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Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma – Current Concepts and Contentions in the Era of Immune Checkpoint Inhibitors

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ABSTRACT

Cytoreductive nephrectomy (CN), or the removal of the primary kidney tumor in the setting of metastatic disease, plays a critical role in the treatment of metastatic renal cell carcinoma (mRCC). The benefits of CN, are multifactorial including alleviating symptoms but also eliminating cells potentially prone to future metastasis, and potentially extending a patient's survival. As innovations in mRCC treatment continue to emerge, the importance and timing of CN in patient care remains the subject of ongoing debate in the scientific community. With advancements in modern therapies and the introduction of immune checkpoint inhibitors (ICI), the optimal integration of CN in mRCC management becomes even more important to investigate. This manuscript reviews the key literature related to CN and critically evaluates data that investigated CN efficacy. Furthermore, this article summarizes data to help identify ideal candidates for CN, and explores options for integrating CN within the contemporary systemic therapy landscape.

KEYWORDS

Cytoreductive nephrectomy, Immune Checkpoint Inhibitors, Renal Cell Carcinoma, Patient Selection.

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INTRODUCTION

Renal cell carcinoma will affect about 82,000 people in the U.S. in 2023. Unfortunately, around 30% of the individuals who present with RCC will have metastatic disease either within their regional lymph nodes or at distant sites at the time of their presentation[1,2]. While the majority of patients with metastatic RCC are not curable, there has been a consistent improvement in the overall survival of patients who develop mRCC over the last two decades[3]. Much of this improvement has come from a deeper understanding of RCC tumor biology, and the host immune response within the tumor microenvironment[4]. One of the most important advancements in mRCC management has been the development of immune checkpoint inhibitor therapy[5-9], which has led to a substantial improvement in survival for mRCC patients compared to single agent tyrosine kinase inhibitor (TKI) therapies. As a result, standard first line therapies for mRCC are combinations of ICI/ICI or ICI/TKI therapies.

While there have been significant improvements in the survival of patients with mRCC due to advancements in systemic therapy, surgery continues to remain a critical component of the management of a subset of patients with mRCC. CN has been used throughout the history

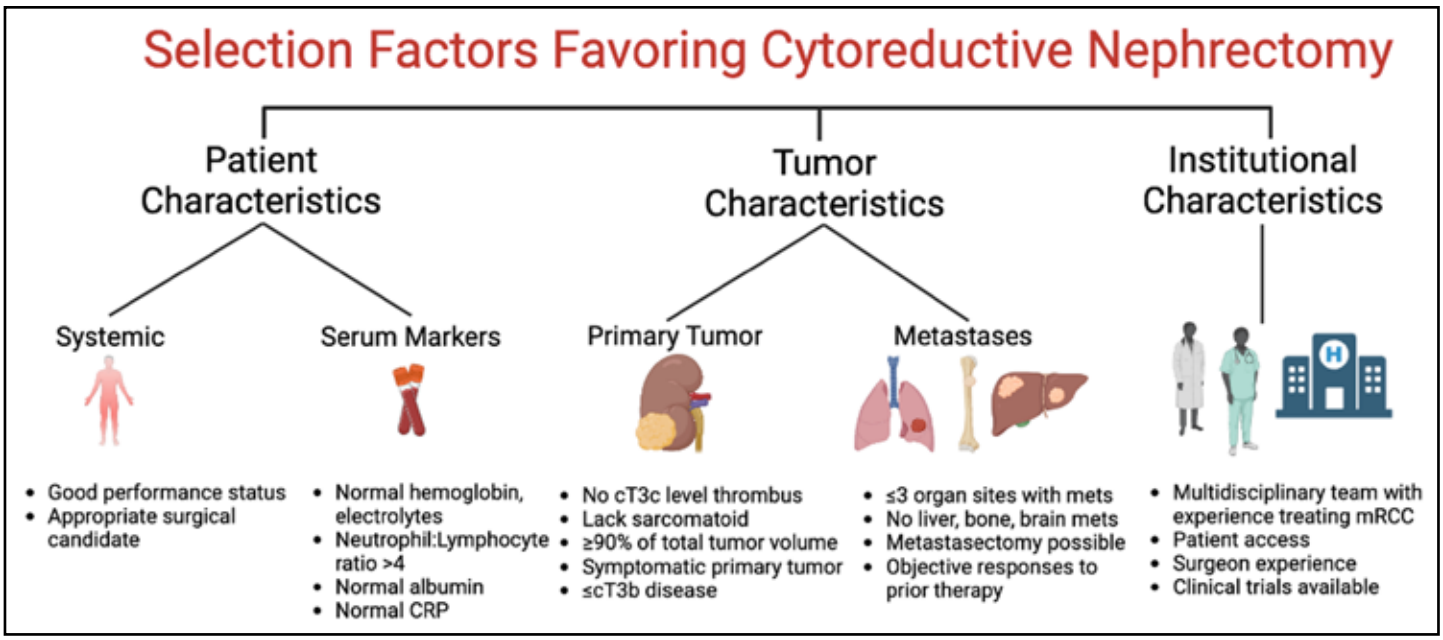

FIGURE 1. . Selection factors favoring cytoreductive nephrectomy. Multiple factors must be considered when deciding on candidacy for cytoreductive nephrectomy. This figure highlights the variables that have been shown to impact outcomes following cytoreductive nephrectomy. CRP = C-reactive protein, mRCC = metastatic renal cell carcinoma.

