



Nephrectomy in metastatic renal cell carcinoma with venous thrombus: more thrombus equals less benefit?

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Complete surgical resection of the tumor by means of either partial or total nephrectomy is the only curative therapy for localized renal cell carcinoma (RCC). However, as we move into the metastatic setting (mRCC), nephrectomy was historically limited to a palliative role, in efforts to control pain, hematuria or paraneoplastic syndromes. This changed in 2001 when two randomized trials comparing interferon alone versus nephrectomy followed by interferon showed an overall survival (OS) advantage for the surgery arm (1,2) which led to a significant increase in the proportion of mRCC patients undergoing nephrectomy, reaching almost 40% of cases by 2004 (3). Fast forward to 2018, the first prospective study on nephrectomy in the targeted therapy era becomes available, showing that nephrectomy does not increase OS in this setting, as systemic treatment with sunitinib resulted in non-inferior OS compared to surgery followed by sunitinib in the CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) trial (4).

When trying to understand these differing results, we must broadly consider two very significant factors. First, the increasing efficacy of systemic therapy, and thus the potential impact of delaying systemic treatment to perform the surgical procedure and achieve full patient recovery. The second factor is patient selection. It's generally accepted that patients with high volume of metastatic disease, poor performance status and advanced age are not optimal candidates for surgery. But besides this broad generalization, we still lack data to clearly define which

patients may benefit from removing the primary tumor.

In this context, Lenis *et al.* (5) have published an interesting analysis on the clinical results of nephrectomy for the subset of patients diagnosed with mRCC who have intraluminal extension of the tumor into the venous circulation, or “tumor thrombi”. To do this they reviewed medical records from the National Cancer Database (NCDB), a large registry covering more than 1,500 centers in the United States, between years 2010 and 2013. They found 8,134 patients diagnosed with mRCC, out of which 71.3% had no thrombus and 28.6% did, distributed as follows: 22.4%, 4.7% and 1.5% had renal vein, infradiaphragmatic and supradiaphragmatic inferior vena cava (IVC) thrombus, respectively. Nephrectomy was performed in 65.1% of patients overall, which is higher than reported from the SEER (Surveillance, Epidemiology, and End Results) database (3). They found patients with a tumor thrombus were more likely to undergo nephrectomy than those who did not have thrombus (78.6% *vs.* 59.7%, $P < 0.01$). They also describe several factors associated with a decreased likelihood of nephrectomy: supradiaphragmatic IVC, age over 65 years, black race and Medicaid or no health insurance. They also analyzed the effect of nephrectomy on survival, showing a positive effect for surgery in those patients with renal or infradiaphragmatic IVC thrombus, but not for those with supradiaphragmatic extension.

The article has several strong points, such as the large

patient population, the ability to analyze clinical and demographic factors associated with nephrectomy, and the ability to separate different patient populations according to thrombus level. Its main limitation as a retrospective study is patient selection bias; patients undergoing surgery in this study were younger, healthier and had lower tumor burden, all of which may confound the survival analysis, even when comparing to a matching cohort. Another limitation is the lack of information regarding systemic treatments, they do describe that 39.7% of patients did not receive any systemic therapy, which is surprising for metastatic disease in the period in which the study was performed; this may reflect patient ineligibility due to bad performance status, or a medication access problem, among others.

In light of these results, should we consider nephrectomy a standard of care for patients with venous thrombus? Once again, patient selection is of primordial importance. As shown in this study, we need to evaluate the extension of the thrombus, as patients with supradiaphragmatic thrombus do not seem to benefit, which is consistent with another large retrospective analysis in the same setting by Abel *et al.* (6). Thrombus extension may reasonably reflect the worse prognosis associated with higher tumor burden: higher tumor size means less benefit, more metastatic sites means less benefit, and more extensive thrombus follows the same line. Of course, we also need to consider general factors for surgical morbidity such as age, performance status and medical comorbidities, which is highlighted by CARMENA results (4).

Looking forward, prospective studies of nephrectomy in the era of checkpoint inhibitors will add information about the impact of this strategy. There are also ongoing phase II studies looking into neoadjuvant therapies in patients with tumor thrombus using axitinib to reduce the extension of the thrombus (7) and stereotactic body radiotherapy to reduce local recurrences, lower the likelihood of embolic complications and systemic metastasis (8).

This publication by Lenis *et al.* shows nephrectomy is a valid alternative when facing a patient with mRCC and venous thrombus, however retrospective evidence in this scenario is another piece in the puzzle, multidisciplinary discussion and clinical judgment will probably remain the best approach to decide when to perform this procedure in each particular case.

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Footnotes

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