ELSEVIER

Urologic Oncology: Seminars and Original Investigations 37 (2019) 525–528

UROLOGIC ONCOLOGY

News and Topics

Does CARMENA mark the end of cytoreductive nephrectomy for metastatic renal cell carcinoma?

Steven L. Chang, M.D., M.S.[a,b,*], Toni K. Choueiri, M.D.[b], Lauren C. Harshman, M.D.[b]

[a] *Division of Urology, Center for Surgery and Public Health, Brigham and Women's Hospital, Boston, MA*
[b] *Dana-Farber Cancer Institute, Boston, MA*

Received 5 November 2018; received in revised form 15 January 2019; accepted 16 April 2019

Abstract

Cytoreductive nephrectomy (CN) was established as the standard of care for the management of metastatic renal cell carcinoma (mRCC) in the early 2000s. Since that time, systemic therapeutic options for mRCC have rapidly expanded and progressed. The CARMENA trial was a phase III prospective, randomized clinical trial that accrued patient from 2009 to 2017, and the results show that treatment with sunitinib is noninferior to treatment with CN followed by sunitinib. Because the findings of CARMENA suggest that systemic therapy should be considered alongside CN as frontline therapy for mRCC, it is therefore important to define the clear indications for CN in the management of mRCC which include palliation, nonclear cell histology, consolidative therapy after systemic therapy, and oligometastic disease. Furthermore, CN may become increasingly important as immunotherapeutic options become widely adopted in the future. Given the heterogeneous nature of mRCC, a multidisciplinary approach should be taken to tailor the use of systemic therapy and CN for each individual patient.

Keywords: Renal cell carcinoma; Metastasis; Clinical trial; Cytoreduction surgical procedures; Drug therapy

Renal cell cancer (RCC) is one of the few cancers where it has been common practice to surgically remove the primary tumor (i.e., cytoreductive nephrectomy [CN]) in the setting of metastatic disease. RCC is notable for its heterogeneity even once metastatic, and its spectrum of clinical presentations can range from indolent asymptomatic cancers to symptomatic disease with associated paraneoplastic syndromes thought related to the primary tumor's secretion of inflammatory cytokines. Similarly, while some primary tumors can be easily resected with a minimally invasive technique others are locally advanced with encasement of the renal hilar vessel as well as extension into the inferior vena cava necessitating a drastically more complex surgical approach. The burden of disease beyond the kidney may be solitary, oligometastatic or more extensive and widespread disease affecting multiple organ systems. Furthermore, metastatic RCC (mRCC) encompasses a host of histologies with varied prognoses from the most common clear cell histologic subtype to more than ten distinct entities under the umbrella term "nonclear cell."[1] Given the clinical heterogeneity of mRCC and consequential heterogeneity in effect of available therapies, it is not surprising that there has been substantial challenge in establishing a uniform approach for its management.

CN was established as the standard of care for mRCC after 2 randomized studies in the early 2000s, comparing CN followed by interferon alpha (IFN) versus IFN alone, demonstrated statistically and clinically significant improvements in overall survival for patients with mRCC [2,3]. Combined, the studies revealed a median survival of 13.6 months for patients undergoing CN followed by IFN compared with 7.8 months for those receiving IFN alone, representing a 31% risk reduction for mortality [4]. However, the role of CN was questioned once more broadly effective systemic therapies were developed for mRCC. In the mid-2000s, cytokine therapy was supplanted, as the mainstay of systemic therapy for mRCC, by the targeted therapies (TT), which were comprised mainly of vascular endothelial growth factor-targeted tyrosine kinase inhibitors. Given the ability to control disease in upwards of 80% of patients with significant improvements in progression

*Corresponding author. Tel.: +16175253117; fax: +16175256348
E-mail address: slchang@bwh.harvard.edu (S.L. Chang).

https://doi.org/10.1016/j.urolonc.2019.04.014
1078-1439/

free survival and overall survival compared to the cytokine era [5], experts questioned whether CN was still necessary and worth the associated morbidity and mortality risks. These questions led to retrospective and population-based studies [6,7], which continued to demonstrate support for frontline CN reporting overall survival benefits associated with surgery even in the setting of TT. Consequently, when the primary tumor was deemed resectable, CN remained a standard of care initial step in management of mRCC with systemic therapy employed postoperatively [8].

