, need for rapid response, and tolerability considerations.

With the accumulation of more robust clinical data, immune checkpoint inhibitor–based combination therapies have become increasingly supported as the preferred first-line approach for patients with clear cell mRCC exhibiting sarcomatoid differentiation. This shift is in alignment with contemporary international guideline recommendations, which emphasize the superior efficacy of immunotherapy-based regimens in this high-risk subgroup.^{40,71}

Most evidence for sarcomatoid mRCC is derived from patients with clear-cell histology and IMDC intermediate- or poor-risk disease. In this population, immune checkpoint inhibitor–based combinations consistently demonstrate superior response rates and survival outcomes compared with TKI monotherapy, supporting their role as the preferred first-line treatment. Although data in favorable-risk patients remain limited, immunotherapy-based combinations may be considered in selected cases with aggressive tumor biology.

Management of patients with non-clear cell mRCC

Non-clear cell RCC accounts for approximately 25% of all RCC cases and comprises a heterogeneous group of histological subtypes, with papillary RCC being the most prevalent, followed by chromophobe RCC, collecting duct carcinoma, renal medullary carcinoma, translocation-associated RCC, and other rare variants.⁷² Given this diversity, treatment approaches can vary across subtypes, and several international guidelines provide subtype-specific recommendations where evidence is available.⁵³



Evidence for non-clear cell metastatic RCC remains limited because most studies include heterogeneous histological subtypes. Nevertheless, recent data support immunotherapy-based combinations as preferred first-line treatment options. Regimens such as pembrolizumab plus lenvatinib, pembrolizumab plus axitinib, and nivolumab plus cabozantinib have demonstrated promising efficacy, while nivolumab plus ipilimumab and cabozantinib monotherapy remain reasonable alternatives in selected patients.

Evidence supporting first-line treatment strategies in non-clear cell mRCC is largely derived from phase II studies and indirect comparisons across trials. Data from recent studies, including SWOG 1500⁷³, KEYNOTE-B61⁷⁴, NCT03635892⁷⁵, and SUNNIFORECAST⁷⁶, suggest that immunotherapy in combination with TKIs (IO+TKI), particularly pembrolizumab plus lenvatinib and nivolumab plus cabozantinib, may provide superior clinical outcomes compared with either TKI monotherapy or dual immunotherapy. Across these studies, IO+TKI regimens have been associated with improved PFS, OS, and ORR in patients with non-clear cell histology.

Among available combinations, findings from larger cohorts evaluating pembrolizumab plus lenvatinib indicate a trend toward more favorable survival outcomes compared with nivolumab plus cabozantinib, although such observations should be interpreted cautiously due to differences in study design and patient populations.^{74,75} Importantly, no direct head-to-head randomized trials have been conducted to compare these regimens, and therefore treatment selection should consider individual patient characteristics, histological subtype, and tolerability profiles.

A growing body of evidence supports the use of combination strategies in the first-line treatment of non-clear cell mRCC. A systematic review and meta-analysis of 23 studies evaluating various histological subtypes demonstrated that regimens combining immune checkpoint inhibitors with TKIs (IO+TKI) were associated with improved OS, PFS, and ORR compared with either immunotherapy or TKI monotherapy.⁶

These findings are reinforced by real-world data from the global retrospective ARON-1 study, which showed that IO+TKI combinations, in particular pembrolizumab plus lenvatinib,

were associated with superior clinical outcomes compared with dual immunotherapy (IO+IO) in patients with non-clear cell mRCC.⁷

For specific non-clear cell RCC subtypes, evidence remains limited and is often derived from smaller studies. Examples include the use of durvalumab plus savolitinib in papillary RCC²⁵, dual TKI strategies in chromophobe RCC⁷⁷, cabozantinib monotherapy in collecting duct carcinoma⁷⁸, cytotoxic or targeted combinations such as gemcitabine plus doxorubicin or bevacizumab plus erlotinib in renal medullary carcinoma^{79,80}, and axitinib in combination with nivolumab in translocation-associated RCC⁸¹. Ongoing research is exploring biomarker-driven approaches to better individualize therapy across these diverse subtypes.⁸²

Current evidence supports immunotherapy-based combinations, particularly IO+TKI regimens, as a preferred first-line therapy for advanced non-clear cell RCC, while cabozantinib remains a reasonable alternative in selected patients.