of mRCC management, but became standard of care in 2001 based on the results of two randomized trials[10-12]. Cytoreductive nephrectomy is defined as the removal of the primary renal mass in the setting of synchronous metastatic disease[13]. This can either occur prior to the receipt of any systemic therapy (termed "upfront" CN) or after systemic therapy has been delivered (termed "deferred" CN). There are multiple reasons that CN is performed: 1) to remove tumor that harbors cells capable of metastasizing or are resistant to therapy, 2) to palliate symptoms such as pain, gross hematuria, early satiety, which thereby improves the patient quality of life, and 3) to extend patient survival. Despite these indications, the role of CN has become controversial due to publication of a randomized trial in 2018 that demonstrated non-inferior outcomes for CN combined with sunitinib compared to sunitinib alone[14]. This clinical trial was controversial and had significant limitations, which reduced the impact of the findings in the context of modern mRCC management. The goal of this review is to concisely summarize the historical context of CN leading up to the current era of ICI therapy, including a critical analysis of the controversies surrounding CN and how CN can best be incorporated into the management of patients with mRCC.

CYTOREDUCTIVE NEPHRECTOMY – A BRIEF HISTORY

Prior to the implementation of effective systemic therapies, CN was used sparingly and was considered more for symptomatic purposes. Spontaneous regression of metastatic disease after patients received CN was reported but exceptionally rare[15]. Cytoreductive nephrectomy became a standard of care after the publication of two clinical trials in 2001: SWOG 8949 and EORTC 30947[10,12]. The two trials had similar study designs and randomized patients to either IFN-α alone or upfront CN followed by IFN-α. A combined analysis of these trials demonstrated an overall survival benefit favoring the CN arm (13.6 months vs 7.8 months, P=0.001)[11]. While these data are older, and IFN-α is significantly less effective than modern ICI therapy, the data from these trials provide a unique view of the benefit of CN. When these trials were conducted, there were no approved second line systemic therapy options available. Therefore, the survival data from these trials is less influenced by subsequent

STUDY	Treatment arm	% with Prior Nephrectomy
Motzer et al *NEJM* 2007 (17)	Sunitinib	91%
Escudier et al *NEJM* 2007 (18)	Sorafenib	94%
Motzer et al *Lancet* 2008 (77)	Everolimus	96%
Rini et al *JCO* 2008 (78)	Bevacizumab + IFN	85%
Sternberg et al *JCO* 2010 (79)	Pazopanib	89%
Motzer et al *NEJM* 2013 (80)	Pazopanib	82%
Motzer et al *NEJM* 2015 (81)	Nivolumab	89%
Choueiri et al *NEJM* 2015 (82)	Cabozantinib	85%
Motzer et al *NEJM* 2018 (83)	Nivolumab + Ipilimumab	82%
Motzer et al *NEJM* 2019 (84)	Avelumab + Axitinib	80%
Rini et al *NEJM* 2019 (6)	Pembrolizumab + Axitinib	83%
Rini et al *Lancet* 2019 (9)	Atezolizumab + Bevacizumab	74%
Choueiri et al *NEJM* 2021 (8)	Nivolumab + Cabozantinib	69%
Motzer et al *NEJM* 2021 (85)	Lenvatinib + Pembrolizumab	74%
Choueiri et al *NEJM* 2023 (86)	Cabozantinib + Nivolumab + Ipilimumab	65%

TABLE 1. Percent of patients who received a prior nephrectomy in phase III trials for metastatic RCC

Randomized Trial	Median Overall Survival in Sunitinib Arm
Mejean et al. *NEJM*. 2018 (CARMENA trial) (14)	18.4
Powles et al. *Lancet Oncol*. 2020 (21)	Not Reached
Motzer et al. *Cancer*. 2022 (20)	38
Rini et al. *Lancet*. 2019 (9)	34.9
Motzer et al. *NEJM*. 2014 (87)	29.1
Motzer et al. *NEJM*. 2007 (17)	26.4

TABLE 2. Median overall survival of patients randomized to sunitinib treatment in the CARMENA trial compared to other phase III randomized trials for metastatic renal cell carcinoma. CN=cytoreductive nephrectomy

therapies that patients might have pursued outside the trial setting. This offers a clearer understanding of the impact of CN on overall survival, devoid of the effects created by different second line therapies on patient survival. These data demonstrate a significant benefit for appropriately selected patients undergoing CN.