To determine the role of CN in the TT era, the phase III clinical trial, CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques, NCT00930033), was designed specifically to assess overall survival for upfront CN in addition to sunitinib compared to sunitinib alone, akin to the design of the prior IFN trials [9]. After nearly a decade of slow accrual between 2009 and 2017, interim analysis was performed after 450 of the planned 576 patients were enrolled. At a median follow-up of 50.9 months, overall survival for sunitinib alone was comparable to CN and sunitinib (hazard ratio [HR] 0.89, 95% confidence interval [CI]: 0.71−1.10; the threshold for noninferiority was HR ≤1.20). The study concluded that systemic therapy with sunitinib alone produced noninferior survival outcomes compared to upfront CN followed by sunitinib. The response to this trial has been mixed. While some have concluded that CARMENA marks the end of the era for CN, critics of CARMENA cite that the results may have been impacted by the relatively high number of poor-risk patients (~43%) who may not have generally considered candidates for CN, a higher portion of T3/T4 tumors in the CN arm (70.1% vs. 51.0%), and inclusion of low surgical volume centers thus skewing the results in favor of sunitinib [10].

We assert that the CARMENA trial simply reinforces that systemic disease needs systemic therapy and that CN should not automatically be considered the initial step in management of mRCC. We believe that CARMENA demonstrates that the contemporary standard of care should be a *multimodal approach* tailoring the treatment plan to the individual patient whether it be frontline systemic therapy or CN. Arguably, at least for some comprehensive cancers centers, this practice has been the de facto standard for years [11,12], and as such the CARMENA results are not actually disruptive. Given the demonstrated efficacy of contemporary systemic therapy, which has now expanded to include the newer generation immune checkpoint inhibitors, the clinically relevant question then becomes: under what situation(s) is it appropriate to perform CN?

Palliation of symptoms

Pain, hematuria, blood loss, and paraneoplastic symptoms are all plausible reasons to consider CN when those symptoms are attributed to the primary tumor. Daily pain can be a common symptom for patients with metastatic disease [13], and 36% have pain severe enough to impair the ability to function [14]. Albeit rarely, some patients may require transfusions from the blood loss related to the primary tumor and consequent symptomatic anemia. While it may be reasonable to expect that pain and hematuria attributed to the primary tumor can be effectively address with CN, paraneoplastic symptoms may also resolve with a palliative CN [15]. Hypercalcemia may be seen in as many as 20%, hypertension in up to 40%, erythrocytosis in up to 8%, and constitutional symptoms in up to a third of patients [16]. Stauffer syndrome, an IL-6 driven transaminitis is a prime example of a paraneoplastic syndrome known to resolve after surgery [17]. Because mRCC is still considered an incurable condition despite recent advances in therapy, quality of life is of paramount importance and thus intractable symptoms that fail supportive care measures are an appropriate indication for CN.

Nonclear cell histology

The CARMENA trial restricted the study cohort to patients with clear cell histology. Nonclear cell RCC, however, can nevertheless progress to metastatic disease at which point there are fewer effective systemic therapy options [18]. These varied histologic subtypes are genetically and histologically distinct cancers. Although nonclear cell histology represent ~15% of all RCC [1] some series of CN reports up to one-third of patients with mRCC have no clear cell component [19,20]. While TT may be effective for nonclear cell mRCC [21,22], the magnitude of benefit appears lower than for clear cell disease and thus CN may be able to provide a more significant additive benefit in terms of disease control for patients with nonclear cell histologies. Retrospective analyses of large datasets including the Surveillance, Epidemiology, and End Results (SEER) database[23] and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)[24] suggest that CN is associated with improved survival when compared to no CN after adjustment for other know prognostic risk criteria. Until clinical trials demonstrate substantial improvement in overall survival with systemic therapy, we recommend that upfront CN is an appropriate initial therapy for patients with metastatic nonclear cell RCC, especially in the light of less efficacious systemic agents.

Consolidative surgery

Among patients with an objective response to systemic therapy, CN can serve as consolidative therapy to eradicate residual disease in hopes of achieving the goal of a durable remission. Though data are limited, phase II studies have shown that some patients can have substantial reductions in disease burden with consolidative CN following initial systemic therapy with sunitinib [25] and pazopanib [26]. Arguably the most compelling data in favor of consolidative CN is derived from the SURTIME trial (Immediate Surgery or

Surgery After Sunitinib Malate in Treating Patients with Metastatic Kidney Cancer, EORTC 30073), which was a phase III prospective randomized study comparing immediate CN followed by sunitinib versus initial sunitinib with subsequent delayed CN. While the validity of the study findings are limited due to small cohort size, the results demonstrated a statistically significant prolongation of overall survival by approximately 15 months for patients who underwent sunitinib followed by CN (versus CN followed by sunitinib, HR 0.57, 95% CI: 0.34 to 0.95, $P = 0.032$) [27]. Another potential benefit of this strategy is that it serves as a litmus test to identify patients with more favorable tumor biology who will benefit from a multimodal approach. For instance, patients who progress rapidly in their metastatic disease on systemic therapy may be less likely to benefit from CN.