Management of oligometastatic RCC

Definitions of oligometastatic and oligoprogressive disease

Oligometastatic RCC generally refers to the presence of a limited number of metastatic lesions, typically ≤ 3 , identified either at diagnosis (synchronous) or after treatment of the primary tumor (metachronous). Oligoprogressive RCC describes progression at a limited number of sites (commonly ≤ 3 lesions) in the setting of otherwise controlled systemic disease. These definitions are supported by studies evaluating metastasis-directed therapies, including metastasectomy and stereotactic body radiotherapy (SBRT).^{27,83} However, outcomes from these studies suggest that the greatest clinical benefit—particularly in terms of local control and survival—tends to be observed in patients with a lower disease burden, typically those with three or fewer metastatic sites.

Accordingly, adoption of a more restrictive definition of oligometastatic and oligoprogressive disease (≤ 3 lesions) may better reflect the subgroup of patients most likely to benefit from MDT and facilitate timely integration of systemic therapy in those with a more extensive stage of the disease.

Beyond the number of metastatic lesions, the timing of metastatic presentation is a key determinant in the management of oligometastatic RCC.²⁷ Approximately 25–30% of patients present with metastatic disease at initial diagnosis (synchronous mRCC), while a similar proportion develop metastases following treatment for localized disease, often after a prolonged interval such as more than one year after nephrectomy (metachronous mRCC).⁸⁴

**In addition, some patients may experience progression characterized by the emergence of new lesions or the enlargement of existing metastases during or after systemic therapy.^{85,86} With the advent of more effective systemic treatments that improve disease control and extend progression-free intervals, the clinical scenario of oligoprogression has become increasingly recognized.

Optimal management of oligometastatic and oligoprogressive RCC should therefore incorporate not only the extent of disease but also the timing of the development of the metastasis, anatomical distribution of lesions, IMDC risk stratification, and prior treatment history, including response to systemic or adjuvant therapies.²⁷

Management of oligometastatic RCC

Management of oligometastatic RCC should be individualized according to the disease biology and patient characteristics. Patients with poor-risk features, brain metastases, non-clear cell histology, sarcomatoid differentiation, or rapidly progressive disease are generally best managed with upfront systemic therapy. In contrast, selected patients with limited metastatic burden may benefit from a multimodal approach incorporating CN, MDT, systemic treatment, and, in selected cases, adjuvant pembrolizumab following complete resection.

Systematic reviews support metastasis-directed surgery in carefully selected patients with metastatic RCC. Complete metastasectomy has been associated with improved survival when compared with incomplete or no resection (median 40.8 vs. 14.8 months) and may provide meaningful symptom palliation, particularly for bone metastases. The lungs, bone, and liver are the most commonly treated sites.⁸⁵

Several factors have been associated with more favorable outcomes following metastasectomy, including good performance status, IMDC favorable or intermediate-risk disease, limited

metastatic burden (solitary or oligometastatic lesions), metachronous presentation, absence of sarcomatoid differentiation, clear cell histology, and the ability to achieve complete resection.⁸⁵ Additional evidence suggests that pulmonary metastasectomy may confer superior survival outcomes compared with resection of metastases at other anatomical sites.⁸⁶ However, it is important to note that the current evidence base is derived exclusively from retrospective studies, and thus remains subject to inherent selection bias.

In selected patients with indolent disease characteristics, active surveillance may represent a reasonable strategy to delay systemic therapy and avoid treatment-related toxicity, particularly in those with very favorable prognostic features.⁴⁶ This approach may also be applicable to patients with oligometastatic RCC who have undergone complete MDT which has achieved no evidence of disease.

Achievement of a state of M1 NED following complete metastasectomy provides an opportunity to consider adjuvant systemic therapy. Data from the KEYNOTE-564 trial suggest that adjuvant pembrolizumab may prolong DFS in high-risk patients, although only a small proportion (5.8%) of participants had M1 NED status, and all underwent metastasectomy within one year of nephrectomy.^{5,24} In contrast, earlier randomized trials evaluating adjuvant targeted therapies, including pazopanib, atezolizumab, and sorafenib, did not demonstrate improvements in recurrence-free or DFS in patients rendered disease-free after metastasectomy.^{25,87,88}

****CN may contribute to improved outcomes through several potential mechanisms, including reduction of tumor burden harboring resistant clones, limitation of further metastatic dissemination, and modulation of the host immune response.⁸⁹⁻⁹³ As discussed earlier, both upfront and deferred CN may be appropriate in carefully selected patients with metastatic RCC. Similarly, in the oligometastatic setting, a multimodal strategy incorporating nephrectomy and complete MDT, either before or after systemic treatment, may be considered in selected patients and has the potential to improve long-term outcomes.

