Cytoreductive Nephrectomy in the Era of Tyrosine Kinase and Immuno-Oncology Checkpoint Inhibitors

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KEYWORDS

• Kidney cancer • Renal cell carcinoma • Cytoreductive nephrectomy • Systemic therapy

KEY POINTS

- The role of cytoreductive nephrectomy (CN) in the management of metastatic renal cell carcinoma (mRCC) continues to evolve with advancements in systemic therapy.
- Although CN previously was standard of care for all patients with mRCC, the vascular endothelial growth factor (VEGF)-targeted therapy era highlighted the importance of systemic therapy in improving oncologic outcomes and the importance of risk stratification to identify patients more likely to benefit from CN.
- Immuno-oncology (IO) checkpoint inhibitors and combination IO and VEGF-targeted therapy agents (IOVE) currently are transforming the management of mRCC.
- CN continues to play an important role in specific patient populations, including those with low-volume, favorable-risk mRCC and those with stable or regressive disease on systemic therapy, and in delaying initiation of toxic systemic therapy in patients who can be observed.
- The role of CN needs to be re-examined in the new IO/IOVE era.

INTRODUCTION

Renal cell carcinoma (RCC) is the twelfth most common cancer. In the United States, in 2019, there were approximately 74,000 new cases diagnosed and 15,000 deaths.[1] The incidence has increased with routine use of imaging modalities, increasing the number of incidentally diagnosed renal malignancies, which has resulted in stage migration, leading to approximately 70% of newly detected kidney tumors being low stage, clinically localized (cT1) renal masses.[2] Historically, 25% to 30% of patients presented with distant metastases, but with earlier detection the current metastatic rate at presentation is closer to 10% to 15% in the United States and Europe.[3–7] Disseminated disease still carries a dismal prognosis, with 5-year survival rates at approximately 10%, although survival rates over the past 30 years have improved with the advent of novel targeted therapies.[3,8–11]

Extirpative surgery has been a primary treatment option for patients with locally advanced, lymph node–positive, and distant metastatic RCC (mRCC), although its role in metastatic disease continues to evolve with advancements in

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systemic therapy.[12,13] Cytoreductive nephrectomy (CN) refers to the removal of the kidney with the primary tumor in patients with synchronous mRCC. During the cytokine therapy era, CN provided a clear survival benefit in patients with metastatic disease.[14–16] The development of targeted therapies, such as tyrosine kinase inhibitors (TKIs), vascular endothelial growth factor (VEGF) monoclonal antibodies, and mammalian target of rapamycin (mTOR) inhibitors, have made the indications for CN less clear, and the recent advent of novel immune-oncologic (IO) agents have blurred its value further.

New efforts have been made to define the indications for CN, considering patient characteristics and disease pathology, the oncologic benefits of surgical management compared with modern systemic therapy, and the morbidity of surgery. Exploration into the timing of CN in relation to systemic therapy also is needed. This article aims to critically review the current literature to provide guidance on the therapeutic role of CN, including patient selection and surgical timing, in treating patients with mRCC in the modern systemic therapy era.

BENEFIT OF CYTOREDUCTIVE THERAPY ALONE IN METASTATIC RENAL CELL CARCINOMA

CN until recently has been considered standard of care for all patients with mRCC. Its mechanism in altering the course of disease is unclear, but the pathophysiologic benefit likely is multifactorial. The elimination of the primary tumor reduces disease burden and the potential for development of aggressive biological clones capable of metastases.[17] RCC is known to be highly immunogenic, and CN has been proposed to alter the immune systems response to metastases. In the early 1990s, prior to Food and Drug Administration approval of interleukin (IL)-2, CN alone was observed to result in spontaneous regression of distant metastatic lesions in a minority of patients.[18–20] Although cure in these cases is rare and unpredictable even with risk stratification, the witnessed abscopal effect led to the realization of RCC immunogenicity. In theory, the immune system may be primed to target renal cancer cells, but the response is consumed by the primary tumor until it is removed, possibly due to the volume of disease or the immunosuppressive nature of the tumor microenvironment, inhibiting T-cell function.[21,22] Recent clinical studies have demonstrated correlation of RCC metastatic immunogenicity, in particular pulmonary and skeletal metastases, with clinical outcome.[23,24] CN had a theoretic basis to improve survival in patients with mRCC, by removing a potential source for new metastases and freeing the immune system to combat existing metastatic disease.[25]