Management of oligometastatic disease

We believe that another indication for CN is the patient with oligometastatic disease, an intermediate state between locally advanced disease and widespread metastatic disease, which was not a well-represented type of patient in the CARMENA study cohort. For mRCC, prolonged survival has been reported for patients with oligometastatic disease amenable to resection. The first such report was in 1945 in which a pulmonary metastasectomy achieved a surgical complete remission; that patient had a durable response without ever developing evidence of disease recurrence [28]. While the literature on this topic is admittedly limited and suffers from selection bias, prior investigations report that for patients with oligometastatic disease, complete surgical resection of all known disease, primary and metastatic, has been associated with a significant increase in median cancer-specific survival by 3.5 years [29]. While the site of metastatic disease may be addressed with extirpative surgery, thermal ablation, or radiation therapy, CN is the critical step to remove the primary burden of disease among patients with oligometastatic disease.

CN in the era of immuno-oncology

With the rapid pace of developing therapeutic agents, the landscape of systemic therapy continues to evolve and arguably sunitinib, the pharmacotherapeutic agent of interest for the CARMENA trial, is no longer the optimal choice for most patients with treatment-naive mRCC. We are now observing a transition from TT monotherapy to immuno-oncology (IO) and combinations of both pharmacotherapeutic classes. The CheckMate 214 trial [30] recently led to the FDA approval of frontline nivolumab-ipilimumab in patients with poor and intermediate risk factors. Furthermore, strategies combining IO agents and TT are eliciting promising results [31]. Patients undergoing therapy with an IO agent potentially have an additional benefit from CN because resection of the primary tumor may remove a source of immunosuppressive cytokines and other proteins that thwart the immune response [32]. Similarly, other investigational strategies such as adoptive cell transfer to individualize systemic therapy require surgical removal of tumor as the initial step to obtain tumor-infiltrating lymphocytes (TIL) or neoantigens from the primary tumor. Therefore, CN will likely continue to play an important role in the era of IO though future studies will be necessary to define the optimal role of surgery.

In conclusion, we view the CARMENA trial as a landmark study in the contemporary management of mRCC. It is practice-changing in that it eliminates what has arguably been a routine consideration for CN prior to systemic therapy since the early 2000s. Due to the variability in treatment effect of CN based on the clinical scenario, the medical community as a whole must more selectively choose which patients warrant CN as a complementary measure alongside the growing number of options for systemic therapy or for those with refractory disease. These decisions will require a multidisciplinary approach between urologists and medical oncologists as well as possibly radiation oncology and radiology to customize a plan for the individual patient with mRCC. Given the heterogeneous nature of this disease, it is unlikely that there will ever be a single therapeutic approach to care, and the role of CN will continue in concert with the advances in systemic therapy for mRCC.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.04.014.

References

[1] Valenca LB, Hirsch MS, Choueiri TK, Harshman LC. Non-clear cell renal cell carcinoma, part 1: histology. Clin Adv Hematol Oncol 2015;13(5):308–13.

[2] Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. NEJM 2001;345(23):1655–9. https://doi.org/10.1056/NEJMoa003013.

[3] Mickisch G, Garin A, Van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. The Lancet 2001;358(9286):966–70. https://doi.org/10.1016/S0140-6736(01)06103-7.

[4] Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 2004;171(3):1071–6. https://doi.org/10.1097/01.ju.0000110610.61545.ae.

[5] Heng DYC, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol 2009;27(34):5794–9. https://doi.org/10.1200/JCO.2008.21.4809.

[6] Heng DYC, Wells JC, Rini BI, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma

Database Consortium. Eur Urol 2014;66(4):704–10. https://doi.org/10.1016/j.eururo.2014.05.034.

[7] Hanna N, Sun M, Meyer CP, et al. Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: A National Cancer Data Base Study. J Clin Oncol 2016;34(27):3267–75. https://doi.org/10.1200/JCO.2016.66.7931.

[8] Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. Longo DL, ed. N Engl J Med 2017;376(4):354–66. https://doi.org/10.1056/NEJMra1601333.

[9] Mejean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 2018;379(5):417–27. https://doi.org/10.1056/NEJMoa1803675.

[10] Motzer RJ, Russo P. Cytoreductive nephrectomy - patient selection is key. N Engl J Med 2018;379(5):481–2. https://doi.org/10.1056/NEJMe1806331.

[11] Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? Cancer 2010;116(14):3378–88. https://doi.org/10.1002/cncr.25046.

[12] Margulis V, Shariat SF, Rapoport Y, et al. Development of accurate models for individualized prediction of survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. Eur Urol 2013;63(5):947–52. https://doi.org/10.1016/j.eururo.2012.11.040.

