Editorial Commentary

Cytoreductive nephrectomy in patients with metastatic renal cell carcinoma and venous thrombus—trends and effect on overall survival

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Cytoreductive nephrectomy (CN) combined with cytokine therapy was once the standard of care for metastatic renal cell carcinoma (mRCC) (1,2). In the past decade, there have been a myriad of novel therapies in metastatic renal cell carcinoma treatments including targeted therapies such as tyrosine kinase inhibitors (TKIs), mammalian target or rapamycin (mTOR) inhibitors, VEGF inhibitors, and PD-1 inhibitors. Additionally, two recent phase 3 clinical trials, the Clinical Trial to Assess the Importance of Nephrectomy (CARMENA) and the Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients with Kidney Cancer (SURTIME), have made the role of cytoreductive nephrectomy controversial. The CARMENA trial, which randomized patients with mRCC to CN plus sunitinib or to receive sunitinib alone, concluded that Sunitinib alone was not inferior to nephrectomy in patients with mRCC having intermediate or poor risk disease (3). Similarly, the SURTIME trial randomized mRCC patients to CN followed by sunitinib therapy *vs.* treatment with 3 cycles of neoadjuvant sunitinib followed by CN followed by adjuvant sunitinib (4). SURTIME concluded that deferred CN did not improve 28-week progression free rate and that overall survival was higher without Sunitinib (4). Despite the findings and limitations of both CARMENA and SURTIME, both trials confirm the need for careful patient selection for CN. Presently, there is a paucity of data on patients with mRCC and tumor thrombus as SWOG 8949 did not include all levels of tumor thrombus (5).

Lenis *et al.* provide a more definitive answer as to which patients are ideal candidates for CN. The authors successfully compare outcomes of CN *vs.* no CN by querying the National Cancer Database from 2010 to 2013 with mRCC. In particular, Lenis *et al.* focused on patients with tumor thrombi and stratified patients into renal vein thrombus, infradiaphragmatic IVC thrombus, and supradiaphragmatic IVC thrombus. It is evident from their study that tumor thrombi are common in the setting of mRCC, as thrombi were present in 28.7% of cases. Patients with tumor thrombi underwent CN more often, however, overall survival (OS) depended on the level of tumor thrombus (6). It will be crucial when selecting ideal candidates for CN to understand that supradiaphragmatic IVC thrombus in the setting of mRCC will not benefit from surgical intervention. In the era of immunotherapy, CN still plays a role and can offer an OS benefit in mRCC patients with no thrombus, renal vein thrombus, or infradiaphragmatic thrombus (6).

This study by Lenis *et al.* is not, however, without its limitations. Any large retrospective database may be prone to selection bias. Additionally, it is also not documented what therapy the no CN arm of the study received, especially in the current era of immunotherapy.

CN is a major surgical procedure and it is paramount to avoid unnecessary morbidity in patients who would benefit

more from systemic targeted therapy. Furthermore, CN would cause a lapse in the delivery of targeted therapies which could worsen OS. Thus, patient selection is key. Post CARMENA and SURTIME, populations that benefit from systemic therapy are better defined; however, there are still populations that were underrepresented in these trials (2). Additional prospective studies will be necessary to stratify patients on their risk and individualize their treatment. Populations that may benefit the most from CN include younger patients with minimal comorbidities and the populations demonstrated by Lenis *et al.*, mRCC patients with no thrombus, renal vein thrombus, or infradiaphragmatic thrombus (2-6).

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Footnote

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

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