Review Article

The current role of cytoreductive nephrectomy for metastatic renal cell carcinoma

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ABSTRACT

The management of metastatic renal cell carcinoma (mRCC) continues to be a therapeutic challenge; however, the options for systemic therapy in this setting have exploded over the past 20 years. From the advent of toxic cytokine therapy to the subsequent discovery of targeted therapy (TT) and immune checkpoint inhibitors, the landscape of viable treatment options continues to progress. With the arrival of cytokine therapy, two randomized trials demonstrated a survival benefit for upfront cytoreductive nephrectomy (CN) plus interferon therapy and this approach became the standard for surgical candidates. However, it was difficult to establish the role and the timing of CN with the subsequent advent of TT, just a few years later. More recently, two randomized phase III studies completed in the TT era questioned the use of CN and brought to light the role of risk stratification while selecting patients for CN. Careful identification of the mRCC patients who are likely to have a rapid progression of the disease is essential, as these patients need prompt systemic therapy. With the continued advancement of systemic therapy using the immune checkpoint inhibitors as a first line therapy, the role of CN will continue to evolve.

INTRODUCTION

Renal cell carcinoma (RCC) detection rates have increased over the past two decades as incidental renal masses are picked-up on the cross-sectional imaging performed for other symptoms.[1,2] While the number of patients with localized RCC has been increasing, the incidence of advanced or metastatic RCC (mRCC has remained stable.[1,2] In the 1980s and early 1990s, cytokine therapy (i.e., interleukin-2 [IL-2] and interferon-α [IFN-α]) was heavily explored for the treatment of mRCC, spurred on by the excitement of remarkable durable responses in a select group of patients.[3] However, even prior to the wide spread use of systemic therapy, the spontaneous regression of metastases, in a small percentage of patients undergoing debulking nephrectomy, had been documented.[4,5] Subsequently, in a landmark trial, Flanigan *et al.* demonstrated that cytoreductive nephrectomy (CN) with cytokine therapy had a tangible survival advantage over cytokine therapy alone.[6]

The theory of debulking nephrectomy revolves around optimizing the immune response for systemic therapy, alleviating the local symptoms, and reducing the effects of paraneoplastic syndromes (i.e., hypercalcemia).[7] Despite hope in cytokine therapy and CN to improve survival, the mortality rate did not appreciably reduce until the advent of targeted therapy (TT) and the approval of sunitib in 2006.[2,6,8,9] Most of the patients in these original trials evaluating targeted therapies had already undergone CN, making its role in the improved survival over targeted agents alone unknown.[9-11] In addition, the CN-associated complications andpostoperative disease progression have become the major concerns in the patients who undergo upfront nephrectomy and thus receive delayed systemic treatment or are unable to receive it.[12-15]

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Disease biology and proper patient selection have gained increasing attention, as the treatment must balance the morbidity of the surgery with a potential of therapeutic advantage. Two studies have been conducted to answer the role of CN in the TT era: the CARMENA and the SURTIME trials.[16,17] These trials questioned the timing of CN and highlighted the importance of patient selection. Here, we critically review the potentially therapeutic role of CN in mRCC patient, exploring the current literature and its limitations.

THE IMMUNE HYPOTHESIS OF CYTOREDUCTIVE NEPHRECTOMY

Before the approval and widespread use of IL-2 in the 1990s, CN was known to be associated with spontaneous regression of metastases in a small percentage of the patients.[4,5] These rare, but well-documented events, established RCC as a possible immunogenic tumor. This tumor environment activates a pro-inflammatory process and accumulates lymphocytes, natural killer cells (NK cells), and dendritic cells within the tumor, with subsequent deactivation of the T-cell immunity and, thus, promoting the metastatic process.[18-24] In the early cytokine era, administering IL-2 while the primary RCC had not been resected, showed a limited response, but this immunosuppressive state could be reversed by CN.[25] Fujikawa *et al.* measured the serum C-reactive protein (CRP) levels from 55 mRCC patients before and after CN.[25] Disease-specific survival rates among the patients who had normal serum CRP levels was not different whether they had CN or not. In contrast, the survival benefits were significantly observed in the patients with elevated serum CRP level preoperatively and who underwent CN as compared to the ones who did not ($P = 0.005$). Patients whose serum CRP level returned to normal after CN demonstrated a better survival than the ones' in which it remained elevated ($P = 0.003$). The immunogenic characteristics of microenvironments have been confirmed in pulmonary and skeletal metastases.[26,27]