The cytokine era of systemic therapy (prior to 2006) consisted of IFN-α and IL-2, both of which had limited efficacy and high toxicity[16].After the cytokine era of systemic therapy, TKI therapy became standard of care starting with sorafenib and sunitinib therapy, after two phase III trials in 2007 demonstrated benefit of these agents over IFN-α[17,18]. In 2015, nivolumab (an anti-PD1 antibody that activates exhausted CD8+ T cells) became the first FDA approved ICI therapy for the treatment of mRCC, bringing about the ICI therapy era of mRCC management[19]. Since that time, multiple phase III trials have demonstrated the ability of ICI therapy to extend patient survival in the setting of mRCC. For example, the phase III trial CheckMate 214 published extended follow-up showing a median overall survival of 56 months for patients treated with nivolumab plus ipilimumab, and the KEYNOTE-426 trial demonstrated a median overall survival of 46 months among patients treated with pembrolizumab plus axitinib[20,21]. These results are nearly two fold higher than the median overall survival of patients receiving sunitinib, which was 26 months upon the trial's final analysis[22]. Thus, there has been a clear improvement in the survival of patients with mRCC being treated in clinical trials with modern ICI therapies.

It is important to note that all of the phase III trials investigating modern systemic therapies for mRCC included a large proportion of patients that had received a prior nephrectomy (either prior to metastatic progression or at the time of synchronous metastatic disease) (TABLE 1). Thus, the survival benefits of all modern systemic therapies for mRCC have to be interpreted knowing that most patients had their primary tumors removed prior to systemic therapy administration. In truth, randomized clinical trial data for systemic therapies in mRCC do not exist in the absence of surgery, which is a key reason that surgery is considered part of the multidisciplinary care of mRCC.

CONTROVERSIES REGARDING CYTOREDUCTIVE NEPHRECTOMY

The most recent catalyst for CN controversy was publication of the results of the CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) clinical trial[14], randomized 1:1 mRCC patients treated with upfront CN followed by sunitinib versus sunitinib alone. This was designed as a non-inferiority trial with overall survival as the primary endpoint and statistically powered to include 576 patients. The trial was published in 2018 and demonstrated non-inferior survival outcomes in the systemic therapy alone arm vs CN plus systemic therapy arm (18.4 vs 13.9 months, respectively). The results and trial design sparked immediate debate in the literature and at scientific conferences.

Despite providing the first randomized clinical trial data in two decades, the CARMENA study had significant limitations. First, the trial enrolled extremely slowly and did not reach its accrual goal. Two planned interim analyses (after 152 and 304 deaths) were performed and both concluded that the trial should continue. However, immediately after the second interim analysis, the sponsor closed the trial because of poor accrual. At the time of publication, the trial was able to enroll 450 patients across 79 centers over 8 years, significantly short of enrollment goal of 576 patients. In both study cohorts, there was significant contamination from not receiving the primary treatment or receiving other secondary treatments, which could bias the outcomes.

The trial was analyzed according to the intention-to-treat principle, but patients were frequently managed differently than their designated trial arm protocol. Seven percent of patients in the surgical arm did not receive a CN and 18% of patients did not receive subsequent sunitinib therapy and 5% did not get sunitinib. In both groups, about half of patients received additional lines of systemic therapies after sunitinib. One of the strongest criticisms of this study was the enrichment of the study cohort for poor risk patients with high volume metastatic disease. In CARMENA, the median patient had 2 sites of metastatic disease with 14 cm of overall tumor burden with 8.8 cm primary tumors. Nearly half (44%) of patients enrolled in the CN arm had poor risk disease according to the Memorial Sloan Kettering Cancer Center (MSKCC) mRCC risk classification. Multiple prior retrospective studies have demonstrated that poor risk patients with high volume disease outside of the kidney are least likely to derive a survival benefit from CN and should be counseled against upfront surgery. Evaluation of the CARMENA patients and known predictors of poor outcomes after CN demonstrate a high-risk patient population enrolled in the study to receive CN. The MD Anderson Cancer Center investigators published preoperative predictors of worse overall survival after CN[23]. These predictors included node positive disease (N+), bone metastases, and high stage disease (clinical T4 disease). The CARMENA patients included 35% with N+ disease and 36% with bone metastases. Additionally, 70% within the surgery arm had cT3-T4 disease compared to only 51% within the sunitinib only arm. The selection of high-risk patients for inclusion in this trial is further supported by the fact that the median overall survival in the sunitinib arm is much lower than the median survival in the sunitinib arm from other modern

phase III randomized trials (TABLE 2). A post hoc analysis of the CARMENA trial demonstrated that patients with one IMDC risk factor had significantly longer OS in comparison to those with two or more IMDC risk factors[24]. Lastly, it should be noted that systemic therapy options evolved considerably during the eight-year study and when the trial results were published, sunitinib was no longer used for first line therapy for mRCC patients, further limiting the applicability of the results to modern clinical practice. Strong conclusions from the CARMENA trial should be that appropriate patient selection is critical for successful outcomes[25].