CYTOKINE-BASED IMMUNOTHERAPY ERA

The recognition of RCC's immunogenicity led to the evaluation of immunotherapy, including IL-2 and interferon (IFN)-α, in treating metastatic disease.[26] In 2001, the Southwest Oncology Group (SWOG) and European Organisation for Research and Treatment of Cancer (EORTC) published 2 randomized controlled trials (RCTs) with nearly identical protocols, randomizing patients with mRCC to CN followed by IFN-α or to IFN-α alone (**Table 1**).[14,15] Both studies demonstrated improved overall survival in patients receiving surgery plus immunotherapy. SWOG 8949 included 241 total patients and showed an improved median overall survival of 3 months (11.1 mo vs 8.1 mo respectively; $P = .05$).[14] EORTC 30947 included 85 total patients and had a difference in median overall survival of 10 months (17 mo vs 7 mo respectively; $P = .03$).[15] A combined analyses of these 2 trials with 331 patients showed an improved median survival of 13.6 months in the CN plus IFN-α group in comparison to 7.8 months for IFN-α alone (31% decrease in the risk of death), independent of performance status and metastatic site.[16] When evaluating CN in mRCC, it is important to note the percentage of patients who actually receive systemic therapy, because surgery can consequently delay initiation of or eliminate the possibility of systemic treatment. In these trials, only 1.8% of patients in the IFN-α–only arm did not receive IFN-α, whereas 5.6% of patients in the combined treatment arm did not receive IFN-α after nephrectomy. Therefore, CN improved overall survival despite fewer patients receiving systemic treatment. This combined analysis led to the conclusion that CN significantly improves overall survival in patients receiving IFN-α.[16]

After these trials, CN with cytokine therapy became standard of care in surgical candidates with synchronous mRCC. Despite the limited survival advantage, however, overall outcomes remained poor, emphasizing the need for more effective systemic treatments.

RISK STRATIFICATION AND PATIENT SELECTION

Metastatic RCC is a disease spectrum encompassing varied pathology at presentation and diverse natural history. As SWOG 8949 and

Table 1
Summary of randomized control studies in metastatic renal cell carcinoma

			Memorial Sloan Kettering Cancer Center or International Metastatic Renal Cell Carcinoma Database Consortium Risk Category				Arms		Outcomes		
Trial Name	Authors	N	Favorable	Inter-mediate	Poor	Un-known	Arm	Arm Description	Complete Response, Partial Response, or Objective Response Rate	Survival (Median Survival, Overall Survival, Progression-Free Survival)	Notes
SWOG 8949	Flanigan et al,[14] 2001	241	—	—	—	241	Arm 1	CN followed by IFN-α	—	MS 11.1 mo	
							Arm 2	IFN-α	—	MS 8.1 mo	
EORTC 30947	Mickisch et al,[15] 2001	85	—	—	—	85	Arm 1	CN followed by IFN-α	CR 11.9%	MS 17 mo	
							Arm 2	IFN-α	CR 2.3%	MS 7 mo	
N/A	Motzer et al[8]	750	264	421	48	0	Arm 1	Sunitinib	OR 31%	Median PFS 11 mo	MSKCC
							Arm 2	IFN-α	OR 6%	Median PFS 5 mo	
Global ARCC Trial	Hudes et al,[36] 2007	626	0	164	462	0	Arm 1	Temsirolimus	OR 8.6%	MS 10.9 mo	
							Arm 2	IFN-α	OR 4.8%	MS 7.3 mo	

