Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma

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Abstract: The incidence of renal cell carcinoma is increasing, with up to one-third of patients presenting with metastatic disease. Combination therapy is used to prolong survival in patients with metastatic renal cell carcinoma, which carries a poor prognosis. Although two pivotal phase 3 trials have demonstrated the efficacy of immunotherapy after cytoreductive nephrectomy for metastatic disease, for now, targeted therapy has replaced immunotherapy as the preferred systemic treatment in these patients. Two ongoing phase 3 trials are evaluating the role of cytoreductive nephrectomy prior to targeted therapy. Proper patient selection is paramount in achieving successful outcomes.

Epidemiology of Renal Cell Carcinoma

An estimated 61,560 new cases of kidney cancer occurred in 2015, and approximately 14,080 people died of their disease.[1] The majority of kidney cancer cases consist of renal cell carcinoma (RCC).[2,3] The incidence of kidney cancer has increased over the past several decades, and metastatic disease is present in approximately 30% of patients with newly diagnosed RCC.[1,4] In addition, up to 25% of patients develop metastatic disease after surgical treatment.[5,6] Metastatic RCC (mRCC) is highly fatal, with a median overall survival (OS) of just 10 months.[7] As such, mRCC has been the focus of various treatment strategies over the past several decades. This review addresses the history and current state of cytoreductive nephrectomy (CN) for the treatment of mRCC.

Rationale for Cytoreductive Nephrectomy

The definitive treatment for localized kidney cancer is extirpative surgery. However, the proper management of metastatic kidney cancer has been a challenge to clinicians for quite some time. CN is defined as the surgical removal of the primary RCC lesion before initiation of systemic therapy. Combination therapy has been used to treat mRCC since the 1950s, given that patients with advanced disease responded poorly to surgery alone.[8] The optimal type of therapy to use in conjunction with surgery has varied over time, and has included radiotherapy, hormonal therapy, cytotoxic

chemotherapy, and immunotherapy.[9] The idea that the immune system played a role in the treatment of RCC was based on the rare phenomenon of spontaneous regression of metastases after removal of the primary tumor.[10-12] This led clinicians to believe that the primary tumor may play a role in modulating the immune system's ability to combat tumor cells.

The pursuit of immunomodulation in the treatment of mRCC led to the discovery of 2 novel treatments. In 1983, interferon alfa-2b (IFN) was shown to have a biological response in mRCC.[13,14] However, the overall response rate was only 15%, and few complete responses occurred.[15] Subsequently, in 1986, interleukin 2 (IL-2) was also shown to have efficacy, with approximately one-third of patients having an objective response.[16,17] However, the complete response rates were modest, ranging from 5% to 11%,[17,18] and clinicians continued to seek ways to improve outcomes. Evidence supported the idea that patients with a prior nephrectomy fared better than patients with the primary tumor in situ.[14,19-23] Additionally, there were instances in which metastatic sites responded to immunotherapy, but the primary tumor had a poor response.[24] This led to further investigation into the use of CN.

The benefits of CN include decreasing the total tumor burden and palliation of local symptoms (such as hematuria or pain) or paraneoplastic symptoms (such as anemia or hypercalciuria). Such palliation increases the likelihood that patients will be able to tolerate systemic therapy. However, CN also can be harmful to patients, given that surgery for advanced tumors is associated with perioperative morbidity and mortality. In addition, metastatic sites remain untreated while the patient recovers from surgery, and a prolonged recovery can delay time to systemic treatment. Retrospective studies have provided conflicting information on the role of CN in these patients. Some showed a benefit from CN,[7] including longer durations of partial response and higher rates of response. Other studies, however, showed no improvement or worse outcomes with CN.[25]

Phase 3 Trials

The conflicting data from retrospective studies led researchers to design 2 randomized controlled trials, the results of which were published in 2001. Flanigan and colleagues from the Southwest Oncology Group (SWOG) randomly assigned 241 patients to CN followed by IFN or to IFN therapy alone.[26] All patients had histologically proven RCC that was metastatic beyond regional lymphatics. All patients had a performance status of 0 or 1 according to SWOG criteria. The CN group contained 120 patients and the IFN-only group contained 121 patients. A greater number of patients in the IFN-only group had a performance status of 1 (58.1% vs 45.0%; *P*=.04). Median follow-up in this study was 368 days.