Treatment Era	Study	Study type	Number undergoing CN	Number without CN	Median Follow-up (months)	Median OS for CN Patients (months)	HR OS (95% CI)
ICI ERA	Bakouny et al 2023 (74)	Observational	234	203	12	54	0.61 (0.41-0.90)
	Hahn et al 2023 (88)	Observational (Sarcomatoid mRCC only)	118	39	33.9	30.1	0.98 (0.65-1.47)
	Singla et al 2020 (89)	Observational	221	170	14.7	Not reached	0.23 (0.15-0.37)
TKI ERA	Chakiryan et al 2022 (90)	Observational	5005	7761	36	NR	0.49 (0.47-0.51)
	Marchioni et al 2019 (50)	Observational	575	276	9	10	0.38 (0.30-0.47)
	Mejean et al 2018 (14)	Prospective RCT	226	224	50.9	13.9	1.13 (0.91-1.40) †
	Klatte et al 2018 (29)	Observational	97	164	14.6	25.6	0.63 (0.46-0.84)
	Patel et al 2017 (30)	Observational	289	773	52	NR	0.53 (0.24-1.15)
	de Groot et al 2016 (32)	Observational	73	73	NR	17.9	0.61 (0.41-0.92)
	Hanna et al 2016 (33)	Observational	5374	10,016	NR	17.1	0.49 (0.46-0.52)
	Heng et al 2014 (35)	Observational	982	676	39.1	20.6	0.60 (0.52-0.69)
	Abern et al 2014 (36)	Observational	2629	4514	13	NR	0.40 (0.37-0.43)
	Conti et al 2014 (37)	Observational	6915	13,189	12	15	0.41 (0.39-0.43)
	Choueiri et al 2011 (38)	Observational	201	113	16.3	19.8	0.68 (0.46-0.99)
	You et al 2011 (91)	Observational	45	33	8.2	21.6	0.53 (0.24-1.15)

TABLE 3. Studies investigating the survival associations with cytoreductive nephrectomy by treatment era. *CN = cytoreductive nephrectomy, OS = overall survival, HR = hazard ratio comparing patients receiving CN to those who did not receive CN, ICI = immune checkpoint inhibitor, TKI = tyrosine kinase inhibitor, NR = Not reported*
†HR reported as patients who did not undergo CN compared to patients who did undergo CN

Another question that was attempted to be investigated with a randomized clinical trial is optimal timing of CN (before or after systemic therapy). The SURTIME trial (Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients with Metastatic Kidney Cancer) investigated the timing of CN and sunitinib therapy[26]. Patients were randomized to either upfront CN followed by sunitinib or sunitinib therapy followed by deferred CN. Like CARMENA, SURTIME had difficulty enrolling patients and only 99 patients were recruited to the trial before it was closed. In the intention to treat population, the 28-week progression free rate (PFR) was 42% compared to 43% in the upfront versus deferred CN patients (P=0.61) and the median overall survival was 15 months versus 32.4 months in the upfront versus deferred CN patients (P=0.03)[26]. The trial indicated no significant improvement in the 28-week PFR with a possible survival benefit for deferred CN but results are difficult to interpret with small patient numbers. As a response to poor enrollment, 28-week PFR became a revised primary endpoint. Additionally, within the deferred CN arm, 29% of patients did not undergo surgery while 92% of patients in the upfront CN received surgery. The trial was not powered to detect an overall survival benefit and the survival analysis was exploratory. A per-protocol analysis ultimately did not demonstrate a significant overall survival difference between the two arms. Lastly, sunitinib as first line therapy is no longer clinically applicable to modern management of mRCC. In summary, the SURTIME trial suggested minimal difference in endpoints with different timing of CN but did not definitively answer the question.

The CARMENA and SURTIME trials fueled significant controversy regarding the utility and timing of CN in the management of patients with mRCC. Following the publication of these trials, the European Association of Urology (EAU) guidelines regarding CN were modified and recommended poor risk patients (based on MSKCC risk criteria) should not undergo CN and intermediate and poor risk patients should receive systemic therapy first before CN is considered[27]. The findings of these clinical trials, however, need to be balanced with the large number of observational data that suggest a continued survival benefit for patients receiving CN (TABLE 3)[28-38]. The conflicting evidence between randomized trials and observational studies likely resides in surgical selection bias. The appropriate selection of patients for CN is critical to successful outcomes, and this concept is reflected in many modern guideline recommendations (TABLE 4).