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Table 1
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			Memorial Sloan Kettering Cancer Center or International Metastatic Renal Cell Carcinoma Database Consortium Risk Category				Arms		Outcomes		
Trial Name	**Authors**	**N**	**Favorable**	**Inter-mediate**	**Poor**	**Un-known**	**Arm**	**Arm Description**	**Complete Response, Partial Response, or Objective Response Rate**	**Survival (Median Survival, Overall Survival, Progression-Free Survival)**	**Notes**
TARGET Study	Escudier et al,[12] 2016	903	461	441	0	1	Arm 1	Sorafenib	PR 10%	MS 17.8 mo, PFS 5.5 mo	MSKCC; 48% of patients in placebo group crossed over to receive sorafenib
							Arm 2	Placebo	PR 2%	MS 14.3 mo, PFS 2.8 mo	
CARMENA	Mejean et al,[52] 2018	450	0	256	193	0	Arm 1	CN + sunitinib	OR 27.4%; CR 0.6%	MS 13.9 mo	MSKCC
							Arm 2	Sunitinib	OR 29.1%; CR 0%	MS 18.4 mo	
SURTIME	De Bruijn et al,[56] 2019	99	0	87	12	0	Arm 1	Sunitinib + deferred CN	—	MS 32.4 mo	MSKCC
							Arm 2	Immediate CN + Sunitinib	—	MS 15.1 mo	

Check-Mate 214	Motzer et al[59]	1096	249	847 (inter-mediate risk or poor risk)	0	Arm 1	Ipi-nivo	OR 42%; CR 11%	MS not reached	IMDC	CheckMate 214
						Arm 2	Sunitinib	OR 29%; CR 2%	MS 26.6 mo		
KEY-NOTE-426	Rini et al[64]	861	269	484	108	0	Arm 1	Pembro-lizumab + axitinib	OR 59.3%; CR 5.8%	-y OS 89.9%; PFS 15.1 mo	IMDC
							Arm 2	Sunitinib	OR 35.7%; CR 1.9%	1-y OS 78.3%; PFS 11.1 mo	IMDC

Abbreviations: CR, complete response; MS, median survival; OR, objective response; OS, overall survival; PFS, progression-free survival; PR, partial response.
Data from Refs.[14,15,55,58,59,61–63]

EORTC 30947 demonstrate, trials with similar entry criteria may result in disparate outcomes, possibly attributable to dissimilar sample sizes or significant differences in baseline disease severity despite randomization. Risk stratification is vital to counsel patients and choose treatments that align with patient goals. Several models have been developed based on functional status and serum factors to prognosticate outcomes, guide treatment strategies, and evaluate therapeutic plans.

The Memorial Sloan Kettering Cancer Center (MSKCC) model, also known as the Motzer criteria, was published in 1999 during the immunotherapy era (**Table 2**).[11] It stratifies patients into 3 risk classifications, including favorable risk, intermediate risk, and poor risk, based on time to initiation of systemic therapy, Karnofsky performance scale status, and serum hemoglobin, calcium, and lactate dehydrogenase levels. During the targeted therapy era, the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC), or Heng criteria, was created, separating patients into the same 3 categories based on prognostic factors for overall survival in patients with mRCC treated with VEGF-TKI. IMDC is similar to MSKCC criteria except for the elimination of serum lactic acid dehydrogenase and the inclusion of neutrophil and platelet counts.[27] The performance of the IMDC model was found similar to that of the MSKCC criteria (see **Table 2**).[28]

Other studies have identified important risk stratification factors that can be categorized broadly into patient and tumor characteristics. These include metastatic site and burden, cardiopulmonary function, performance status, sarcomatoid features, lymph node involvement, hypoalbuminemia, sarcopenia, and neutrophil-to-lymphocyte ratio.[29–35] The importance of these risk factors is less understood. The MSKCC and IMDC models remain the 2 most widely adopted and validated risk stratification criteria utilized in clinical trials.

VASCULAR ENDOTHELIAL GROWTH FACTOR–TARGETED THERAPY ERA

VEGF-targeted therapies improved outcomes and changed the treatment paradigm for mRCC. VEGF-TKIs, such as sunitinib and sorafenib, and mTOR kinases, such as temsirolimus, were introduced in the early 2000s with superior efficacy in comparison to previous systemic therapy. Sunitinib was approved by the Food and Drug Administration in 2006 and quickly became the new standard of care for mRCC.