There was no difference in response rate to IFN between the 2 groups. The overall response rate was 3.3% in the CN group and 3.6% in the IFN-only group. However, median OS was 11.1 months in the CN group, compared with 8.1 months in the IFN-only group (*P*=.012). Patients with a performance status of 0 had longer OS when treated with CN than IFN alone (17.4 vs 11.7 months, respectively). Patients with a performance status of 1 also had longer OS in the CN group than in the IFN-only group (6.9 vs 4.8 months, respectively). Multivariable analysis demonstrated that the improved OS in the CN cohort was not due to a greater number of patients with a performance status of 0. At 1 year, OS was 49.7% in the CN group vs 36.8% in the IFN-only group.

Regarding morbidity, mortality, and potential delays in treatment, patients were hospitalized for an average of 8.2 days after surgery. There was 1 operative death (<1%), and 5 patients had severe complications (4.9%). The mean time from surgery to initiation of IFN was 19.9 days. There was no difference in severe complications due to IFN between the 2 groups. There was 1 death attributed to IFN, which occurred in the IFN-only group.

Mickisch and colleagues from the European Organisation for Research and Treatment of Cancer (EORTC) randomly assigned 85 patients to either CN followed by IFN or IFN alone.[27] All patients had histologically proven RCC that had metastasized beyond regional lymph nodes. All patients had a performance status of 0 or 1 according to World Health Organization criteria. There were 42 patients in the CN group and 43 patients in the IFN-only group, with no differences in baseline characteristics between the 2 groups.

The overall objective response rate was not significantly different between the CN group and the IFN-only group (19% vs 12%; *P*=.38). Five patients in the CN group had a complete response, compared with 1 patient in the IFN-only group. Median OS was 17 months in the CN group, compared with 7 months in the IFN-only group (*P*=.03).

A total of 6 perioperative complications and no perioperative deaths occurred. One patient in the CN group developed rapidly progressive disease and did not receive IFN. Toxicity related to immunotherapy did not differ between the 2 groups, and there were no deaths from immunotherapy.

The results of these 2 studies were published in a combined analysis.[28] The patients in the CN group had a median OS of 13.6 months, compared with 7.8 months in the IFN-only group. This equates to a hazard ratio (HR) for death in the CN group of 0.69 (95% CI, 0.55-0.87;

P=.002). There was no difference in the response rate between the 2 groups (6.9% in the CN group vs 5.7% in the IFN-only group; *P*=.60). The vast majority of patients who had CN (76.6%) experienced no surgical complications. The median time from nephrectomy to initiation of IFN treatment was 19 days.

The reason for improved OS with CN is not completely understood. It is postulated that the primary tumor acts to sequester antibodies, immune cells, and treatment. A nephrectomy allows these factors to act on sites of metastasis with increased efficacy. It is also known that RCC secretes growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor beta (TGF-β). Removal of the primary tumor may reduce the circulating levels of these growth factors, inhibiting angiogenesis at metastatic sites.[29]

Which Patients Benefit From Cytoreductive Nephrectomy?

The results of these 2 trials established CN as an effective treatment strategy for mRCC. However, identification of the patient populations most likely to benefit from CN became paramount. Fallick and colleagues retrospectively analyzed 28 patients and identified the following characteristics as predictive of likely benefit from CN: debulking at least 75% of tumor burden; absence of central nervous system, bone, or liver metastasis; adequate pulmonary and cardiac function; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; and predominant clear cell histology.[30] These patients had a median OS of 20.5 months.

