INTRODUCTION

In advanced renal cell carcinoma (RCC) management, cytoreductive nephrectomy (CN) is often considered as a standard care procedure that can only palliate hematuria, mitigate pain or reduce the symptoms of neoplastic syndromes and not to be taken as a curative surgery.\(^1\) In the previous study, CN proved its superiority in prolonging the survival of patients with systemic cytokines over systemic cytokines alone.\(^2\) Furthermore, the surgery brings additional advantages to the patients who initially had more favorable risk disease. These findings are in line with EORTC 30947 trial report outcomes.\(^3\) Despite hope of cytokine therapy plus CN as a protocol to enhance the survival, no substantial reduction in mortality rate was observed until 2006, when targeted therapy (TT) was developed and sunitinib was approved.\(^4\)\(^-\)\(^6\) After the introduction of TT, a considerable improvement in median overall survival was observed.\(^4\)\(^-\)\(^6\)
survival (OS) was observed among patients between 1999 and 2009 i.e., 11 months to 20 months correspondingly. The increasing prevalence of TT, on the other hand, reduced the preference for surgical procedure. However, the interest towards the surgical procedure among the available effective therapeutics did not vanish altogether. Further, the patients involved in original trials that assess the outcomes of targeted therapies already underwent CN. This scenario masks the impact of CN in survival rate among patients who are undergoing TT. Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques (CARMENA) and Immediate Surgery or Surgery After Sunitinib in Treating Patients with Metastatic Kidney Cancer trial (SURTIME), 2 randomized phase-3 clinical trials were conducted recently to find the impact of CN upon survival rate. These trials were real eye-openers and provided practice-changing evidence in 2 aspects as follows; CN should not be done for patients who are diagnosed with intermediate or poor-risk diseases before the initiation of systemic treatment; and the timing of CN should be thoroughly evaluated. These studies emphasized the importance of patient selection process. In spite of the fact that CARMENA and SURTIME trials’ data are the latest ones, the rapidly-expanding RCC armamentarium expressed a doubt on the role of CN. In literatures, the researchers proved the superiority of novel tyrosine kinase inhibitors (TKIs) namely, cabozantinib, pazopanib, and axitinib compared to sunitinib in mRCC. Therefore, it can be understood that novel TKIs may be effective even in reducing the need for CN procedure. In addition, there have been strong arguments to leave the tumor in, as a source of neoantigens versus tumor removal, which may play the role of an immune sink. In this background, the current review discusses the role of CN and how it evolved in the management of mRCC under a rapid changing therapeutic environment encompassing TT and immunotherapy (IO).

**BIOLOGIC RATIONALE OF CYTOREDUCTIVE NEPHRECTOMY**

The rationale behind the justification of cytoreduction has mostly been theoretical. As per the literature, a small group of patients exhibited an association between CN and spontaneous regression of metastases. Though a rare instance, such events are well-documented which in turn made RCC a possible immunogenic tumor. Novel mechanisms are proposed, with an aim to improve the response to systemic therapy. Such mechanisms focus on 2 factors such as removal of any potential humoral interactions that may exist between the primary tumor and its metastases and the removal of possible new metastatic clone sources in line with Halstedean tumor theory. In early cytokine era, a limited response was exhibited during interleukin (IL)-2 administration while CN has the potential to reverse this immunosuppressive state. In this study, the primary RCC was not resected and significant survival benefits were found in patients who underwent CN and had high serum C-reactive protein (CRP) level prior to operation, than those who did not undergo operation. A better survival (p=0.003) was reported among the patients whose serum CRP level returned to be normal after CN over the patients who had still elevated serum CRP levels after CN.