Three RCTs were published in 2007, evaluating the new VEGF-targeted agents in patients with mRCC (see **Table 1**). In these trials, patients randomized to receive sunitinib or temsirolimus demonstrated improved overall survival in direct comparison to patients randomized to IFN-α (sunitinib, 11 mo, vs IFN, 5 mo, and temsirolimus, 10.9, mo vs IFN, 7.3 mo).[7,36] In a separate trial, sorafenib was shown to prolong progression-free survival in comparison to placebo (5.5 mo vs 2.8 mo, respectively) in patients who had failed previous systemic therapy.[37] These trials altered the landscape of systemic treatment, highlighting the improved efficacy of targeted therapy over IFN-α immunotherapy. A majority of patients enrolled in these trials had undergone prior nephrectomy, typically with curative intent prior to the development of metachronous metastases.[38] There are few cases of sustained complete responses with targeted therapy in patients with mRCC without primary nephrectomy or CN.[39] As systemic therapy with targeted agents increased, the utilization of CN decreased, because its importance in conjunction with improved systemic therapy was unclear.[40]

Retrospective studies attempted to determine if CN provided an independent survival benefit to patients in the VEGF-TKI era. These studies unanimously showed overall survival benefit in patients receiving CN with targeted therapy in comparison to targeted therapy alone.[41–49] Choueiri and colleagues[41] found a median overall survival of 19.8 months in the CN combination treatment group versus 9.4 months (unadjusted hazard ratio [HR] 0.44 [95% CI, 0.32–0.59]; $P < .01$) in the VEGF-targeted therapy–only group. A large population study evaluating data from the Surveillance, Epidemiology, and End Results (SEER) database, including more than 20,000 patients, found a survival advantage of 19 months versus 4 months respectively in patients receiving combination CN with VEGF-targeted therapy versus targeted therapy alone.[42] A more recent meta-analysis of 11 nonrandomized trials evaluating approximately 40,000 patients with advanced RCC found a 54% reduced risk of death in combination therapy versus targeted therapy alone.[50] Interpreting the data from these retrospective studies is difficult and fraught with inherent biases. Statistically significant differences in baseline group characteristics tended to favor the CN patient populations, including younger age, better performance status, fewer metastases, and improved MSKCC and IMDC risk criteria.[51] This is not surprising because patients selected for surgery tend to be healthier and with more favorable disease. When patients were stratified by risk on subgroup analyses, favorable-risk and intermediate-risk patients tended to drive surgical benefit, whereas patients

Table 2
Memorial Sloan Kettering Cancer Center and International Metastatic Renal Cell Carcinoma Database Consortium risk criteria

Criteria	Memorial Sloan Kettering Cancer Center	International Metastatic Renal Cell Carcinoma Database Consortium
Time from diagnosis to systemic treatment	If <1 y: 1 point	If <1 y: 1 point
Karnofsky performance scale status	If <80%: 1 point	If <80%: 1 point
Hemoglobin	If < lower limit of normal: 1 point Men (normal): 13.5–17.5 g/dL Women (normal): 12.0–15.5 g/dL	If <lower limit of normal: 1 point Normal: usually ~12 g/dL
Calcium	If >10 mg/dL (>2.5 mmol/L): 1 point	If corrected Ca > upper limit of normal: 1 point Normal: ~8.5–10.2 mg/dL
Lactic acid dehydrogenase	If >1.5× upper limit of normal: 1 point Normal: 140 U/L	N/A
Neutrophils	N/A	If > upper limit of normal: 1 point Normal: ~ 2.0×–7.0× 10⁹/L
Platelets	N/A	If > upper limit of normal: 1 point Normal: 150,000–400,000 cells/μL
Favorable risk	0 points	0 points
Intermediate risk	1–2 points	1–2 points
High/poor risk	3–5 points	3–6 points

Data from Refs.[11,28]

with poor risk seemed to have less or no benefit from CN.[41,47] Prior to the reporting of level 1 evidence, these studies helped provide guidance on patient populations that were more likely to have benefit from CN.