SBRT has emerged as an important modality within MDT for oligometastatic RCC. Available evidence from prospective phase II single-arm



studies suggests that SBRT can achieve meaningful disease control, potentially delaying disease progression and the need for systemic therapy.^{89,90} In selected patients with limited metastatic burden, SBRT may serve as a strategy to defer systemic treatment or, in rare cases, achieve durable remission with local therapy alone.^{8,91}

Prospective data further support the efficacy of SBRT in this context. In one phase II trial, a median PFS of 22.7 months, with a 1-year PFS rate of 64% and an 82% rate of freedom from systemic therapy at one year was achieved in patients with oligometastatic clear cell RCC (≤ 5 lesions) treated with SBRT following nephrectomy.⁹² Another phase II study in systemic therapy-naïve patients with limited extracranial disease (≤ 3 lesions) reported a 1-year local control rate of 100%, with PFS and systemic therapy-free survival rates exceeding 80%.⁹³

Real-world retrospective data also demonstrate that SBRT provides excellent local control, with rates approaching 98% at three years, along with a favorable safety profile in patients with a limited number of metastatic lesions (1–5 sites).^{94,95} Outcomes appear to be more favorable in patients with metachronous disease, solitary metastases, or non-osseous involvement, who may experience prolonged intervals before requiring systemic therapy.^{94,95} In contrast, patients with brain or bone metastases, or those with multiple lesions, may derive greater benefit from early initiation of systemic therapy rather than sequential use of SBRT alone.^{94,95} Overall, SBRT represents a valuable component of a multimodal treatment strategy in oligometastatic RCC, with its role best defined in carefully selected patients based on disease burden, site of metastasis, and overall clinical context.

Further evidence supports the role of SBRT in the management of oligometastatic RCC. A meta-analysis of 28 predominantly retrospective studies demonstrated that SBRT achieves high rates of local control across different clinical settings, including de novo, metachronous, and oligoprogressive disease. In patients with extracranial metastases, SBRT was associated with approximately 90% local control and an OS rate of 87% at one year, with a low incidence of grade 3–4 toxicities (0.7%). Comparable local control rates were observed in intracranial disease, although OS was lower (50% at one year), reflecting the

more aggressive disease course in this subgroup.⁹⁶

Prospective data also highlight the potential synergy between SBRT and immunotherapy. In the phase I/II RAPPORT trial, treatment with SBRT to all metastatic sites followed by pembrolizumab demonstrated favorable safety and efficacy outcomes in patients with oligometastatic clear cell RCC (≤ 5 lesions). At two years, local control was maintained in 92% of treated lesions, with PFS rates of 60% at one year and 45% at two years. Treatment was generally well tolerated, with no grade 4 or 5 toxicities and a 13% incidence of grade 3 adverse events.⁹⁷

Ongoing clinical trials are exploring the integration of SBRT with systemic therapy in both oligometastatic and polymetastatic settings. These include studies evaluating SBRT directed at the primary renal tumor in combination with immunotherapy in newly diagnosed metastatic disease.^{98,99} In addition randomized trials such as EA8211-SOAR, which compare systemic therapy alone with combined systemic and SBRT^{99,100}, and the PE-PE study, which investigates pembrolizumab followed by MDT versus local therapy alone added weight to these findings.¹⁰¹

Taken together, current evidence suggests that SBRT, either as a standalone modality or in combination with systemic therapy, represents a viable treatment option in selected patients with oligometastatic RCC. Approaches incorporating SBRT followed by active surveillance or immunotherapy-based systemic treatment may be considered depending on disease characteristics and treatment goals. However, the role of combining SBRT with adjuvant pembrolizumab remains uncertain, as this strategy was not evaluated in pivotal trials such as KEYNOTE-564, and further prospective data are needed to define its clinical utility.^{4,24}

Management of oligorecurrent and oligoprogressive RCC

The management of oligorecurrent RCC following nephrectomy presents unique clinical challenges, as these patients may exhibit more aggressive disease behavior in comparison with those with de novo oligometastatic presentation. In many cases, early initiation of systemic therapy, in particular immune checkpoint inhibitor-based combination regimens, is warranted to achieve adequate disease control.

In oligorecurrent RCC, MDT, including SBRT, may improve local control and delay disease progression in selected patients. In the case of oligoprogressive disease, MDT can be used to target progressing lesions while maintaining the current systemic therapy, thereby prolonging treatment benefit. However, the optimal sequencing of MDT and systemic therapy remains uncertain and should be individualized within a multidisciplinary framework.