**CYTOREDUCTIVE NEPHRECTOMY IN THE ERA OF CYTOKINE THERAPY**

mRCC has been conventionally treated through cytokines (interferon [IFN] and IL) and other such forms of IO, before TT was introduced. Though CN as well as cytokine therapy’s immune hypotheses were proposed into clinical practice previously, no
obvious therapeutic approach was established.\textsuperscript{21-23} In 1996, Franklin et al.\textsuperscript{21} showed that mRCC patients who underwent CN followed by IL-2-based IO had a 34\% response rate and a 43\% 2-year survival rate. Based on these results, the trials conducting upfront nephrectomy and systemic IO demonstrated enhanced patient survival compared to the patients who underwent only the systemic IO.

Two Phase-III studies were conducted, owing to the need for conducting a multicenter perspective randomized trial with standardized follow-up so as to elucidate the role played by CN.\textsuperscript{2,3} These studies were supported by South West Oncology Group (SWOG) and European Organization of Research and Treatment of Cancer (EORTC). Patients with synchronous metastatic RCC who randomly received INF-\(\alpha\) monotherapy or nephrectomy followed by INF-\(\alpha\) were included in both these studies. The inclusion criteria for both studies were as follows: sufficient end-organ functioning, no prior systemic or radiotherapy, metastatic RCC with resectable primary disease and Eastern Cooperative Oncology Group (ECOG) performance status either 0 or 1. The groups showed no difference when it comes to radiographic response rate of metastatic disease (19\% in CN plus IFN-\(\alpha\) vs. 12\% in IFN-\(\alpha\) alone, \(p=0.38\)). But a notable lengthier median OS i.e., 17 months versus 7 months, \(p=0.03\) was observed in CN plus IFN-\(\alpha\) cohort patients.\textsuperscript{3} Further, a total of 241 eligible patients were included in SWOG 8949 group out of which 120 under CN plus IFN-\(\alpha\) and 121 under IFN-\(\alpha\)-alone groups.\textsuperscript{2} CN was conducted for 98 out of 120 patients. After this, both cohorts exhibited similar response rates though CN plus IFN-\(\alpha\) cohort had a 3-month survival advantage i.e., 11.1 months versus 8.1 months, \(p=0.05\). Further, maximum survival benefit was achieved in CN plus IFN-\(\alpha\) patients with lung-only metastasis, a measurable disease.

Flanigan et al.\textsuperscript{24} performed a combined analysis of EORTC 30947 and SWOG 8949 trials, which demonstrated that the median survival favored the CN plus IFN-\(\alpha\) group (13.6 months vs. 7.8 months, \(p=0.002\)). SWOG findings were complemented using retrospective data i.e., a comparable population containing more than 450 metastatic RCC patients treated with IL-2 from University of California at Los Angeles Kidney Cancer Database. This data was analyzed to establish the relative efficacy of IFN-\(\alpha\) versus IL-2 after CN.\textsuperscript{25} In line with the eligibility criteria set for SWOG 8949 study, a total of 89 patients were treated with IL-2-based regimens after the identification of nephrectomy. The researchers analyzed and compared the survival of this sample population against the survival of 120 patients in the SWOG surgery arm. Median survival of the patients treated with nephrectomy plus IL-2 was 16.7 months, which was twice that of the IFN-\(\alpha\) only SWOG arm, and 4 months (30\%) greater than the nephrectomy plus IFN-\(\alpha\) SWOG arm. With these data findings, the obvious question arose i.e., which adjuvants are effective in increasing the survival benefits among patients with mRCC. Though it has a limited advantage, CN is considered as a vital component in mRCC treatment regimen. In this cytokine era, those who support CN strongly argue the existence of immunosuppressive microenvironment within primary RCC tumors since it can impair tumor immune surveillance and elimination. In addition to these, when performing the surgery, tumor neoantigens get released into circulation. They tend to cross-prime the immune system of the host, resulting in tumor immune attack.\textsuperscript{26,27}

**CYTOREDUCTIVE NEPHRECTOMY IN THE ERA OF TARGETED THERAPY**

In comparison with IO, TT has revolutionized the way in which mRCC is treated more efficiently.
With its effective antiangiogenic and antitumor activities, sunitinib has been proved as the most efficiency drug in treating mRCC. The inhibition activity of sunitinib covers a wide range of tyrosine kinase receptors such as c-stem cell factor receptor, PDGF receptor, VEGF receptor, and FMS-like tyrosine kinase receptor-3. In the prospective randomized trial, sunitinib versus INF-alpha was compared in patients with mRCC. The former group showed excellent progression free survival (PFS) and extended OS than the INF-alpha group (median survival of 26.4 months vs. 21.8 months).6,28