Leibovich and colleagues retrospectively examined 173 patients who had CN followed by IL-2.[31] On multivariate analysis, worse OS after CN was associated with regional lymph node involvement; presence of constitutional symptoms; metastases to multiple sites or to a single site other than the bone or lung; presence of sarcomatoid features; and thyroid-stimulating hormone level greater than 2 mIU/L. Patients were categorized as low risk (0 risk factors), intermediate risk (1-3 risk factors), or high risk (≥4 risk factors). Median OS for these 3 groups was 47 months, 19 months, and 5 months, respectively.

Culp and colleagues retrospectively analyzed 566 patients who underwent CN.[32] This study used a cohort of 110 patients with mRCC who did not undergo surgery but did receive medical treatment as a referent group. On multivariate analysis, 7 preoperative variables were found to be negative predictors of survival: serum albumin below the lower limit of normal, serum lactate dehydrogenase (LDH) above the upper limit of normal, clinical T3 or T4 primary tumor, symptoms at presentation caused by a metastatic site, presence of liver metastasis, and retroperitoneal or supradiaphragmatic adenopathy of at least 1 cm. Patients with at least 4 variables who underwent CN had an OS rate that was less than or equal to the referent group, who had medical treatment only. Margulis and colleagues used a similar data set to create a nomogram for prediction of death from kidney cancer at 6 and 12 months after CN.[33] The preoperative variables included serum albumin and serum LDH. The postoperative variables examined were serum albumin, serum LDH, N stage, receipt of blood transfusion, and T stage of 3 or greater.

Culp and colleagues also reviewed population data from the Surveillance, Epidemiology, and End Results (SEER) program to identify factors associated with survival.[34] Between the years of 2005 and 2010, a total of 2478 patients had a CN. The disease-specific survival (DSS) for all patients undergoing CN was 21 months. On multivariate analysis, an increased risk of RCC-specific death was associated with older age (≥60 years), African American race, tumor stage of at least T3, tumor grade of 3 or 4, primary tumor size of at least 7 cm, sarcomatoid histology, regional lymphadenopathy, and both visceral and distant lymph node metastases. These factors had an aggregate effect, as patients with 2 or less, 3 or 4, or at least 5 adverse factors had a median DSS of 40 months, 18 months, and 7 months, respectively (*P*<.001). Being married, undergoing metastasectomy, and having a more recent diagnosis were associated with decreased risk of RCC-specific death. Variables such as performance status, laboratory values, and type of adjuvant treatment are not included in the SEER database. Although data on the type of treatment after nephrectomy were not available, 2005 was chosen as a start date in an attempt to capture patients treated with targeted therapy.

Ohno and colleagues retrospectively identified neutrophil-to-lymphocyte ratio (NLR) and performance status as predictors of survival in patients who have had CN.[35] They examined the records of 48 patients, and on multivariate analysis, determined that patients with an NLR of less than 4.0 had a median OS of 36.5 months, whereas patients with an NLR of at least 4.0 had a median OS of 10.2 months (*P*=.0020). Patients who underwent CN, but had an NLR of at least 4.0 and an ECOG performance status of at least 1 had a median OS of 8.4 months, which was not significantly different from the 6.1-month median OS of patients not having surgery (*P*=.939).

Studies have also examined the effect of nutritional status on survival after CN. Sharma and colleagues examined sarcopenia as a predictor of survival after CN.[36] A total of 105 patients from a single institution who had CN were evaluated. Twenty-seven patients had preoperative

sarcopenia, and these patients were more likely to have a lower body mass index (BMI), lower preoperative albumin level, and lower preoperative hemoglobin level compared with patients without sarcopenia. Patients with sarcopenia also were more likely to have had neoadjuvant systemic therapy. On multivariate analysis, sarcopenia was an independent predictor of worse survival (P=.006). Median OS for patients with sarcopenia was 7 months, compared with 23 months for patients without sarcopenia. Albumin level and BMI were not found to be predictive of worse survival, and other markers of nutritional status were not evaluated in this retrospective study.