In the setting of oligoprogressive RCC, SBRT has emerged as a valuable strategy to control limited sites of disease progression while maintaining ongoing systemic therapy. This approach aims to delay the need for treatment escalation and prolong the clinical benefit of the current regimen.⁹⁶ A consensus of the guidance from the European Society for Radiotherapy and Oncology supports the use of SBRT in patients with a limited number of progressing lesions (typically ≤ 3), irrespective of patient age, histological subtype, or metastatic location.¹⁰² Additional recommendations include the use of SBRT for bone metastases regardless of site, its consideration as a first-line local therapy for adrenal metastases, and the feasibility of administering immunotherapy concurrently with SBRT within a defined time window.¹⁰²

Prospective data further support this strategy. A phase II single-arm study involving patients with oligoprogressive mRCC (≤ 3 progressing sites) demonstrated that SBRT enabled continuation of the existing systemic therapy for more than six months in approximately 70% of patients, with a median time to next-line therapy or death of 11.1 months.¹⁰³ Similarly, another phase II study reported that the addition of SBRT allowed maintenance of ongoing TKI therapy for a median duration of 12.6 months in patients with limited progression (≤ 5 metastases).¹⁰⁴

Retrospective studies have consistently shown that SBRT, when combined with continuation of the current systemic therapy, is well tolerated and effective in delaying the initiation of subsequent treatment lines.¹⁰⁵⁻¹⁰⁹ Some analyses also suggest a potential OS advantage compared with the continuation of systemic therapy alone in the presence of oligoprogression. However, these findings should be interpreted with caution due to limitations including small sample sizes, retrospective design, and lack of comparator arms.

Ongoing prospective trials are evaluating the integration of SBRT with both immunotherapy-based combinations and TKI monotherapy in patients who develop oligoprogression during systemic treatment, with the aim of defining optimal sequencing and combination strategies.¹¹⁰

In clinical practice, a commonly adopted approach involves temporary interruption of systemic therapy, delivery of SBRT to sites of progression, and subsequent resumption of the original regimen. However, the relative roles of alternative local treatments, such as metastasectomy, or immediate transition to next-line systemic therapy remain uncertain due to the absence of comparative evidence.

Thermal ablation techniques, including cryoablation, radiofrequency ablation, and microwave ablation, have also been explored as local treatment options in oligometastatic RCC. While available studies suggest potential efficacy and safety, the evidence base is limited by retrospective design, small patient cohorts, short follow-up durations, and lack of direct comparisons with established modalities such as SBRT or surgical resection.⁹⁻¹¹ Consequently, the role of these techniques in routine clinical practice remains to be clearly defined.

Discussion

The management of locally advanced and metastatic RCC has evolved substantially with the introduction of immune checkpoint inhibitor-based combinations, adjuvant pembrolizumab, and novel agents such as belzutifan. In addition, increasing recognition of distinct clinical states, including oligometastatic and oligoprogressive forms of the disease, has enabled more individualized treatment strategies integrating systemic and local therapies.

Despite these advances, important challenges remain. Evidence supporting CN in the immunotherapy era, optimal treatment sequencing after adjuvant pembrolizumab, and management of non-clear cell RCC remains limited. Furthermore, the optimal integration of metastasis-directed therapies with systemic treatment requires further prospective evaluation.

The identification of reliable biomarkers to guide treatment selection and predict response continues to be an unmet need. Similarly, current nomograms such as the IMDC risk score may

be insufficient with the evolving treatment paradigms. Emerging prognostic tools such as the SCREEN score may offer greater granularity particularly in patients receiving immune checkpoint inhibitor-based therapy, by incorporating variables associated with systemic inflammation and aggressive disease biology, highlighting a shift towards more individualized and biologically informed treatment stratification.¹¹¹ Future research should focus on prospective validation of emerging treatment strategies, refinement of patient selection criteria and risk stratification, as well as the development of biomarker-driven approaches to optimize therapeutic outcomes.¹¹² Ongoing clinical trials evaluating novel combinations, sequencing strategies, and multimodal interventions are expected to provide further insights into the evolving management landscape.

Conclusion

In conclusion, the treatment of la/mRCC is becoming increasingly complex and individualized. Immunotherapy-based combinations form the cornerstone of modern management, while selected patients may benefit from integration of local therapies within a multidisciplinary framework. Continued efforts to generate high-quality evidence and refine treatment algorithms will be essential to further improve outcomes for patients with this challenging disease.

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