The role of CN was again scrutinized after the induction of antiangiogenic drugs. However, the pivotal trials that led to the approval of antiangiogenic drugs were associated with a very high rate of CN, making any attempt of comparison meaningless.28-30 For this reason, retrospective analysis was performed to sort out this issue. In the study conducted by Choueiri et al.,7 a total of 314 mRCC patients were studied. The patients who underwent CN (201 patients) had a median OS of 19.8 months whereas it was only 9.4 months who had not underwent CN. In spite of this findings, marginal benefits were observed in patients who belonged to poor prognostic risk group. Another retrospective study from Canada concluded that prior CN in patients treated with TKIs is associated with enhanced OS in mRCC on univariate analysis, irrespective of any influence from other prognostic variables.31 A large-scale retrospective study was conducted earlier by International mRCC Database Consortium (IMDC) group among 1,658 patients.32 Of these, 982 underwent CN and they exhibited a significantly high OS even after adjusting their IMDC risk factors (20.6 months vs. 9.6 months: hazard ratio [HR], 0.6; 95% confidence interval [CI], 0.52–0.69; p=0.001). Further, an increased PFS was also observed in group with CN (7.6 months vs. 4.5 months: HR, 0.75; 95% CI, 0.66–0.85; p<0.001). In line with the literature, patients with poor-risk features according to IMDC criteria (especially those with >3 risk factors) exhibited no great benefit even with the addition of CN.32 This outcome was consistent with another study conducted in a similar setting.33

**RANDOMIZED TRIALS IN THE ERA OF TARGETED THERAPY**

As per the literature, TT tends to function at primary tumors and promote surgical extirpation.34 Systemic treatment helps in identifying the appropriate beneficiaries from CN. Therefore, 2 studies started exploring the debates of CN and analyzed the advantages in it. The studies also attempted to find a correct sequence for CN in the perspective of systemic treatment with TKIs. Those 2 studies are as follows: a phase-3 randomized trial was conducted as SURTIME trial with upfront CN and then by sunitinib (“immediate CN”); in second study, upfront sunitinib was followed by CN (“deferred CN”) which was again followed by additional sunitinib in patients with mRCC.11 Though the sample to be enrolled was planned at 498 within a period of 3 years, the study experienced slow accrual and confined it with only 99 patients.

Between the groups i.e., immediate CN and deferred CN, the former group was started with sunitinib after 4 weeks of CN while in the latter group, CN was conducted after 3rd sunitinib cycle; afterwards, sunitinib was continued after 4 months of CN. At the beginning, 50-mg sunitinib was given daily for a cycle of 28 days, after which 14 days off for every 6 weeks. The dosage was modified based on the adverse events observed. With the primary objectives being PFS and OS, the SURTIME trial was forced to close earlier due to poor accrual. As a result, the primary endpoint was modified to the intention-to-treat progression-free rate (PFR) as an alternative. The
28-week PFR was compared between the 2 groups mentioned above with a median follow-up of 3.3 years (42% and 43%; HR, 0.88; 95% CI, 0.56–1.37; p=0.569). But, there was a significant improvement observed in the deferred CN cohort in terms of OS (32.4 months 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, since when the patients groups were reviewed in detail, 18 out of 99 patients (i.e., 18%) received no such assigned treatment. Further, the study included 88% patients who belonged to IMDC intermediate-risk group. While being underpowered, the SURTIME trial showed that the deferred CN group with intermediate-risk patients had survival benefit. In those patients, initial systemic therapy was essential and thus suitable features to undergo surgery were found. The outcomes strongly support the CARMENA trial findings that discussed about the lack of benefits of immediate CN for intermediate-risk patients who require systemic treatment. Moreover, the results also confirmed the safety of targeted therapies prior to surgery, showing no differences in surgical complications between immediate and deferred CN arms in a post hoc analysis. The study outcomes also provided an another advantage i.e., deferred CN group can help in identifying the patients with inherent resistance towards systemic therapy, who probably have no benefit from the surgery.