CYTOREDUCTIVE NEPHRECTOMY IN THE CYTOKINE THERAPY ERA

The immune hypothesis of CN and t cytokine therapy came into clinical practice together, but the best therapeutic approach was not immediately clear.[28-30] In 1996, Franklin *et al.* showed that mRCC patients who underwent CN followed by IL-2-based immunotherapy had a 34% response rate and a 43% 2-year survival rate.[28] On this foundation, trials utilizing upfront nephrectomy followed by systemic immunotherapy revealed improved patient survival versus systemic immunotherapy alone.

In 2001, two landmark trials were published from the Southwest Oncology Group (SWOG) 8949 and the European Organization for the Research and Treatment of Cancer (EORTC) 30947 in which patients were randomized to IFN-α alone or CN followed by IFN-α.[6,31] These trials had the same criteria for recruitment, which included operable primary tumors and a good performance status (PS). EORTC 30947 included 85 eligible patients, 42 in CN plus IFN-α and 43 in IFN-α-alone arms.[31] There was no difference in the radiographic response rate of metastatic disease between the groups (19% in CN plus IFN-α vs. 12% in IFN-α alone, $P = 0.38$). However, patients in CN plus IFN-α cohort had a significantly longer median overall survival (OS) (17 vs. 7 months, $P = 0.03$). SWOG 8949 included 241 eligible patients, 120 in CN plus IFN-α and 121 in IFN-α-alone groups.[6] Of the 120 patients, 98 underwent CN. Again, the response rates were similar for both the cohorts, but there was a 3-month survival advantage for the CN plus IFN-α cohort (11.1 vs. 8.1 months, $P = 0.05$). In addition, CN plus IFN–α provided maximal survival benefit in the patients with lung only metastasis, measurable disease, and/or PS of 0. In 2004, Flanigan *et al.* performed a combined analysis of EORTC 30947 and SWOG 8949 trials, which demonstrated that the median survival favored the CN plus IFN–α group (13.6 vs. 7.8 months, $P = 0.002$).[32]

A follow-up study exploring the effectiveness of IL-2-based regimens by Pantuck *et al.* used the same SWOG criteria and retrospectively compared IL-2 alone and CN followed by IL-2.[33] The median survival was 16.7 months, 5 months longer than the SWOG 8949 study. These raised the questions to the field, which adjuvant agents would be effective to enhance the survival benefits among mRCC patients undergoing upfront nephrectomy. Prior to TT, the systemic cytokine therapy of choice relied on the institutional preference and practice patterns.

CYTOREDUCTIVE NEPHRECTOMY IN THE VASCULAR ENDOTHELIAL GROWTH FACTOR TARGETED THERAPY ERA

The paradigm of treatment shifted with the approval of sunitinib in 2006, which is a TT inhibiting vascular endothelial growth factor (VEGF) pathway. RCC had the ability to secrete growth factors such as VEGF, platelet-derived growth factors, and fibroblast growth factors to nurture itself and its metastases.[34-40] Inhibiting these pathways with targeted agents such as sunitinib, sorafenib, and temsirolimus demonstrated better outcomes in response rate and survival, quickly changing the management of mRCC.[9-11,41] With the simultaneous increase in TT use, CN has decreased in the recent years.[42] However, very few cases have documented complete responses with TT alone and approximately 90% of the patients in the initial TT trials had undergone a prior nephrectomy.[9-11,43]