Cancer du Rein Métastatique Nephrectomie et Antiangiogéniques (CARMENA) was a pivotal study published in 2018 conducted to determine more definitively the role of CN in the targeted therapy era (see **Table 1**). It was a phase III, randomized controlled noninferiority trial that included 450 patients with MSKCC intermediate-risk or poor-risk clear cell mRCC randomized to undergo CN followed by sunitinib versus sunitinib alone. Sunitinib alone was found noninferior to combination therapy. The median overall survival in the sunitinib-only group was 18.4 months (14.7–23.0 mo) in comparison to 13.9 months (11.8–18.3 mo) in patients receiving CN followed by sunitinib. Although the study was not powered for a subgroup analysis, MSKCC intermediate-risk patients' median overall survival was 23.4 months in sunitinib-only versus 19.0 months with combination therapy, and 13.3 months versus 10.2 months, respectively, in poor-risk patients.[52]

Several important conclusions can be drawn from CARMENA. First, patient selection for CN is vital and CN should not be considered standard of care for all-comers with mRCC. Patients with intermediate-risk and poor-risk disease should not undergo CN routinely when systemic medical treatment is required or if it would not improve quality of life.[53] CARMENA included patients who were not expected to benefit from CN based on retrospective studies, with 43% of patients having poor-risk disease and high metastatic burden, explaining why overall survival was lower in CARMENA than in other recent trials. CARMENA further supported that CN not only is ineffective but also may be harmful in patients with poor-risk mRCC.[43] Second, CARMENA highlights that not all patients who undergo CN will receive

systemic therapy, the mainstay of metastatic treatment. In this trial, 17.7% of patients in the combination arm did not receive sunitinib after CN. Lastly, some patients with intermediate-risk and poor-risk disease may benefit from CN by reducing adverse events and improving quality of life. The CN group had fewer grade 3 and grade 4 adverse events (32.8% vs 42.7%, respectively), which included significantly fewer renal or urinary tract disorders (0.5% vs 4.2%, respectively), anemia, and musculoskeletal disorders; 17% of patients in the sunitinib-only arm underwent secondary CN for symptomatic management or in cases of complete or near-complete response.[52] CN may be used palliatively to improve symptoms caused by the primary renal tumor and overall quality of life.

CARMENA helped clarify management of MSKCC intermediate-risk and poor-risk mRCC, but it does not provide guidance for favorable-risk patients. The Targeted Therapy With or Without Nephrectomy in Metastatic Renal Cell Carcinoma: Liquid Biopsy dor Biomarkers Discovery (TARIBO) trial was a similarly designed trial comparing CN with TKI to TKI alone and included MSKCC favorable-risk and intermediate-risk patients. Unfortunately, the trial was terminated due to low recruitment, a common problem in many mRCC trials, leading to underpowered data or trial termination.[54]

A second RCT, Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME) explored the timing of CN in relation to initiation of systemic VEGF-TKI therapy in patients with metastatic disease (see **Table 1**).[55] SURTIME compared predominantly MSKCC intermediate-risk patients (88% intermediate risk and 12% poor risk) receiving upfront CN followed by sunitinib to 3 cycles of sunitinib followed by CN with continued sunitinib. It attempted to determine if delayed CN would improve outcomes in comparison to immediate CN and if presurgical systemic therapy could help select patients who would benefit from surgery. Unfortunately, the trial was underpowered, enrolling 99 patients from an anticipated 458 patients, partly due to strict eligibility criteria, including only the best surgical candidates. The primary endpoint of progression-free survival was not met, but an exploratory secondary endpoint of overall survival substantially favored the deferred CN arm on intent-to-treat analysis with a median overall survival of 32.4 months versus 15.1 months respectively ($P = .032$) and an HR of 0.57 (95% CI, 0.34–0.95).[55,56] Despite the studies' limitations, the data support the conclusions drawn from CARMENA that delaying systemic therapy for immediate CN in patients with intermediate-risk and poor-risk disease decreases survival and systemic therapy is the most important treatment component in improving patient outcomes with mRCC. It remains unclear whether intermediate-risk patients who have stable or regressive disease on initial systemic VEGF-TKI therapy would receive additional benefit from undergoing deferred CN.[53]