PATIENT SELECTION FOR CYTOREDUCTIVE NEPHRECTOMY – CHOOSING WISELY

There are no standardized selection factors for identifying ideal patients for CN. Multiple different prognostic and predictive variables have been identified, all of which have been investigated in observational studies. In general, variables that predict survival outcomes following CN fall into three major categories: institutional associated variables, patient associated variables, and tumor

GUIDELINE COMMITTEE	GUIDELINE RECOMMENDATIONS
2022 European Association of Urology (63)	1. Do not perform CN in MSKCC poor-risk patients. 2. Do not perform immediate CN in intermediate-risk patients who have an asymptomatic synchronous primary tumor and require systemic therapy. 3. Start systemic therapy without CN in intermediate-risk patients who have an asymptomatic synchronous primary tumor and require systemic therapy. 4. Discuss delayed CN with patients who derive clinical benefit from systemic therapy. 5. Perform immediate CN in patients with good performance status who do not require systemic therapy. 6. Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved
2022 National Comprehensive Cancer Network (69)	1. CN before systemic therapy is recommended in select patients with a potentially surgically resectable primary mass. 2. Patients with metastatic disease who present with hematuria or other symptoms related to the primary tumor should be offered palliative nephrectomy if they are surgical candidates. 3. Patients with surgically resectable primary RCC and oligometastatic sites may be candidates for nephrectomy and surgical metastasectomy or ablation for patients who are not metastasectomy candidates. 4. Patients who have undergone a nephrectomy and later develop oligometastatic recurrence also have the option of metastasectomy, radiation, or ablation.
2022 American Society of Clinical Oncology (92)	1. Select patients with metastatic clear cell RCC may be offered cytoreductive nephrectomy. Select patients include those with optimally one IMDC risk factor who can have a significant majority of their tumor burden removed at the time of surgery
American Urological Association	No guideline recommendations

TABLE 4. Guideline recommendations regarding cytoreductive nephrectomy from different guideline committees. CN = cytoreductive nephrectomy, MSKCC = Memorial Sloan Kettering Cancer Center, IMDC = International Metastatic RCC Database Consortium

associated variables. Within each of these categories, multiple variables have been identified that help to select ideal candidates for CN (FIGURE 1).

Tumor Characteristics

Certain characteristics of the primary and metastatic tumors are significantly associated with outcomes following CN. Patients are thought to be more likely to benefit from CN if the primary tumor accounts for the majority of total tumor burden within the patient[39, 40]. One study demonstrated that when assessing both metastatic and primary tumors, if the volume of the primary tumor comprises more than 90% of the total tumor burden, patients are likely to experience improved cancer-specific survival following CN[40].

Also, primary tumors with a tumor thrombus pose a unique challenge in the metastatic setting. Tumors that invade the inferior vena cava can progress rapidly toward the right atrium and cause significant symptoms such as leg swelling, fatigue, weight loss, liver failure and ultimately death. Up to 50% of patients with tumor thrombi can have metastatic disease. Abel *et al.* demonstrated that compared to tumor thrombi that only invade the renal vein (i.e., level 0), tumor thrombi that have advanced above the diaphragm (level IV) have significantly reduced overall survival (median 22 vs 9 months, respectively)[41]. Conversely, tumor thrombi that are still below the diaphragm but above the renal vein did not have significantly worse survival than level 0 thrombi (20 vs 22 months, respectively)[41]. Thus, patients with tumor thrombi invading the IVC should still be considered for CN by experienced surgeons.

The number and location of metastases should also be considered when identifying CN candidates. A greater number of different metastatic sites is associated with inferior outcomes following CN and certain locations portend more aggressive disease[42-45]. Patients with lung, pancreas, thyroid, or adrenal metastases tend to have a more indolent pattern of progression and may be better suited for upfront CN, while patients with liver or brain metastases tend to have worse overall survival and more rapid disease progression and may benefit from upfront systemic therapy followed by deferred CN in those who respond or demonstrate disease stability[42-44]. Metastasectomy should also be considered particularly for patients with oligometastatic disease in surgically resectable locations. Patients undergoing complete metastasectomy with CN (either at the same time or in a delayed fashion) have superior cancer-specific survival; however, patients undergoing metastasectomy typically are highly selected for excellent performance status and more indolent tumor biology[46, 47]. If surgical extirpation is not an option, metastasis directed therapy can be achieved in some circumstances using either ablative technology[48]. or stereotactic body radiotherapy (SBRT). A phase 2 trial by Tang *et al.* recently reported treating 30 patients with ≤5 metastatic tumors with SBRT to all metastatic sites. Median progression-free survival was 22.7 months and authors concluded that SBRT may delay systemic therapy initiation or facilitate breaks from systemic therapy among patients with oligometastatic RCC[49].