In another study examining nutritional status, Corcoran and colleagues reviewed 275 patients treated with CN and determined their nutritional status based upon albumin level, BMI, and unintentional weight loss.[37] Low serum albumin was present in 25% of patients. On multivariate analysis, low serum albumin was associated with worse OS and DSS. Median OS and DSS for patients with serum albumin of less than 3.5 g/dL were 8 months and 11 months, respectively, compared with 23 months and 33 months for patients with normal serum albumin. Patients with low serum albumin also were more likely to die within 6 months of CN than patients with normal serum albumin (6-month DSS, 62.6% vs 84.3%).

Several studies have shown that having multiple sites of metastasis portends a worse survival than a single site of metastasis.[31,34,36,37] Several authors have looked at the specific metastatic distribution and survival after CN. Han and colleagues examined 297 patients with mRCC who had metastasis to either the lung only, the bone only, or multiple organ sites.[38] Patients with lymph node metastases were excluded. A total of 239 patients went on to have CN followed by immunotherapy. The response rates to immunotherapy differed by metastatic site, with an overall response rate of 44% for lung-only metastasis, 22% for bone-only metastasis, and 14% for multiple-site metastasis. Survival also differed, with a median OS of 31 months for lung-only metastasis, 31 months for bone-only metastasis, and 13 months for multiple-site metastasis. Capitanio and colleagues also examined the number and location of metastatic disease in relation to survival after CN.[39] A total of 242 patients with mRCC underwent CN and were placed into 1 of 4 categories based on distribution of metastasis: single metastasis and single organ affected, multiple metastases and single organ affected, single metastasis for each of the multiple organs affected, and multiple metastases for each of the multiple organs affected. The median OS for these 4 groups was 34.7 months, 32.3 months, 29.6 months, and 8.5 months, respectively. On multivariable analysis, the number and location of distant metastases remained a significant predictor of cancer-specific survival.

Lymph node metastasis is associated with a worse survival than localized disease. Several studies have examined the effect of lymph node metastasis in the setting of CN. Vasselli and colleagues[40] looked at 154 patients who had CN before IL-2. The 82 patients with negative lymph nodes had a longer median OS than the 72 patients with positive lymph nodes (14.7 vs 8.5 months, respectively). There was no difference in survival between patients who had a complete lymphadenectomy and those who had negative lymph nodes, although the number of patients who had a complete lymphadenectomy was small (n=7). Pantuck and colleagues studied 322 patients with mRCC who underwent CN, of whom 86 had positive lymph nodes.[41] Patients with positive lymph nodes were more likely to have larger tumors with a higher grade and stage than those with negative lymph nodes. Sarcomatoid features also were more common in the lymph node–positive group. Median DSS for lymph node–positive patients was 10.5 months, compared with 20.4 months for lymph node–negative patients. On subanalysis, immunotherapy did not improve survival for patients with lymph node–positive disease. Trinh and colleagues examined SEER data to identify 1415 patients who had CN.[42] A total of 619 patients had positive lymph nodes. Median cancer-specific survival for lymph node–positive patients was 7.0 months. Five-year OS was 40.2% for patients with lymph node–positive disease, compared with 65.8% for patients with lymph node–negative disease.

Surgical Approaches to Cytoreductive Nephrectomy

A desire to hasten patient recovery and time to initiation of systemic treatment caused CN to evolve away from the standard open procedure. The initial experience with laparoscopic CN was reported in 1999 by Walther and colleagues.[43] These researchers prospectively compared 3 groups of patients: 19 received open CN, 5 received laparoscopic CN with removal through a small incision, and 6 received laparoscopic CN with morcellation of the tumor. No difference in complications occurred. The operative time in the laparoscopic groups was longer than that in the open group (466 vs 210 minutes). Patients in the morcellation group were discharged sooner than those in the open CN group (6.3 vs 8.2 days), and received earlier treatment with IL-2 (37 vs 67 days). As the laparoscopic technique evolved, more studies demonstrated the benefits of laparoscopic CN. Rabets and colleagues retrospectively compared 22 laparoscopic CNs with 42 open CNs.[44] Laparoscopic CN resulted in a shorter hospital stay (2.3 vs 6.1 days) and quicker time

to receipt of systemic therapy (36 vs 61 days) than open CN. There was no difference in complications. One-year OS was not statistically different between the 2 groups. Since then, several additional studies have been published showing that laparoscopic CN is a safe procedure and can be utilized in select patient populations.[45-49] These studies show equivalent operative times, complication rates, ability to receive adjuvant therapy, and time to receipt of adjuvant therapy.