ACTIVE SURVEILLANCE

Metastatic RCC is characterized by diverse biology and wide-ranging natural history. The prospective trials from the VEGF-TKI era fail to elucidate the possible benefits of CN in patients with good performance status, low-volume metastatic disease, and favorable risk or intermediate risk who may not require systemic therapy. In 2016, a phase II trial evaluated patients with mRCC using an active surveillance protocol, waiting for evidence of progression to initiate systemic therapy.[57] All patients were MSKCC favorable risk or intermediate risk, 98% had undergone prior nephrectomy, and median time on active surveillance until systemic therapy initiation was 14.9 months. A favorable-risk subset, defined by few IMDC risk criteria and at most 2 metastatic sites, had a median surveillance time of 22 months versus 8.4 months in the unfavorable-risk subset.[57] This study emphasizes not all patients with mRCC require immediate systemic therapy and that patients with favorable-risk, low-volume disease, who undergo nephrectomy or CN, may benefit from a substantial period free from toxic systemic treatment.

NEW ERA—IMMUNO-ONCOLOGY

The development of VEGF-TKI therapy altered the treatment paradigm of mRCC, highlighting the importance of systemic treatment in improving outcomes in patients with intermediate-risk and poor-risk disease. A new transition is under way with immune-oncology (IO) checkpoint inhibitors. The landmark CheckMate 214 study published in 2018 was a phase III RCT comparing combination ipilimumab and nivolumab (ipi-nivo) to sunitinib in patients with mostly IMDC intermediate-risk and poor-risk disease (see **Table 1**).[58,59] Patients receiving checkpoint inhibition had superior outcomes to those receiving VEGF-TKI in 18-month overall survival rate (75% vs 60%, respectively), median overall survival (not reached vs 26.6 mo, respectively), objective response rate (42% vs 29%, respectively; $P < .001$), complete response (11% vs 2%, respectively), and grade 3 or grade 4 adverse events (46% vs 63%, respectively).[58,59]

Following CheckMate 214, ipi-nivo replaced sunitinib as first-line treatment of intermediate-risk and poor-risk mRCC.

New trials are under way to evaluate combinations of IO and VEGF-targeted therapy (IOVE) to further advance systemic treatments.[60] IOVE therapy has universally demonstrated improved response rates and progression-free survival in direct comparison over sunitinib monotherapy, and the combination of axitinib plus pembrolizumab additionally has demonstrated improved overall survival (see **Table 1**).[61–63] In comparing IOVE to ipi-nivo, a recent retrospective review found no significant differences in first-line outcomes, such as time to treatment failure, but suggested a greater response to second-line VEGF-based therapy when ipi-nivo was used as the first-line treatment.[64] New prospective studies are needed to determine optimal systemic treatment of each mRCC risk group.

Implementing immune checkpoint inhibitors into the treatment of mRCC has renewed excitement through the observation of complete responses and improved prognosis. In addition to determining the most efficacious IO combination, trials are needed to re-evaluate the role of CN with these more potent therapies.

CYTOREDUCTIVE NEPHRECTOMY IN METASTATIC NON–CLEAR CELL METASTATIC RENAL CELL CARCINOMA

Limited data exist evaluating CN in patients with non–clear cell mRCC. The landmark studies of the cytokine and targeted therapy eras, including SWOG 8949, EORTC 30947, CARMENA, and SURTIME, all excluded patients with non–clear cell histology. Several retrospective series have demonstrated favorable outcomes with CN in non–clear cell mRCC, but these trials are fraught with bias. A retrospective analysis of the SEER database from 2001 to 2014 included 851 patients with non–clear cell mRCC and showed that patients who underwent CN had a 2-year mortality rate of 52.6% in comparison to 77.8% in the group that did not receive CN.[65] A similar analysis of the IMDC database for 353 patients with synchronous papillary mRCC treated with targeted therapy with or without CN found a median overall survival advantage in the CN group of 16.3 months versus 8.6 months, respectively.[66] Overall, CN appears to improve survival in patients with non–clear cell mRCC based on retrospective data from the targeted therapy era. As learned from CARMENA and SURTIME, the favorable outcomes seen in retrospective series may not persist with more rigorous RCTs. Prospective trials are needed to evaluate the role of CN in patients with non–clear cell mRCC, particularly in the IO/IOVE era, to determine its efficacy.