Additional tumor related characteristics that should be considered when deciding on CN are tumor associated symptoms, tumor histology, and sarcomatoid dedifferentiation. Patients may present with a symptomatic primary tumor with pain, gross hematuria, or paraneoplastic syndromes. In these situations, CN should be considered for appropriate surgical candidates to palliate symptoms and improve patient quality of life. Regarding non-clear cell histology, outcomes following CN are less well defined, but in general similar principles apply to patient selection and observational studies have demonstrated a survival benefit for patients receiving CN even with non-clear cell histologies.[50, 51]. Tumors harboring sarcomatoid dedifferentiation are particularly aggressive. Prior to ICI therapy, patients with metastatic sarcomatoid RCC often had rapid disease progression and short median overall survival, and observational studies of CN for patients with metastatic sarcomatoid disease showed worse survival compared to patients without sarcomatoid disease[52]. Sarcomatoid disease appears uniquely responsive to ICI therapy, however, and patients with sarcomatoid disease have experienced impressive responses with ICI therapy compared to older systemic therapy

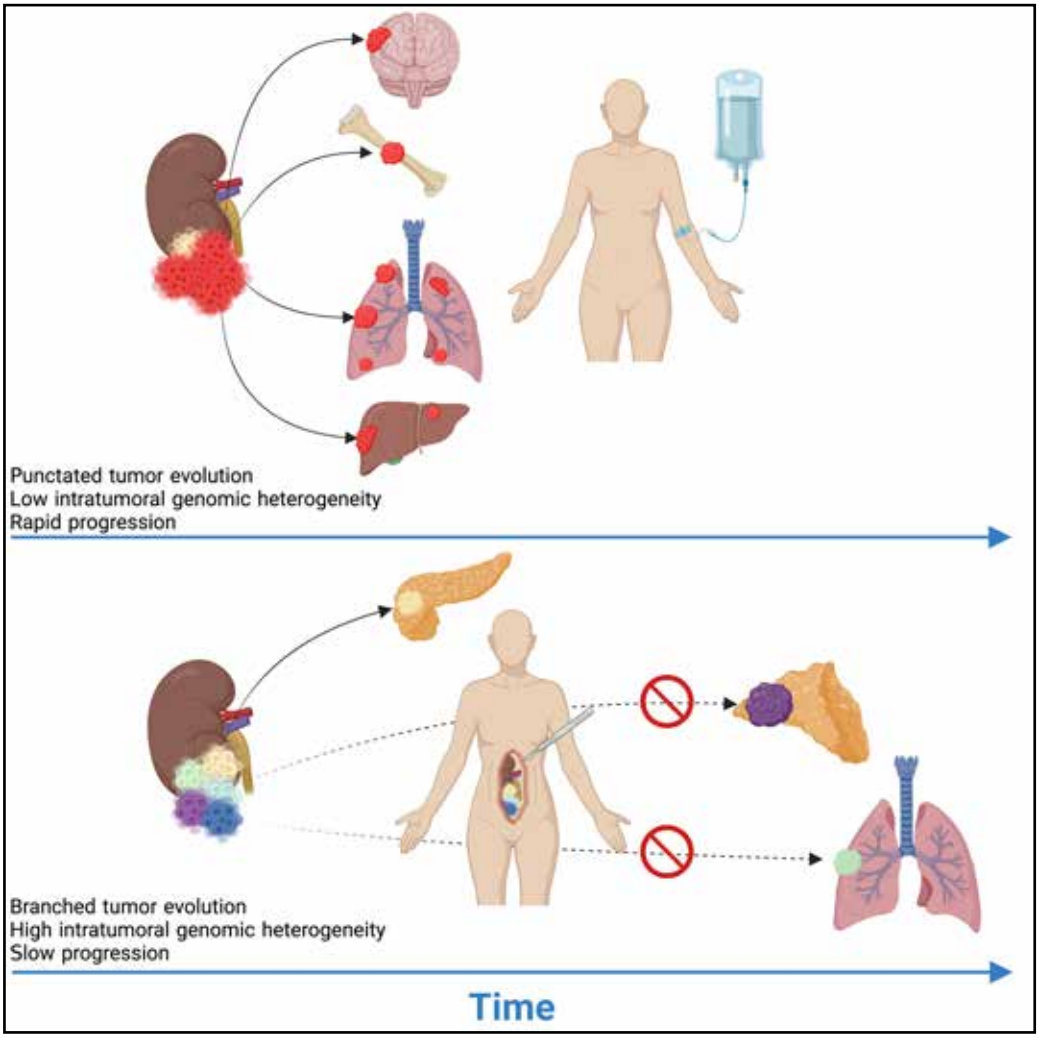

FIGURE 2 | Renal cell carcinoma tumor evolution and management overtime. Two different evolutionary patterns are represented in the figure. In the top panel, the renal cell carcinoma tumor evolution consists of a largely monoclonal cell population that acquired early, aggressive genetic change (e.g., BAP1 mutation) resulting in a genetically homogenous tumor cell population (indicated by the primarily red color cells making up the primary tumor). This results in rapid, widespread metastatic development, and these patients are often better suited for upfront systemic therapy. The bottom panel reveals a branched tumor evolution in which a genetically heterogenous tumor contains multiple different clonal populations. These tumors typically metastasize slowly and in an oligometastatic fashion with different metastatic tumors derived from different clonal populations within the primary tumor (represented by the different colored cells in the primary tumor). Cytoreductive nephrectomy is ideally suited for these patients by removing clonal populations of cells that potentially have future metastatic potential to different sites.

agents. The KEYNOTE-426 trial evaluating pembrolizumab+axitinib and the CheckMate 214 trial evaluating nivolumab+ipilimumab both demonstrated improved disease response among sarcomatoid tumors compared to the sunitinib control arm[5,6]. Thus, patients with sarcomatoid dedifferentiation and mRCC should be considered for upfront ICI/ICI or ICI+TKI therapy and later treated with surgery if there has been significant response to systemic therapy and a residual primary tumor. One challenge with sarcomatoid dedifferentiation is that clinicians frequently do not know if the tumor harbors sarcomatoid dedifferentiation at presentation or prior to offering surgery as it is not reliably detected on imaging or biopsy and is mainly determined after nephrectomy has been performed.