In spite of these findings, there was no sufficient information available from SURTIME trial to arrive at a decisive conclusion that can resolve the issue i.e., whether CN is necessary in this TKI era. To answer the debate, CARMENA trial was conducted among mRCC patients which is a phase-III noninferiority trial that compared 2 scenarios such as CN followed by sunitinib and sunitinib alone. In this trial, a total of 450 patients were enrolled and were grouped under administered CN followed by sunitinib and administered sunitinib alone. These patients were assigned (1:1) in a random manner to any one of the 2 treatment protocols at 79 centers in France and other centers spread across Europe. The stratification of the patients was done in line with Memorial Sloan Kettering Cancer Center (MSKCC) model and all patients had 0 or 1 ECOG performance status. The patients with only the intermediate and poor-risk categories were included. Of the total population, poor-risk patients formed 44.4% in CN+sunitinib and 41.5% in sunitinib alone groups respectively. Within 28 days of randomization, CN was conducted after which sunitinib was initiated within after 3–6 weeks of CN. In sunitinib alone group, sunitinib was initiated within 21 days of randomization. At the beginning, 50-mg sunitinib dosage was maintained daily for a cycle of 28 days after which 14 days off was maintained for every 6 weeks. The dosage was modified based on the adverse events observed.

OS was set as the primary endpoint which defines the time from randomization till they die, irrespective of the cause or till the date of last contact for alive patients. The median follow-up was maintained as 50.9 months. In case of CN followed by sunitinib group, the median OS was 13.9 months (95% CI, 11.8–18.3) whereas in case of sunitinib alone group, it was 18.4 months (95% CI, 14.7–23.0). When analyzing the OS, the HR for death was 0.89 (95% CI, 0.71–1.10; upper bound for noninferiority was ≤1.20). The researchers found similar PFS (HR, 0.82; 95% CI, 0.67–1.00 for sunitinib alone) and response rates (sunitinib: 29.1% vs. sunitinib+CN: 27.4%; p=0.02) between the groups. Thus, the study found that sunitinib alone is noninferior to CN followed by sunitinib.

The study recorded numerous crossovers in terms of treatment received. 16 of 226 patients (7.1%) who were actually assigned to undergo CN followed by sunitinib treatment missed CN whereas 40 out of 226 (17.7%) missed to receive sunitinib. On the other hand, of 224 patients in sunitinib
alone group, 11 patients (4.9%) missed to take the study drug whereas 38 (17%) underwent CN within a median OS of 11.1 months of random assignment for symptom management.

It must be taken into consideration that the accrual of trial was slow and faced an incomplete enrollment of the patients over 8 years, with planning went for 576 patients. Every center enrolled <1 patient on an average in a year. This reveals how challenging it is, to recruit the patients for study and the possibilities of selection bias.

A post hoc analysis was conducted, supplementing CARMENA trial and the analysis arrived at different conclusions for IMDC intermediate-risk patients. This analysis compared 2 groups such as 1 risk factor patients (100% time to systemic therapy <1 year) assigned to CN followed by sunitinib and sunitinib alone. These outcomes showed a statistically nonsignificant inferiority of sunitinib alone group (OS: 31.4 months vs. 25.2 months; HR, 1.29; 95% CI, 0.85–1.98; p=0.23). In case of patients with 2 risk factors, sunitinib alone was found to be noninferior while CN followed by sunitinib was irrelevant to any benefits (OS: 17.6 months vs. 31.2 months; HR, 0.63; 95% CI, 0.44–0.97; p=0.03).37

In the systematic review including CARMENA trial conducted by Massari et al.38 CN followed by TT was compared against TT alone. The results were in favor of CN group with a pooled HR of 0.48 (95% CI, 0.42–0.56). No survival benefit was observed among patients who had poor-risk stratification, poor PS, and brain metastasis. The results emphasized the importance of multiple therapy modalities in the management of mRCC with patient-specific risk factors.

