Editorial Commentary

Current landscape of cytoreductive nephrectomy: who, when, and why?

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The use of cytoreductive nephrectomy (CN) in the cytokine therapy era was well supported by two randomized controlled trials conducted by the Southwest Oncology Group and the European Organization for Research and Treatment of Cancer (1,2). However, due to the rapid advancement of novel therapies, the benefits of CN for metastatic renal cell carcinoma (mRCC) have been widely questioned. As CN remains a morbid procedure with perioperative death rate of 3–4% (3), the consensus is to offer surgery in only select patients. In order to better define survival benefit, Margulis *et al.* developed a predictive model of postoperative death after CN using single institutional data ranging from 1991 to 2008 including patients treated with cytokine therapy either preoperatively or postoperatively (4). This model attempted to predict 6-month postoperative death (PoD), which plays an important role in decision making for both patients and physicians. In a recent article published in the *World Journal of Urology* titled "External validation of a predictive model of survival after cytoreductive nephrectomy for metastatic renal cell carcinoma", Marconi *et al.* sought to externally validate this model by using multi-institutional data from European and North American centers in the targeted therapy era (5). Both pre- and postoperative models were well calibrated (AUC: 0.68, 95% CI: 0.62–0.74 and 0.73, 95% CI: 0.68–0.78; respectively) for predicting PoD following CN. A decision curve analysis was used to determine the clinical value of the model in the preoperative setting. The model performed well when CN was examined within threshold survival probabilities of 20–50%. The authors estimated the range of probability thresholds in a typical CN population as the probability of death at 6 months to be 20–40%. Thus, the model offers prognostic clinical value for patients and clinicians considering CN.

While the benefits of CN have been established for decades, two recent studies have challenged the benefits and sequence of nephrectomy at the time of tyrosine kinase inhibitor (TKI) therapy. Bex *et al.* recently reported the result of the SURTIME trial (6). A total of 99 patients were randomized into 2 treatment groups: immediate CN followed by sunitinib therapy versus treatment with 3 cycles of sunitinib followed by CN (in the absence of progression) to be followed by more sunitinib therapy. It should be noted that this study initially aimed for 458 patients with a primary endpoint of progression-free survival. Due to poor accrual, the trial closed early with only a 99-patient cohort. In addition, the primary endpoint was changed to a 28-week progression-free rate. The results showed no difference in 28-week progression-free rates between the groups. Overall survival (OS) was greater in the deferred CN group (HR: 0.71, 95% CI: 0.40–1.24), but the difference was no longer statistically significant (P=0.23). Complementing these results, CARMENA (7), a phase 3 non-inferiority trial, randomized intermediate- and poor-risk patients with mRCC to CN followed by sunitinib versus sunitinib alone, and showed OS favored the sunitinib-only group

compared to CN + sunitinib (18.4 *vs.* 13.9 months), though not statistically significant. Similarly, this study suffered from very slow accrual rate. Nevertheless, it demonstrated non-inferiority in the intention-to-treat population for sunitinib-only treatment. The results should be interpreted with caution as a significant portion of patients were in the MSKCC poor-risk group: 44.4% in the nephrectomy-sunitinib group and 41.5% in the sunitinib-alone group. This risk group is typically at a high risk for postoperative death and thus any delay in systemic therapy could undermine survival. Another prospective study is currently underway evaluating OS in mRCC treated with TKI with our without surgery. Biological correlates will also be collected and will shed some light on potential mechanisms of resistance or response to therapy (8).

So far, emerging evidence has substantiated a more limited role for CN mandating careful patient selection. Unfortunately, well-known prognostic models were initially developed in the cytokine and targeted therapy era and may not be applicable in today's immunotherapy landscape (9). Both MSKCC and IMDC models have been widely used in the decision-making process of offering CN although they lack perioperative predictive value after CN. Besides prognostic models, other independent risk factors have been explored. In a systematic review of the literature, Bhindi *et al.* reported factors most consistent with decreased OS such as progression on presurgical systemic therapy, high C-reactive protein, high neutrophil-lymphocyte ratio, poor IMDC/MSKCC risk classification, sarcomatoid differentiation, and poor performance status (10). On the other hand, good performance status and good/intermediate IMDC/MSKCC risk classification were most consistently predictive of OS benefit with CN. Similarly, other systematic reviews have demonstrated the survival advantage of CN in patients with clear cell and non-clear cell histologies, notwithstanding those with brain metastasis, poor performance status, or poor risk classification (11). Ultimately, both IMDC and MSKCC models can only be considered prognostic and not predictive of outcomes after surgery, in which case this predictive preoperative model estimating an individual's probability of death at 6-month can be a valuable tool in patient counseling and expectations prior to CN.

Although CARMENA and SURTIME have begun a paradigm shift in the management of patients with mRCC, dismissing CN altogether would be premature as there are still a subset of patients who benefit from surgical resection (12). At this point in time, the literature clearly shows poor risk patients should not undergo CN, while those with intermediate risk who require systemic therapy benefit from immediate treatment. In the future, the role of CN will need to be re-evaluated in the checkpoint inhibitor era especially for intermediate and poor risk patients. With available risk stratification models for perioperative outcomes, clinicians may better define patients unlikely to benefit from surgery. It is reasonable to offer upfront CN to patients with good performance status, a high-volume renal tumor and a low metastatic burden. CN may potentially be considered in patients with favorable response after initial systemic therapy or for symptom palliation. The authors should be congratulated for their effort in contributing these predictive models which can be valuable resources in terms of patient counseling and treatment planning.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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