Among patients with borderline unfavorable tumor characteristics, some propose using upfront systemic therapy as a "litmus test" to determine whether or not the patient will progress even in the setting of systemic therapy. If a patient progresses, they are unlikely to benefit from surgical intervention. However, if a patient has a durable response to therapy, they may be more likely to benefit from surgery. In these situations, CN can be considered in the deferred setting. This is particularly relevant in the ICI therapy era, where significant responses to ICI/ICI and ICI/TKI therapy have been observed.

Patient Characteristics

One of the fundamental challenges faced by clinicians is determining the fitness of patients preoperatively and estimating a patient's individual risk of morbidity and mortality for a complex operation such as CN. Various measures of performance status have been used to estimate these risks including the Eastern cooperative group performance status scale[53], Karnofsky performance status[54], and Charlson comorbidity index[55]. While each of these measures can give a general idea of the patient level of fitness and comorbidity, none were specifically designed to measure a patient's risk of morbidity from CN or their subsequent survival following CN. In general, patients with poor performance status are felt to be higher-risk candidates for CN and favored to receive initial systemic therapy. Patient performance status is dynamic, however, and may improve after receiving systemic therapy making them eligible for CN after initial systemic therapy. This demonstrates the importance of a multidisciplinary approach to mRCC patient management when determining surgical eligibility, which should be considered not only during the initial evaluation of the patient but throughout a patient's disease course.

Other serum-based markers have been identified as predictive of patient outcomes. The presence of preoperative anemia, hypercalcemia, and hypoalbuminemia have been associated with worse survival following CN[56, 57]. Markers of systemic inflammation such as the elevated neutrophil lymphocyte ratio and

elevated C-reactive protein have also been associated with worse survival outcomes following CN[58-60]. While each of these variables may incrementally better inform selection of patients for CN, none has been routinely incorporated into patient selection and most require further external validation. Additionally, the majority of these markers were evaluated in the TKI therapy era, and require further study in the setting of modern ICI therapy.

Prognostic scores

Various prognostic scores have also been developed that incorporate many of the previously described variables. Two frequently used prognostic scoring systems are the Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria and the International Metastatic RCC Database Consortium risk criteria[61, 62]. The MSKCC and IMDC risk criteria are similarly designed but incorporate different prognostic variables that predict survival outcomes for patients with mRCC. Currently, the IMDC risk criteria are more frequently utilized as they were more recently developed in the TKI therapy era. Each variable in the IMDC risk criteria is assigned 1 point and the variables included are neutrophilia, thrombocytopenia, anemia, hypercalcemia, Karnofsky performance status <80, and time from diagnosis to systemic therapy of <1 year. Patients with mRCC are categorized into favorable (0 risk factors), intermediate (1-2 risk factors) and poor (≥3 risk factors) risk groups. The EAU guidelines recommend that intermediate and poor risk patients should receive systemic therapy first and poor risk patients do not benefit from CN[63] The limitation of using these risk stratifications to make decisions regarding CN is that they were not designed specifically to address survival outcomes following CN. Also, the risk classifications are often dynamic and may change during the disease course. A patient may initially present with poor risk disease (due to lab abnormalities such as anemia, hypercalcemia, and neutrophilia) but these may improve after receipt of systemic therapy or CN[64, 65].

In order to address these limitations, prognostic scoring systems have been developed specifically in CN patient populations to help identify appropriate candidates for CN[23, 66] Updating their prior prognostic classification system[66], the MD Anderson Cancer Center group recently evaluated a modern cohort of CN patients and identified 9 predictors of worse overall survival following CN[23]. The advantage of this study is that it incorporates variables that can be obtained preoperatively to risk stratify patients and was designed specifically in a CN patient population. Similarly, a study using the European registry for metastatic RCC (REMARCC) developed a scoring system to predict overall survival following upfront CN. The study incorporated BMI, metastatic location (lung, liver, bone), number of metastatic sites, and performance status into their model for predicting survival[67]. Both studies require further external validation and given the time periods within which patients were included, it is unlikely that many patients received ICI therapy during the course of their mRCC treatment, highlighting the need for prospective registries of mRCC patients receiving CN to identify predictors of favorable outcomes.