The utilization of nephron-sparing surgery (NSS) in the face of mRCC was mainly confined to a few cases within larger case reports[50-53] until 1996. At that point, Krishnamurthi and colleagues published a series of patients with mRCC who were treated with partial nephrectomy.[54] The majority of these patients had a previous radical nephrectomy for RCC, and had disease recurrence. The patients who benefited most were those with asynchronous bilateral RCC who had their metastatic disease treated before NSS. The patients in this study who received systemic therapy were treated prior to surgery. Krambeck and colleagues were the first to directly compare NSS with radical nephrectomy in the setting of metastatic disease.[55] Sixteen patients with mRCC who underwent NSS were compared with 404 patients with mRCC who underwent radical nephrectomy. The majority of patients (12 of 16) in the mRCC NSS cohort had a solitary kidney. There was also a comparison between the 16 patients who underwent NSS for mRCC and the 139 patients who underwent NSS for localized disease. Early (33% vs 9.9%) and late (50.0% vs 19.1%) complications after surgery were higher in the mRCC NSS cohort when compared with radical nephrectomy. When comparing the metastatic NSS cohort with the localized NSS cohorts, however, the early and late complication rates were not significantly different. In the mRCC NSS cohort, there was 1 recurrence in the ipsilateral kidney at 28 months. None of the 16 patients who had NSS for mRCC received adjuvant systemic therapy. For the mRCC NSS cohort, cancer-specific survival at 1, 3, and 5 years was 81.3%, 49.2%, and 49.2%, respectively. For the mRCC radical nephrectomy cohort, cancer-specific survival at 1, 3, and 5 years was 50.5%, 21.1% and 12.8%, respectively. However, there were differences between the 2 cohorts, as surgical resection of all metastatic disease was accomplished in 87.5% of the mRCC NSS cohort and 22.6% of the radical nephrectomy cohort. In this study, the differences in survival were likely due to inherent biological and oncologic differences in tumors that were amenable to NSS. Hutterer and colleagues attempted to account for this by matching 38 patients who had NSS for mRCC with 99 patients who had radical nephrectomy for mRCC, based on tumor stage, grade, and histology.[56] They demonstrated no statistically significant difference in survival between the 2 cohorts; however, they recognized that their analysis was underpowered to confirm equivalence. Hellenthal and colleagues utilized SEER data to compare cancer-specific survival for patients with mRCC undergoing NSS (n=70) vs radical nephrectomy (n=2950).[57] On multivariate analysis, the HR for cancer-specific survival in the NSS group was 0.49 (P<.001). However, this was attributed to difference in tumor size, which was shown to be an independent predictor of cancer-specific survival. There have been no prospective trials assessing the efficacy of partial nephrectomy compared with radical nephrectomy as a means of CN, but the data from these studies appear to show that this can be utilized in carefully selected patient populations.

