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Primary Cytoreductive Nephrectomy: Standing the Test of Time?

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Some 15% of patients with renal cell carcinoma (RCC) present with synchronous metastases. Primary cytoreductive nephrectomy (CN) has historically been a cornerstone of therapy for metastatic RCC (mRCC), and reports documenting spontaneous regression of metastases after nephrectomy have demonstrated the immunomodulatory role of cytoreduction [1]. It is this well-described but rare phenomenon that provided the rationale for a series of landmark trials solidifying the role of CN in the cytokine era. Overall, these studies demonstrated an improvement in overall survival after primary cytoreduction and established CN as a standard for patients with de novo mRCC [2].

With the dawn of VEGF-targeted therapy associated with better efficacy in comparison to cytokine treatment, the role of cytoreductive surgery became more ambiguous. Two important studies, CARMENA and SURTIME, shifted the approach away from upfront CN for many patients with mRCC with an intact primary tumor. CARMENA was a phase 3, randomized noninferiority trial that evaluated CN followed by sunitinib versus sunitinib alone in patients with mRCC. While CARMENA enrolled a substantially increased number of patients with high disease burden and poor risk disease, it showed that sunitinib alone was noninferior to CN followed by sunitinib in patients with intermediate- and poor-risk disease (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.71–1.10; upper boundary of the 95% CI 1.20 for noninferiority) [3]. SURTIME was a phase 3 study evaluating the sequencing of either CN followed by sunitinib or sunitinib followed by CN [4]. While the study did not meet the anticipated accrual target and failed to meet its primary endpoint, there was a modest survival advantage with the deferred CN approach.

While affirming the use of systemic therapy without need for CN in poor-risk mRCC, the applicability of the CARMENA and SURTIME findings for all patients with de novo mRCC has been questioned for two primary reasons: (1) the setting of low-volume mRCC and (2) the modern era of combination immunotherapy treatment [5]. For the low-volume mRCC setting, updated CN guidelines promulgated by the European Associate of Urology recommend immediate CN in selected patients with good performance status who do not require systemic therapy and in whom cytoreduction and metastasectomy may lead to complete resection of disease [6]. Regarding the second issue, the role of primary CN in the immune checkpoint inhibitor (ICI) era requires further investigation. In 2018, the same year in which the CARMENA results were published, the combination of nivolumab and ipilimumab (Checkmate 214) demonstrated better overall survival and objective response rates for patients with intermediate- and poor-risk RCC [5]. Subsequently, a series of landmark studies demonstrated a survival advantage of dual immune checkpoint blockade and VEGF-targeting agents, including pembrolizumab plus axitinib (Keynote 426), nivolumab plus cabozantinib (Checkmate 9ER), and pembrolizumab plus lenvatinib (Clear), for patients with advanced RCC or mRCC [7,8]. Interestingly, while the rate of prior nephrectomy was 81% in Checkmate 214 and 83% in Keynote 426, it was lower in later trials that accrued patients in the post-CARMENA era: 69% for Checkmate 9ER and 73% for Clear.

In this issue of *European Urology*, given the shifting landscape for CN utilization and the expansion of immunotherapy treatments for patients with RCC, Bakouny and colleagues [9] examine the role of CN in a modern cohort

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of patients. They retrospectively analyzed the impact of primary CN in a cohort of 4639 patients from the prospectively maintained International Metastatic RCC Database Consortium (IMDC). Primary CN was used in 2326 of 4202 (55%) patients who were treated with targeted therapy and 234 of 437 (54%) of patients treated with ICI therapy. A greater proportions of patients who received primary CN had intermediate-risk disease (60% vs 46% in targeted therapy group, and 72% vs. 47% in the ICI group). In addition, multivariable analyses demonstrated that CN was associated with significantly better overall survival in the ICI group (HR 0.61; $p = 0.013$) and the targeted therapy group (HR 0.72; $p < 0.001$), although there was no difference in survival benefit from primary CN between the treatment groups (interaction $p = 0.6$).

The findings from this study bring the debate full circle and suggest a benefit from primary CN for well-selected patients (younger, better performance status/fewer IMDC risk factors, and without adverse metastases such as brain, bone, and liver), similar in many ways to candidates for primary CN from early studies of the impact of cytokine therapy. In fact, a post hoc analysis for the CARMENA study demonstrated longer overall survival for patients with only one IMDC risk factor [10]. Furthermore, the similarity of the CN benefit between the two therapeutic groups suggests the immunomodulatory impact of excision of the primary tumor on the subsequent host response as opposed to a differential synergy with the therapeutic modality.

As the authors readily acknowledge, while their results suggest a sustained role for primary CN in the modern immunotherapy era, their findings are limited by study design and the inherent biases and confounders associated with retrospective analyses. Nevertheless, it may very well be these biases that lead to better outcomes in selected patients. It is nearly impossible to capture the complexity of patient, tumor, and host factors for any given individual who presents with mRCC in the context of a randomized trial. For instance, the presence or absence of hematuria or local symptoms, the proportion of disease within the kidney, the surgical complexity of performing nephrectomy, and host immune factors, which remain largely unknown, are all relevant. The need for nuanced and individualized decisions will probably shift the management of mRCC and advanced RCC towards multimodal teams that can contribute to decisions on the optimal timing of surgery, systemic therapy, and the ever-expanding role of radiotherapy to optimize outcomes.

As we await more definitive answers on the role of CN in the ICI setting from trials such as NORDIC-SUN (NCT03977571) and SWOG-1931/PROBE (NCT04510597), Bakouny and colleagues suggest that CN may very well stand the test of time.

Conflicts of interest: The authors have nothing to disclose.

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