[13] Portenoy RK, Lesage P. Management of cancer pain. The Lancet 1999;353(9165):1695–700. https://doi.org/10.1016/S0140-6736(99)01310-0.

[14] Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. NEJM 1994;330(9):592–6. https://doi.org/10.1056/NEJM199403033300902.

[15] Walther MM, Patel B, Choyke PL, et al. Hypercalcemia in patients with metastatic renal cell carcinoma: effect of nephrectomy and metabolic evaluation. J Urol 1997;158(3 Pt 1):733–9.

[16] Palapattu GS, Kristo B, Rajfer J. Paraneoplastic syndromes in urologic malignancy: the many faces of renal cell carcinoma. Rev Urol 2002;4(4):163–70.

[17] Blay JY, Rossi JF, Wijdenes J, et al. Role of interleukin-6 in the paraneoplastic inflammatory syndrome associated with renal-cell carcinoma. Int J Cancer 1997;72(3):424–30.

[18] Valenca LB, Hirsch MS, Choueiri TK, Harshman LC. Non-clear cell renal cell carcinoma, part 2: therapy. Clin Adv Hematol Oncol 2015;13(6):383–91.

[19] Renshaw AA, Richie JP. Subtypes of renal cell carcinoma. Different onset and sites of metastatic disease. Am J Clin Pathol 1999;111(4):539–43.

[20] Lee C, Park J-W, Suh JH, Nam KH, Moon KC. Histologic variations and immunohistochemical features of metastatic clear cell renal cell carcinoma. Korean J Pathol 2013;47(5):426–32. https://doi.org/10.4132/KoreanJPathol.2013.47.5.426.

[21] Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): a multicentre, open-label, randomised phase 2 trial. Lancet Oncol 2016;17(3):378–88. https://doi.org/10.1016/S1470-2045(15)00515-X.

[22] Tannir NM, Jonasch E, Albiges L, et al. Everolimus versus sunitinib prospective evaluation in metastatic non-clear cell renal cell carcinoma (ESPN): a randomized multicenter phase 2 trial. Eur Urol 2016;69(5):866–74. https://doi.org/10.1016/j.eururo.2015.10.049.

[23] Aizer AA, Urun Y, McKay RR, Kibel AS, Nguyen PL, Choueiri TK. Cytoreductive nephrectomy in patients with metastatic non-clear cell renal cell carcinoma. BJU Int 2013(September). https://doi.org/10.1111/bju.12442.

[24] Graham J, Wells C, Donskov F, et al. Cytoreductive nephrectomy in metastatic papillary renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). J Clin Oncol 2018;36(6_suppl). https://doi.org/10.1200/JCO.2018.36.6_suppl.581:581-581.

[25] Powles T, Kayani I, Blank C, et al. The safety and efficacy of sunitinib before planned nephrectomy in metastatic clear cell renal cancer. Ann Oncol 2011;22(5):1041–7. https://doi.org/10.1093/annonc/mdq564.

[26] Powles T, Sarwar N, Stockdale A, et al. Safety and efficacy of pazopanib therapy prior to planned nephrectomy in metastatic clear cell renal cancer. JAMA Oncol 2016;2(10):1303–9. https://doi.org/10.1001/jamaoncol.2016.1197.

[27] Bex A, Mulders P, Jewett MAS, et al. Immediate versus deferred cytoreductive nephrectomy (CN) in patients with synchronous metastatic renal cell carcinoma (mRCC) receiving sunitinib (EORTC 30073 SURTIME). *Ann Oncol* 2017;28(suppl_5). https://doi.org/10.1093/annonc/mdx440.030:mdx440.030-mdx440.030.

[28] Barney JJ. A twelve-year cure following nephrectomy for adenocarcinoma and lobectomy for solitary metastasis. Trans Am Assoc Genitourin Surg 1945;37:189–91.

[29] Alt AL, Boorjian SA, Lohse CM, Costello BA, Leibovich BC, Blute ML. Survival after complete surgical resection of multiple metastases from renal cell carcinoma. Cancer 2011;117(13):2873–82. https://doi.org/10.1002/cncr.25836.

[30] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378(14):1277–90. https://doi.org/10.1056/NEJMoa1712126.

[31] Motzer RJ, Penkov K, Haanen JBAG, et al. JAVELIN renal 101: a randomized, phase III study of avelumab + axitinib vs sunitinib as first-line treatment of advanced renal cell carcinoma (aRCC). *Ann Oncol* 2018;29(suppl_8). https://doi.org/10.1093/annonc/mdy424.036:mdy424.036-mdy424.036.

[32] Flanigan RC. Debulking nephrectomy in metastatic renal cancer. Clin Cancer Res 2004;10(18 Pt 2):6335S–41S. https://doi.org/10.1158/1078-0432.CCR-sup-040026.