The medical system impact on cytoreductive nephrectomy

Another critical aspect of outcomes following CN is the system in which the patient is treated. Management of patients with mRCC is nuanced and complex, requiring coordination between multiple disciplines. Patients with mRCC interact with oncologists (including urologic, medical and radiation), pathologists, radiologists, interventional radiologists, anesthesiologists, nursing staff (in the clinic, infusion centers, inpatient units, research coordinators, and operating room), medical technologists (in the operating room and clinics), phlebotomists, billing and insurance staff, fellows, residents, and medical students to name only a few. Coordination of these components requires a system designed to and experienced in delivering care to patients with mRCC. Poor access to centers such as these may limit the ability for a patient to receive CN and negatively impact the survival outcomes of patients following CN. Cytoreductive nephrectomy has been shown to be more frequently performed at academic institutions and among the privately insured[30]. Higher hospital volume is also independently associated with improved mortality following CN[68]. Thus, patient access to systems that routinely manage mRCC and a thoughtful multidisciplinary discussion of these complex cases is critical for favorable outcomes.

CYTOREDUCTIVE NEPHRECTOMY IN THE ERA OF IMMUNE CHECKPOINT INHIBITORS

Since nivolumab approval in 2015, there has been rapid incorporation of ICI therapy into the management of mRCC, and ICI/ICI or ICI/TKI combinations are now first line therapy[69]. The improvements in response rates to modern systemic therapy again begs the question if there is still a role for CN. Given ICI therapy's relatively recent approval, very few studies have addressed the impact of CN on survival outcomes in the setting of ICI therapy and those that have are often small sample sizes with limited follow-up[70-73]. Cytoreductive nephrectomy following ICI therapy does appear safe and feasible. One of the largest multi-institutional studies by Shapiro et al. demonstrated that among 75 patients undergoing deferred CN following ICI therapy, the high-grade complication rate was only 3% with no 90-day mortalities. Additionally, 48% of patients were able to enter a period of surveillance following their CN, delaying further systemic therapy.(71) Thus, patients being treated with CN at experienced centers face low morbidity rates even compared to historic CN series[57].

Regarding survival outcomes, a recent study by Bakouny *et al* used the IMDC database to evaluate the impact of upfront CN (N=234) vs no CN (N=203) on survival outcomes among patients treated with ICI therapy. Multivariable analysis demonstrated upfront CN was associated with significantly improved overall survival compared to no CN among patients treated with ICI therapy (HR 0.61, 95% CI 0.41-0.9, P=0.013)[74]. These studies again appear to confirm that among appropriately selected patients, CN is safe and associated with improved survival.

CYTOREDUCTIVE NEPHRECTOMY FUTURE DIRECTIONS

As we gain a deeper understanding of RCC tumor biology, we may begin to better select patients for CN based on tumor biology. The TRACERx studies have demonstrated that tumors harboring BAP1 mutations are associated with rapid tumor progression and low intratumoral genomic heterogeneity. These patients may not derive a survival benefit from CN compared to tumors harboring primarily PBRM1 mutations without BAP1 mutations, which are associated with slow progression and high intratumoral genomic heterogeneity (FIGURE 2)[75]. The Memorial Sloan Kettering group also demonstrated that BAP1 mutations negatively affected OS among patients undergoing CN, while SETD2 and KDM5C mutations were associated with reduced risk of death[76]. Additional explorations into the tumor and immune microenvironments may help identify predictive biomarkers associated with patient survival following CN[4].

Clinical trials investigating CN are currently being conducted. Active trials include PROBE (NCT04510597), NORDIC-SUN (NCT03977571), and Cyto-KIK (NCT04322955). While these trials will provide insight on the role of CN in the deferred setting, there are currently no large trials investigating the use of upfront CN, which is utilized in healthy patients with minimal metastatic disease. Prior studies including CARMENA and SURTIME have demonstrated the difficulties accruing to CN specific trials, thus other mechanisms for studying CN in a robust and generalizable manner are necessary to supplement clinical trials. An additional robust method for studying CN in the future will be multi-institutional prospective registries to investigate CN outcomes, particularly in the upfront setting. While not randomized, prospective registry data can still provide important insight into CN practice patterns, perioperative morbidity, and survival outcomes, particularly in the rapidly changing treatment landscape of mRCC.

An additional unexplored area of research is the study of patient reported outcomes and quality of life following CN using validated HRQoL instruments used in most studies of systemic therapy. One of the primary proposed benefits of CN is that it improves patient symptoms and quality of life, but evidence to support this hypothesis is absent. Additionally, it is critical to involve multidisciplinary care across the patient's journey of treatment. Future studies to address these issues must be conducted.

CONCLUSION

Cytoreductive nephrectomy remains a critically important component of the multidisciplinary approach to management of patients with mRCC. A large body of evidence supports the use of CN in appropriately selected patients. Patients with good performance status and limited metastatic burden are ideal candidates for CN. The use and timing of CN will continue to evolve as our understanding of RCC tumor biology advances and systemic therapies continue to improve.

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CONFLICTS OF INTEREST

None

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