Early studies supporting CN in the TT era were retrospective analyses of the practice patterns. Choueiri *et al.* reviewed mRCC patients treated with sunitinib, sorafenib, or

bevacizumab (2004–2008) from eight cancer centers in the US and Canada.[44] A total of 331 TT-naïve mRCC patients were included; 201 patients underwent CN, which demonstrated an improved median OS compared to systemic TT alone (19.8 vs. 9.4 months, $P < 0.01$). Patients in the CN cohort were significantly younger and had Karnofsky Performance Score (KPS) ≥80, >1 site of metastasis, and normal corrected serum calcium levels. Further subgroup analyses based on the MSKCC risk factors and the KPS revealed that the majority of the patients in the favorable risk group underwent CN (22 of 23). In addition, CN demonstrated a survival benefits among the intermediate-risk group patients (hazard ratio [HR]: 0.46; 95% confidence interval [CI]: 0.27–0.78), but only a marginal benefit among the patients in the poor-risk group (HR: 0.67; 95% CI: 0.44–1.01). Analysis based on the KPS (≥80% versus <80%) demonstrated a survival advantage among the CN cohort in the good KPS cohort (23.9 versus 14.5 months, $P < 0.01$). The median OS in the poor KPS cohort was 10 and 6 months in the patients with and without CN, respectively ($P = 0.08$). Abern *et al*. included the patients diagnosed with mRCC (2005–2009) from the Surveillance, Epidemiology, and End Results.[45] Of the 7143 patients, 2629 (37%) underwent CN and correlated with an improved OS (HR: 0.40; 95% CI: 0.37–0.43) on the multivariate analysis.

International Metastatic RCC Database Consortium (IMDC) developed a model to predict OS in mRCC patients treated with TT.[46] A total of 645 patients with TT-naïve mRCC were included. Four of five predictors in the MSKCC model remained predictors of survival: low hemoglobin (Hgb), high corrected calcium (Ca), KPS <80%, and time to initiate treatment <1 year. In addition, high neutrophil and platelet counts were noted predictors for poor survival. The patients were classified based on the number of risk factors: favorable (0), intermediate (1–2), and poor (3–6). The 2-year survival rates were 75%, 53%, and 7% for the favorable-, intermediate-, and the poor-risk groups, respectively. On the univariate analysis, the presence of nephrectomy was associated with prolonged survival. However, when added to the modeling, there was no significant value to CN. The authors hypothesized that 82.5% of patients underwent CN and the homogenous nature of the cohort made the evaluation difficult.

Later, Heng *et al*. evaluated a cohort of patients, who received VEGF or mTOR inhibitors, from 20 international centers.[47] With a median follow-up of 39 months, the OS was significantly improved for the patients undergoing CN (median OS: 20.6 vs. 9.6 months; $P < 0.001$). In addition, CN was associated with a longer progression-free survival (PFS; 7.6 vs. 4.5 months, $P < 0.001$). When adjusted for IMDC risk factors, CN still offered an OS and PFS benefit. When stratifying the patients by the estimated survival, they observed that the OS benefit from CN increased with increasing favorable factors. Other studies have substantiated these findings.[48] Overall, retrospective data supports the continued use of CN in properly selected patients in the TT era.

RANDOMIZED TRIALS DURING THE TARGETED THERAPY ERA

While the retrospective evidence suggests that the disease-modifying effect of CN continues in the TT population, results are now available from the randomized Clinical Trial to Assess the Importance of Nephrectomy (CARMENA).[17] This landmark, randomized trial enrolled 450 patients comparing the patients who received CN followed by sunitinib with those who received sunitinib alone. Patients were randomly assigned (1:1) to either of the treatment protocols (2009–2017) at 79 centers in France and at other centers in Europe. All patients had an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1 and were stratified based on the MSKCC model. Only the intermediate- and poor-risk patients were included. The poor-risk patients comprised 44.4% and 41.5% in the CN plus sunitinib and the sunitinib alone group, respectively. All patients had an operable kidney tumor and were eligible for sunitinib. A planned noninferiority trial, it demonstrated a similar OS for the intermediate and the poor risk clear cell mRCC patients receiving sunitinib alone (median OS: 18.4 months; 95% CI: 14.7–23.0 months) as compared to upfront CN followed by sunitinib (median OS: 13.9 months; 95% CI: 11.8–18.3 months). The median follow-up was 50.9 months. Sixteen patients (7%) in the CN plus sunitinib cohort did not undergo CN, while 38 patients (17%) in the sunitinib-alone cohort underwent CN. It should be noted that the trial accrued slowly and had an incomplete enrollment (planned for 576 patients) over 8 years, with each center averagely enrolling <1 patient per year. This reflects a real difficulty in recruitment and a potential selection bias. Patients who seemed to have benefits from the surgery might be convinced to undergo CN before the randomization. Regarding the noninferiority design, as noted in the retrospective studies during the TT era, patients with poor MSKCC risk factors were unlikely to derive a benefit from CN.[45-48] In addition, the patients in the CN plus sunitinib cohort were questionable CN candidates with a high metastatic burden. Further, the generalizability of CARMENA was complicated by a considerably shorter OS than would have been predicted based on the previously reported, but similar, cohorts.[49,50]