**PATIENT SELECTION FOR CYTOREDUCTIVE NEPHRECTOMY**

Patient selection for CN has remained an area of considerable debate. Since it is not a curative procedure and should be recommended only for informed and consented patients who are carefully selected after much consideration. Bennett et al.39 mentioned that most patients who are recommended for CN are unfit due to their old age and advanced stage of the disease. Even if they undergo surgical procedure, surgical morbidity and mortality remain a primary issue for them. These complications further suppress the patient’s capability to receive IO.

The previous study showed some inclusion criteria to scrutinize the ideal patients.40 The criteria include more than 75% debulking of tumor burden, sufficient pulmonary and cardiac function, clear cell histology, 0 or 1 ECOG status, no bone or liver metastases and no central nervous system metastases. When these criteria were applied upon 28 patients, 26 patients i.e., 93% were qualified enough to be enrolled for systemic therapy with 39% overall response rate and 20.2 months of median survival.

As per the literature, 2 prognostic models are generally used in patient risk stratification such as IMDC risk score and MSKCC risk score.32,41 The MSKCC model was developed in cytokine era and the score categorizes mRCC patients under 3 risk categories such as favorable (MSKCC score 0), intermediate (MSKCC score 2–1), and poor (MSKCC score ≥3) in line with the criteria given herewith; Karnofsky PS <80% from diagnosis to systemic treatment time, concentration of hemoglobin below low level of normal and calcium >10 mg/dL, and lactate dehydrogenase (LDH) >1.5 times the upper limit of normal. On the other hand, IMDC risk score was developed during TT period which categorizes mRCC patients under 3 risk groups such as favorable (IMDC score 0), intermediate (IMDC score 2–1), and poor (IMDC score ≥3). Though same criteria, as followed in MSKCC prognostic model, is followed in this IMDC risk score too, increased LDH is the only difference here. Further,
this score adds 2 more novel prognostic variables such as neutrophils and platelets above the upper limit of normal.

In spite of the fact that these prognostic scores are utilized to predict the OS in mRCC patients, the original purpose behind the construction of these scores is not an evaluation of survival benefit related with CN. A retrospective study was conducted to enhance patient selection process for CN. This study was conducted by UTMDACC (University of Texas MD Anderson Cancer Center) group who explored for preoperative variables that have a relationship with outcomes of the patients, who are currently under consideration for CN. Of the variables investigated, a total of 7 variables were found to have an association with inferior OS in surgical patients such as liver metastasis, supradiaphragmatic adenopathy, elevated LDH, low albumin level, symptoms at presentation caused by metastatic sites, retroperitoneal adenopathy and clinical T stage ≥T3. A positive correlation was found between high risk of death and the number of risk factors present whereas patients who had ≥4 risk factors received no benefit from CN.42

One of the studies conducted recently proposed a prognostic model on the basis of tumor and patient-related features so as to find the predictors of CN survival benefit. A retrospective study was conducted by Marchioni et al.43 among 519 mRCC patients enrolled at Registry for Metastatic Renal Cell Carcinoma (REMARCC) undergoing CN between the periods 2005 and 2019. High overall mortality rate was recorded among patients who reported more than 3 metastatic sites, poor PS and with bone, liver, and lung metastases. Interestingly, obesity was found to be a favorable preoperative factor that had an association with low mortality rate. The study classified the patients under 3 categories such as favorable (no risk factors), intermediate (1–2 risk factors), and poor (≥2 risk factors) prognosis. However, the REMARCC prognostic score also needs further external validation.