The risk of perioperative complications or death has always been a factor in determining candidacy for CN. Perioperative complications from surgery can delay administration of systemic therapy, potentially diminishing any benefits of combined therapy. Abdollah and colleagues examined population data from Florida that compared 1063 people undergoing CN with 16,625 people who had a radical nephrectomy for localized disease.[58] The in-hospital mortality rate (2.4% vs 0.9%) and the in-hospital complication rate (26.5% vs 18.9%) were higher in the CN group compared with the radical nephrectomy group. Trinh and colleagues examined administrative data and found that among 16,285 patients who underwent CN, 30.5% had at least 1 complication.[59] Age older than 75 years, increased comorbidities, undergoing a secondary procedure, and having 2 or more metastatic sites were associated with an increased complication rate. They also noted a decrease in complications for high-volume hospitals and hospitals with a higher number of hospital beds. The mortality rate in this study was 1.5%. Silberstein and colleagues studied 195 nephrectomies for mRCC at a single institution.[60] Complications that were grade 2 or higher in the Clavien-Dindo classification system were seen in 27% of patients. Nine deaths occurred within 56 days of surgery; however, 4 of these were from progression of disease, leaving 5 deaths (2.6%) from surgery. On multivariable analysis, decreased Karnofsky performance status and increased age were individually associated with an increased risk of complications. However, the rate of complications from CN varies, with a recent study from Gershman and colleagues showing an overall complication rate of 12% and a perioperative mortality rate of 1% in a single-institution cohort of 294 patients.[61] These studies show that CN can be associated with a rate of morbidity and mortality greater than that seen in nephrectomy for localized disease. Proper identification of patients who are least likely to develop complications and most likely to benefit from surgery is imperative.

The Targeted-Therapy Era

In 2007, the results of three randomized phase 3 clinical trials on targeted therapy for mRCC were published. Motzer and colleagues randomly assigned 750 patients with untreated clear cell mRCC to either sunitinib (Sutent, Pfizer) or IFN.[62] Median progression-free survival (PFS) was longer with sunitinib than with IFN (11 vs 5 months), and the objective response rate was higher (31% vs 6%). Escudier and colleagues randomly assigned 903 patients with advanced clear cell RCC whose disease had failed to respond to prior immunotherapy or radiation to sorafenib (Nexavar, Bayer) or placebo.[63] The median PFS was 5.5 months in the sorafenib group vs 2.8 months in the placebo group. The HR for death with sorafenib compared with placebo was 0.72 (95% CI, 0.54-0.94; *P*=.02). Additionally, 10% of patients in the sorafenib group had a partial response, compared with 2% in the placebo group. Hudes and colleagues randomly assigned 626 patients with poor-prognosis mRCC to temsirolimus (Torisel, Pfizer), IFN, or both.[64] Patients in the temsirolimus group had a longer OS (HR for death, 0.73; 95% CI, 0.58-0.92; *P*=.008) and a longer PFS (5.5 vs 3.1 months; *P*<.001) compared with those in the placebo group. The combination treatment group was not statistically different from the temsirolimus-only group. The shift in treatment of mRCC from immunotherapy with IL-2 or IFN to targeted therapy with either the tyrosine kinase inhibitors sorafenib or sunitinib or the mammalian target of rapamycin kinase inhibitor temsirolimus was based on the higher response rate seen with use of targeted therapy.

Although it was evident that targeted therapy was able to treat mRCC, the presence and magnitude of the response of the primary tumor were variable.[65-68] In addition, complete response of the primary tumor is rare.[69] As such, the treatment paradigm of nephrectomy in combination with systemic therapy remained, with targeted therapy replacing immunotherapy. In contrast to immunotherapy, there is currently no level 1 evidence of the benefit of CN in the setting of targeted therapy. Retrospective studies have shown mixed results.

You and colleagues retrospectively compared 45 patients with mRCC who underwent CN followed by sunitinib or sorafenib (the CN group) vs 33 patients with mRCC treated with sunitinib or sorafenib alone (the non-CN group).[70] There was no difference in the response rate (23.1% vs 30.3%; *P*=.488), PFS (11.7 vs 9.0 months; *P*=.270), or median OS (21.6 vs 13.9 months; *P*=.128) in the CN group vs the non-CN group, respectively. However, evidence in support of CN includes a subgroup analysis of the first study to examine sunitinib vs IFN. This study showed an advantage in PFS in patients who had a nephrectomy before treatment with sunitinib vs sunitinib treatment without prior nephrectomy (11 vs 6 months).[62]