A systematic review from Massari *et al*. included 15 retrospective studies and the CARMENA trial comparing CN plus TT versus TT alone.[51] The results favored CN cohort with a pooled HR of 0.48 (95% CI: 0.42–0.56). There was no survival benefit among patients with brain metastasis, poor PS, and poor risk stratification. Although there was a high heterogeneity in this meta-analysis, the

results emphasized on the substantial role of proper patient selection and limited benefit expected in the patients with poor PS and high disease burden.

DEFERRED CYTOREDUCTIVE NEPHRECTOMY

Instead of enhancing the immunological response, TT works at the primary tumors and may facilitate surgical extirpation.[52] Systemic treatment can act as a litmus test and may aid in the selection of patients who are most likely to benefit from CN. Exploring this concept, Bex *et al*. published the results of the Immediate Surgery or Surgery After Sunitinib in Treating Patients with Metastatic Kidney Cancer trial (SURTIME) in 2018, a randomized phase III trial, investigating if presurgical sunitinib before planned CN could provide PFS benefits.[16] Only 99 patients with clear cell mRCC were randomized within 5.7 years (goal sample size was 458). Patients in the deferred CN cohort received 3 cycles of sunitinib followed by CN. Inclusion criteria included good PS, absence of central nervous system involvement, and a life expectancy >3 months. In addition, the patients had to have 3 or fewer of the following risk factors: decreased albumin, metastases-related symptoms, retroperitoneal or supradiaphragmatic lymphadenopathy, organ dysfunction, or stage cT3–cT4 disease. Culp *et al*. had previously pointed out these poor prognostic factors for the patients undergoing CN.[53] Interestingly, these same exclusions were not a part of the CARMENA trial, which included a significantly less healthy population.

The SURTIME trial unfortunately required early closure secondary to poor accrual. Subsequently, the primary endpoint was adjusted to the intention-to-treat progression-free rate (PFR) as an alternative to the prespecified PFS. With a median follow-up of 3.3 years, the 28-week PFR was comparable between the immediate CN and the deferred CN groups (42% and 43%; HR: 0.88; 95% CI: 0.56–1.37; $P = 0.569$). However, the OS was significantly improved in the deferred CN cohort (32.4 vs. 15.0 months, HR: 0.57; 95% CI: 0.34–0.95; $P = 0.032$). However, these survival benefits need to be interpreted with caution, as a detailed review of the patient groups demonstrated that a total of 18 (18%) of 99 patients did not receive the assigned treatment. The authors concluded that deferred CN was not associated with an improved 28-week PFR and proposed that a trial of sunitinib prior to CN would help identify patients at risk for rapid disease progression and unlikely to benefit from CN.