In the systematic review, the researchers reviewed a total of 16 studies which focused on CN survival benefit on specific subgroups of mRCC patients. Though the studies included were heterogenic in nature, OS benefit was found in clear cell and nonclear cell RCC patients’ studies only who received CN (HR, 0.48; 95% CI, 0.42–0.56). Further, IMDC-poor-risk patients, patients with brain metastases and poor PS showed no survival benefit at all. At the end, the study concluded that mRCC symptoms play an important role in patient selection for CN. Likewise, symptomatic patients undergoing CN exhibited an improvement of any symptoms and local symptoms or signs in 71% and 95% of cases, respectively.44,45

Though previous retrospective studies are in favor of CN to select the patients with less number of risk factors, there has been less evidence available for prospective studies. 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 guidelines offer only a category 2A recommendation that CN may be performed in “select patients with surgically resectable primary disease.”46 The most recent European guidelines provide additional granularity in their recommendation for CN patient selection i.e., CN cannot be recommended specifically in case of MSKCC poor-risk patients.47 In alignment with these, the recent guidelines suggest to delay CN for intermediate-risk patients who require systemic therapy whereas CN is to be immediately performed for good-risk patients who require no systemic therapy.

Furthermore, upfront CN seems to produce no benefit to patients who belong to groups such as poor MSKCC/IMDC risk patients, poor PS patients, and patients with high metastatic burden. So, such patients should be recommended with systemic
treatment. To conclude, authentic prognostic scores are required to have an appropriate scrutiny of mRCC patients who may gain benefit out of CN.

NEW CHALLENGES FOR CYTOREDUCTIVE NEPHRECTOMY IN THE ERA OF IMMUNOTHERAPY

More recently, IO is the most preferred standard of care for treating mRCC patients. As per the literature, CheckMate-214 (nivolumab plus ipilimumab vs. sunitinib), KEYNOTE-426 (pembrolizumab plus axitinib vs. sunitinib), and JAVELIN Renal 101 (avelumab plus axitinib vs. sunitinib) trials showed enhanced oncological outcomes among mRCC patients in IO-combination therapy in comparison with TKI monotherapy. Singla et al. conducted a retrospective study using 391 patients’ data from National Cancer Database who received IO therapy with or without CN. In this study, a total of 221 patients received IO therapy and CN whereas IO therapy alone was offered to 170 patients. A superior OS was achieved by IO therapy plus CN group than the IO therapy alone group (HR, 0.23; p<0.001).

Various retrospective investigations and case study reports reveal the benefits of CN in IO therapy patients. For example, a retrospective study was conducted among 391 mRCC patients using United States National Cancer Database collected between 2015 and 2016. Superior OS was observed among patients with CN+IO therapy than those who received IO therapy alone. Further, 2 out of 20 patients with IO followed by CN accomplished a complete pathologic response of the primary tumor. At the same time, 3 remains a concern that the benefits of surgery with IO could be negated by the obligatory inflammatory, neuroendocrine, and metabolic events that alter cytokine levels induced by surgical trauma. Immunosuppression forms the major negative outcome after surgery. This effect peaks at 3 days after surgery and may extend to many weeks too, due to the expansion of regulatory T cells, myeloid cells with increased PD-1/CTLA-4 expression, and impaired natural killer cell activity. These consequences may theoretically impair the healing process. Table 1 presents a summary of the results from a selected number of studies conducted in mRCC patients to evaluate benefit of CN from the cytokine therapy era to the current IO era.

IO has been revolutionized in the treatment of mRCC. These agents tend to increase the autitumor immune response by modifying the interaction