EUROPEAN ASSOCIATION OF UROLOGY RECOMMENDATIONS AND NATIONAL COMPREHENSIVE CANCER NETWORK GUIDELINES

In August 2018, the European Association of Urology (EAU) updated guidelines for CN in patients with synchronous metastatic clear cell RCC based on the results of the recent prospective RCTs evaluating the role of CN with VEGF-TKsI systemic therapy. In their statements, the EAU strongly recommends against the use of CN in MSKCC poor-risk patients. In MSKCC intermediate-risk disease, they recommend systemic therapy. They recommend against performing immediate CN but suggest discussing delayed CN in patients who derive long-term sustained benefit and/or minimal residual metastatic burden on VEGF-TKI therapy. Immediate CN is recommended only in patients with good performance status and who do not require immediate-risk systemic therapy.[53]

The EAU and National Comprehensive Cancer Network (NCCN) guidelines for management of metastatic disease with systemic therapy reflect emerging data. In the 2019 update, the EAU recommends pembrolizumab plus axitinib (IOVE) for IMDC favorable-risk, intermediate-risk, and poor-risk disease or ipi-nivo for intermediate-risk and poor-risk disease as first-line therapy.[67] Similarly, NCCN guidelines recommend axitinib plus pembrolizumab followed by sunitinib or pazopanib as first line for favorable-risk clear cell RCC and ipi-nivo followed by axitinib plus pembrolizumab or cabozantinib as first line for intermediate-risk or poor-risk disease. In non–clear cell histology, NCCN recommends sunitinib or a clinical trial as first-line systemic therapy.[13] Current guidelines have not been updated to reflect the role for CN in the IO and IOVE era due to lack of trials and evidence.

TAKE-HOME POINTS AND CLINICAL RECOMMENDATIONS

Advancements in systemic therapy have altered how surgical management should be utilized in patients with mRCC. Although CN was once standard of care during the cytokine-based immunotherapy era, it no longer should be offered to all-comers with systemic disease. CN offers a survival advantage only when thoughtfully combined with systemic therapy. Unfortunately, upfront CN leads to a delay in initiation of systemic treatment and not all patients who undergo CN may be able to receive

systemic therapy. This delay likely explains why CN may be harmful to patients with more advanced metastatic disease and highlights the importance of systemic therapy. Results from CARMENA and SURTIME suggest that MSKCC intermediate-risk and poor-risk disease patients have worse outcomes when they undergo upfront CN in comparison to delayed CN or VEGF-TKI monotherapy. In general, patients with poor risk disease and most with intermediate risk disease need immediate systemic therapy and should not undergo upfront CN. IO and IOVE therapy are now surpassing VEGF-TKI therapy as first-line treatments of mRCC.

CN may still be beneficial when limited to specific mRCC patient populations. First, patients with good performance status, low-volume, favorable-risk mRCC may have a survival advantage with CN, although level 1 evidence does not exist. Second, CN still may be appropriate in patients who do not require urgent systemic therapy. Patients who can be observed without immediate initiation of systemic therapy can proceed with CN and then be followed on an active surveillance protocol, possibly benefiting from a substantial delay in initiation of toxic systemic treatment. Third, patients with favorable-risk or intermediate-risk mRCC who respond to systemic therapy, with stable or regressive disease, may consider delayed CN. In this capacity, response to systemic therapy could serve as a litmus test for selecting appropriate patients for CN. Fourth, CN may be offered to patients with symptomatic mRCC to improve quality of life. Overall, CN in the modern IO/IOVE era requires further evaluation to identify which mRCC patient populations may still receive benefit from CN, and to understand how CN should be optimally timed with systemic therapy.

CONFLICTS OF INTEREST

None.

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