PATIENT SELECTION FOR CYTOREDUCTIVE NEPHRECTOMY

Current clinical practice guidelines are variable in providing a framework by which to assess a patient's suitability for CN. The National Comprehensive Cancer Network (NCCN) guidelines offer only a category 2A recommendation that CN may be performed in "select patients with surgically resectable primary disease."[54] Furthermore, those considered for CN prior to the systemic therapy should have excellent PS (ECOG PS <2) and no brain metastasis. Recently updated European guidelines for the utilization of CN offer additional granularity in their recommendations, specifically recommending against CN in the MSKCC poor-risk patients.[55] Furthermore, the authors generally support the consideration of delayed a CN in the intermediate-risk patients who require systemic therapy and the performance of immediate CN in those good-risk patients who do not require systemic therapy. The challenge in patient selection for CN is predicting which patients can tolerate a major surgical procedure with the goal of prolonging survival, while simultaneously minimizing the risk of interrupting or precluding the systemic therapy. Historically, many clinicians have utilized the MSKCC risk criteria to determine which patients are the candidates for CN [Table 1].[56] The authors of the CARMENA trial utilize the MSKCC criteria to risk stratify their trial comparing sunitinib alone or after nephrectomy in mRCC.[17] These criteria, however, were never intended to determine a patient's suitability for surgery; rather, they assess a patient's prognosis and response to the systemic therapy. In fact, 65% of the original MSKCC cohort had a prior nephrectomy which was not performed for the

Table 1: Risk stratification models for metastatic renal cell carcinoma

MSKCC		IMDC risk factor		MDACC	
Risk factor	**Classification**	**Risk factor**	**Classification**	**Risk factor**	**Classification**
KPS <80%	Good (0)	KPS <80%	Good (0)	Systemic symptoms at diagnosis	Low (0-1)
LDH >1.5 × ULN	31% OS at 3 years	Neutrophil > ULN	75% OS at 2 years	Neutrophil/Lymphocyte ratio >3	58.9 month median OS
Hemoglobin < LLN	Intermediate (1-2)	Hemoglobin < LLN	Intermediate (1-2)	Hemoglobin < LLN	Intermediate (2-3)
Corrected calcium >10 mg/dL	7% OS at 3 years	Calcium > ULN	53% OS at 2 years	Albumin < LLN	30.6 month median OS
Absence of nephrectomy	Poor (>2)	Time from diagnosis to treatment <1 year	Poor (>2)	LDH > ULN	High (>3)
	0% OS at 3 years	Platelet > ULN	8.8 month median OS	cT4 disease Retroperitoneal adenopathy Supradiaphragmatic adenopathy Bone metastasis	19.2 month median OS

IMDC=International metastatic renal cell database consortium, KPS=Karnofsky performance status, LDH=Lactate dehydrogenase, LLN=Lower limit of normal, MDACC=MD Anderson Cancer Center, MSKCC=Memorial Sloan Kettering Cancer Center, OS=Overall survival, ULN=Upper limit of normal

purpose of cytoreduction.[56] There have been several notable efforts to objectively risk stratify the mRCC patients being considered for CN. Prognostic factors for mRCC initially published by the IMDC were subsequently utilized to determine the OS benefit of the CN compared with no CN in mRCC patients treated with targeted therapies and found that patients with four or more IMDC criteria may not benefit from CN [Table 1].[46,47] The IMDC adverse criteria include Hgb < lower limit of normal (LLN), corrected Ca > upper limit of normal (ULN), KPS <80%, time from diagnosis to treatment of < one year, neutrophils > ULN, and platelets > ULN. In an incremental benefit analysis, the authors found that the longer a patient is estimated to survive, the more likely it is that the CN would provide an additional OS benefit. After adjusting for prognostic factors, those who lived <12 months did not benefit from CN (HR: 0.97 [95% CI: 0.81–1.17], $P = 0.76$), which corresponded to the patients with ≥4 IMDC risk criteria.

An early effort at our institution to identify the patients unlikely to benefit from CN yielded objective preoperative risk factors that were associated with decreased OS following the CN on a multivariate analysis.[53] A total of 566 mRCC patients who underwent CN (2002–2007) were retrospectively reviewed for OS and a separate cohort of mRCC patients receiving systemic therapy alone were evaluated to establish a minimum OS in which CN would be likely to benefit. Patients undergoing CN who died within 8.5 months of the diagnosis were found unlikely to benefit from CN. Ultimately, seven preoperative risk factors were identified: serum albumin < LLN, serum LDH > ULN, ≥clinical T3, symptoms caused by metastatic disease, liver metastases, and radiographic evidence of retroperitoneal or supradiaphragmatic lymphadenopathy (>1 cm). Patients who had ≥4 risk factors did not benefit from CN. A recent update intended to focus on the patients treated in the TT era ($n = 608$, 2005–2017) further identified systemic symptoms at diagnosis (HR: 1.27 [95% CI: 1.03–1.57], $P = 0.02$), serum Hgb < LLN (HR: 1.27 [95% CI: 1.01–1.58], $P = 0.037$), bone metastasis (HR: 1.38 [95% CI: 1.1–1.72], $P = 0.005$), and neutrophil/lymphocyte ratio ≥4 (HR: 1.49 [95% CI: 1.17–1.9], $P = 0.001$) as the preoperative risk factors associated with decreased OS on the multi-variable analysis [Table 1].[57] Only liver metastasis, symptoms due to metastatic disease, and clinical stage T3 disease were no longer associated with a decreased OS.