<table>
<thead>
<tr>
<th>Study Name</th>
<th>No. of patients</th>
<th>Systemic therapy used</th>
<th>HR (95% CI)</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choueiri et al. 2011</td>
<td>314 (CN:201; no CN:113)</td>
<td>TT (sunitinib, sorafenib, bevacizumab)</td>
<td>0.68 (0.46–0.99)</td>
<td>CN vs. no CN: 19.8 mo vs. 9.4 mo</td>
</tr>
<tr>
<td>Heng et al. 2014</td>
<td>1,658 (CN:958; no CN:676)</td>
<td>TT (sunitinib, sorafenib, bevacizumab, axitinib, pazopanib, temsirolimus, everolimus)</td>
<td>0.60 (0.52–0.69)</td>
<td>CN vs. no CN: 20.6 mo vs. 9.5 mo</td>
</tr>
<tr>
<td>Singla et al. 2020</td>
<td>391 (CN:221; no CN:170)</td>
<td>Immunotherapy (ICI)</td>
<td>0.23 (0.15–0.37)</td>
<td>CN vs. no CN: Not reached vs. 11.6 mo</td>
</tr>
<tr>
<td>Flanigan et al. 2001</td>
<td>241 (CN:120; no CN:121)</td>
<td>Cytokine (interferon alfa-2b)</td>
<td>NR</td>
<td>CN vs. no CN: 11.1 mo vs. 8.1 mo</td>
</tr>
<tr>
<td>Mickisch et al. 2001</td>
<td>85 (CN:42; no CN:43)</td>
<td>Cytokine (interferon alfa-2b)</td>
<td>0.54 (0.34–0.94)</td>
<td>CN vs. no CN: 17 mo vs. 7 mo</td>
</tr>
<tr>
<td>Mejean et al. 2018</td>
<td>450 (CN:226; no CN:224)</td>
<td>TT (sunitinib)</td>
<td>0.89 (0.71–1.10)</td>
<td>CN vs. no CN: 18.4 mo vs. 13.9 mo</td>
</tr>
<tr>
<td>Bex et al. 2019</td>
<td>99 (immediate CN:50; deferred CN:49)</td>
<td>TT (sunitinib)</td>
<td>0.57 (0.34–0.95)</td>
<td>Immediate CN vs. deferred CN: 15.0 mo vs. 32.4 mo</td>
</tr>
</tbody>
</table>

CN: cytoreductive nephrectomy, OS: overall survival, mRCC: metastatic renal cell carcinoma, HR: hazard ratio, CI: confidence interval, TT: targeted therapy, ICI: immune checkpoint inhibitor, NR: not reported.
among immune cells, tumor cells, and the antigen-presenting cells. With drastic and dynamic changes experienced in medical therapy from TT to IO +/- TT, performing CN is questioned again. In this IO era, 2 ongoing randomized prospective trials and the expected outcomes may help the guide to use CN and IO in mRCC treatment. PROBE (Prospective Randomized Open, Blinded Endpoint) (NCT04510597) trial is aimed at investigating the hybrid CN and systemic therapy (IO alone or TKI+IO) to treat mRCC against systemic therapy alone (IO or TKI+IO). In another trial i.e., NORDIC-SUN (NCT03977571), the role of deferred CN among patients receiving combination IO (nivolumab+ipilimumab) is evaluated. The outcomes of these studies might provide much knowledgeable insights in the near future, so that the patients gain the most benefits from surgical treatment in new IO era.

CONCLUSIONS

In the setting of cytokine therapy after upfront CN, CN exhibited an improved survival and gained the standard of care for mRCC patients. In the TT era, the recent trials such as CARMENA and SURTIME ensured that there is no need for an immediate CN prior to systemic therapy. Especially, poor-risk disease-patients should be carefully evaluated and given appropriate initial systemic therapy. Based on responding to the systemic therapy and stability, consolidative CN can be recommended for them. The recent advancements in IO-based systemic therapy have challenged the benefits from surgical treatment. In fact, CN is no more a viable standard care option for all mRCC patients. Nevertheless, it is still relevant as a treatment option for specific and carefully selected patients. Future investigations must be conducted in order to define the role of CN in novel IO era.

NOTES

• Conflicts of Interest: No potential conflict of interest relevant to this article was reported.
• Funding: This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
• ORCID
  Jae Duck Choi: https://orcid.org/0000-0003-3257-2508
  Jeong Man Cho: https://orcid.org/0000-0002-0276-0789
  Tag Keun Yoo: https://orcid.org/0000-0002-2972-5166

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