Gore and colleagues also found better outcomes for patients who had a CN followed by sunitinib. In an expanded-access study to determine the efficacy and safety of sunitinib, an interim analysis of the 4543 patients revealed that patients who had a nephrectomy prior to sunitinib had better PFS (12.0 vs 6.5 months; *P*=.021).[71]

Choueiri and colleagues retrospectively examined data on 314 patients with mRCC to determine the effect of CN in patients being treated with targeted therapy.[72] A total of 201 patients had CN followed by sunitinib, sorafenib, or bevacizumab (Avastin, Genentech), whereas 113 patients received targeted therapy alone. On multivariable analysis, the HR for OS was 0.68 (95% CI, 0.46-0.99; *P*=.04) in the CN group vs the targeted therapy–alone group. The overall response rate also was greater with CN than with targeted therapy alone (26.3% vs 11.5%).

Heng and colleagues reviewed data on 1658 patients with mRCC, 982 of whom had CN prior to targeted therapy, and 676 of whom received targeted therapy alone.[73] Patients in the CN group had better median OS than those in the non-CN group (20.6 vs 9.5 months, respectively; *P*<.0001). The adjusted HR for death in the CN group was 0.60 (95% CI, 0.52-0.69; *P*<.0001).

Hanna and colleagues used the National Cancer Data Base to retrospectively compare 5374 patients with mRCC who had CN combined with targeted therapy against 10,016 patients with mRCC who had targeted therapy alone.[74] Patients in the CN group had a lower risk of death (HR, 0.45; 95% CI, 0.40-0.50; *P*=.001) compared with those in the non-CN group. The researchers identified younger age, treatment at an academic center, lower tumor stage, and clinically negative lymph nodes as factors associated with receiving CN.

Petrelli and colleagues performed a meta-analysis of 12 trials that examined OS in relation to the use of CN and targeted therapy in patients with mRCC.[75] A total of 39,983 patients were included in the analysis, which demonstrated a reduced risk of death in patients who underwent CN (HR, 0.46; 95% CI, 0.32-0.64; *P*<.01).

Two large randomized trials that are ongoing are investigating the use of CN in the targeted therapy era. The CARMENA trial (The Clinical Trial to Assess the Importance of Nephrectomy; NCT00930033) is examining the effect of CN followed by sunitinib vs sunitinib alone in patients with biopsy-proven clear cell mRCC. This is a phase 3 noninferiority trial with an estimated enrollment of 576 patients, and an estimated completion date of February 2020. The EORTC is conducting the SURTIME study (Immediate Surgery or

Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer; NCT01099423) to determine whether patients with clear cell mRCC obtain better disease control with nephrectomy followed by sunitinib, or sunitinib followed by nephrectomy. Enrollment is approximately 458 patients, with an estimated completion date of December 2016.

Although both of these trials are expected to provide level 1 evidence, they will not answer all of the current questions surrounding CN and targeted therapy. The CARMENA trial is a noninferiority trial, so it may not give a true estimate of the benefit of CN. In the SURTIME trial, both arms will receive surgery and targeted therapy, so it will be difficult to assess the true benefit of CN. Additionally, both of these studies include only patients with clear cell histology and ECOG performance status of 0 or 1, which is not entirely reflective of the patient population with mRCC. These trials utilize only one of the many targeted therapies that are currently available, which calls into question the generalizability of the results given the number of therapies currently available.

Conclusion

Metastatic RCC is a complex disease with a poor prognosis that has challenged clinicians for decades. The use of CN prior to administration of systemic immunotherapy was validated in two phase 3 trials. Targeted therapy, with its increased efficacy, has supplanted immunotherapy as the preferred first-line treatment for mRCC. As we await the results of two ongoing phase 3 trials that examine the role of CN and targeted therapy, the key to successful outcomes after CN is identification of patients who are most likely to benefit from the procedure.

Disclosures

Drs Chery and Karam have declared no conflicts of interest. Dr Wood is the principal investigator of an Argos trial in metastatic renal cell carcinoma.

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