The European practice guidelines noted above were updated in response to the publication of the CARMENA and SURTIME trials and reflect the practice at our institution for most of the patients, especially the intermediate or poor risk groups, undergoing systemic therapy prior to consideration of CN. It is our view that these important RCTs are practice confirming and with the judicious patient selection using the objective criteria, CN still plays a pivotal role in the management of mRCC. An initial period, or "litmus test," of systemic therapy will serve to select patients in whom the CN will be likely provide a benefit.

FUTURE DIRECTION OF CYTOREDUCTIVE NEPHRECTOMY

As of April 2020, clinical guidelines from the European Society of Medical Oncology, the European Association of Urology, and the NCCN continue to incorporate CN in selected patients, which includes good PS and reasonable metastatic tumor burden.[54,58,59] All guidelines note that poor-risk patients should not undergo upfront CN, but favorable and intermediate-risk patients should not abandon CN as a therapeutic approach. In addition to the concerns surrounding the poor-risk patients enrolled in CARMENA, most of these patients should receive nivolumab + ipilimumab, axitinib + pembrolizumab, or cabozantinib as the first-line therapy and not sunitinib.[50,51,60]

Immune checkpoint inhibitors (ICI) have been a revolution in the treatment of mRCC. These agents augment the antitumor immune response by altering the interaction between the immune cells and the antigen-presenting cells, including the tumor cells themselves. With the medical therapy already changing drastically from TT to ICI +/-TT, the role of CN continues to require reevaluation. One perioperative trial is evaluating the effect of ICI on immunologic response in the tumor tissue assessed by CN (Clinicaltrial.gov identifier: NCT02210117), and the initial results have demonstrated that CN is safe and potentially beneficial to the patients with mRCC.[61] Obviously, these combinations warrant larger phase 3 trials.

As seen in both the CARMENA and the SURTIME trials, timely patient accrual has been a debilitating challenge for the trials evaluating CN. Without a significant culture shift, this challenge will remain for any trial that includes CN and ICI +/-TT. Incomplete enrollment will render future studies, like these two, underpowered. In addition, if there is protracted time between the trials conception, enrollment, and analysis, the therapeutic management of mRCC may have evolved again. These are well known concerns within the genitourinary oncology community and will require significant coordination to be overcome. Future trials may want to consider incorporating a design with randomization to both the systemic therapy agent and CN. Thus, the study agent could be independently evaluated over the standard of care option as well as the potential effect of CN without increasing the overall sample size.

CONCLUSION

Spontaneous regression of the metastases may occur after CN for mRCC, even in the absence of systemic therapy. With the addition of cytokine therapy (i.e., IFN-α and IL-2) following upfront CN in the 1990s, CN was associated

with an improved survival and became the standard of care for surgical candidates. The recent CARMENA and SURTIME trials have eliminated a reflexive upfront CN before systemic therapy in the TT era. However, there still are many indications for upfront CN using risk stratification and proper patient selection and we continue to recommend CN when feasible for properly selected patients with mRCC. Patients with poor-risk disease require a more careful evaluation, should usually initiate systemic therapy, and if stable or responding to the therapy, consolidative CN should be considered. It is unlikely that a single treatment approach will benefit all mRCC patients. Regardless, with the continued collection of data on consolidative CN and the evolution of frontline therapeutic options, the role of CN will inevitably evolve.

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