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Open to Debate – Referee

Partial Nephrectomy for Metastatic Renal Cell Carcinoma: Referee

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The past decade has been characterized by profound evolution in the treatment of renal cell carcinoma (RCC) and the role of cytoreductive nephrectomy has been extensively discussed in light of new evidence on systemic treatment. Although the release of results from the CARMENA trial challenged the role of cytoreductive nephrectomy in metastatic RCC (mRCC), it is undeniable that the trial has been criticized for several meaningful selection biases. Therefore, the trial did not reduce the value of cytoreductive nephrectomy in the setting of favorable and select intermediate-risk mRCC [1,2]. In this scenario, the adoption of cytoreductive partial nephrectomy (PN) in mRCC was the subject of heated discussion in recent years. If, on the one hand, it has been extensively and firmly demonstrated that renal function preservation exerts a beneficial effect on cardiovascular morbidity and all-cause mortality in localized RCC [3–5], it is still controversial whether PN may confer a survival benefit as compared to radical nephrectomy (RN) also in the mRCC setting. Indeed, one might argue that PN may expose the patients to a non-negligible risk of undermining cancer control. Moreover, the risk for

increased perioperative complications might be equally disturbing. Is that so?

In this Open Debate Series, each of the author groups has provided compelling evidence to support their point of view [6,7]. The aim of our arbitration is to balance the arguments from both sides in an attempt to draw final recommendations and valuable take home messages. One premise is key. As the aim of new targeted and combination therapies is to extend the life expectancy of patients with mRCC, one might suppose that an ideal surgical treatment should try to mimic this goal, thus focusing on renal function preservation in an attempt to attenuate the risk of significant chronic kidney disease, limit cardiovascular side effects, and improve the ability of patients to tolerate future treatment lines. The point is, given the relatively limited life expectancy for a non-negligible percentage of patients with mRCC, even in spite of the improved outcomes secondary to the introduction of immune check point inhibitors (ICIs), would you still justify PN for kidney function preservation?

In fact, only a few studies have explored the effects of cytoreductive PN on survival outcomes in comparison to RN. Capitanio et al [8] conducted an interesting analysis using the Surveillance, Epidemiology and End Results (SEER) database and found no difference in cancer-specific survival between the two treatment modalities. These results are in conflict with those reported by Hellenthal and coworkers [9], who evaluated almost the same period from the SEER database and concluded that patients treated with PN were nearly 50% less likely to die from RCC than those undergoing RN. As with any study using the SEER database, it should be kept in mind that retrospective analyses have certain limitations. Thus, it is difficult to provide a comprehensive and unique explanation for such controversial data, although

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the discrepancy may be secondary to smaller numbers in the study by Capitanio and coworkers. Moreover, it should be noted that only 1% of patients included with a primary tumor size ≥ 7 cm underwent cytoreductive PN in the study by Hellenthal et al. Hence, the smaller tumor size in the cytoreductive PN subgroup may have meaningfully influenced survival rates, and could be partly responsible for the survival benefit observed in the PN group. On the basis of these findings, it would appear that PN does not have a detrimental impact on disease-specific survival in comparison to RN. Recent evidence even suggested that cytoreductive PN might be beneficial in terms of other-cause mortality [10]. Nonetheless, does this benefit apply to all mRCC scenarios? Lenis et al [11] tried to provide an answer to this unsolved question. Indeed, as stated above, previous retrospective studies were undermined by meaningful treatment selection bias, with cytoreductive PN mostly achieved in cases with smaller tumors. To provide higher-quality data, the authors performed a matched pair analysis demonstrating that patients treated with cytoreductive PN had a 19% lower risk of dying from any cause than those who received RN. However, when the data were stratified by tumor size, this benefit only applied to cases with a primary tumor < 4 cm [11].

In addition, the clinical lymph node status and tumor burden are two further baseline features that need to be considered. A recent retrospective analysis confirmed a substantial survival advantage of cytoreductive PN over RN. Nonetheless, subgroup analysis demonstrated that the benefit was limited to patients presenting with a tumor size ≤ 7 cm, N0 stage, and isolated distant metastasis, while higher tumor stage and N1 status were associated with even worse survival outcomes after cytoreductive PN [12]. Hence, once again, patient selection appears to be pivotal, with PN potentially recommendable only to the few mRCC cases with a cT1 primary tumor and oligometastatic disease.

In this context, several cornerstones and technical nuances should be kept in mind. Appropriate timing for surgery may represent a further challenge, since cytoreductive PN can be performed either in the setting of newly diagnosed mRCC or after systemic therapy administration in the event of a partial or complete response. Although downsizing can be expected with ICI combination therapy, deferred PN may eventually be even more challenging in terms of tumor isolation and hilar dissection due to a potential peripheral tissue reaction ultimately leading to scar tissue formation and fibrosis. Likewise, upfront cytoreductive PN can also be a demanding task. mRCC with a primary renal mass amenable to nephron-sparing surgery cannot be expected to present the same surgical difficulty as a localized renal mass, even if the two masses have comparable tumor size, localization, and nephrometry scores. Metastatic renal tumors generally have an infiltrative growth pattern, with very blurred limits at the parenchymal level, and a significantly higher tendency to vascular infiltration, so they often require wide resection rather than tumor enucleation. This issue is key, since recent evidence pointed to resection technique as being a driver of local oncological control, volume of vascularized parenchyma preserved, and postoperative renal function [13]. However, such concepts cannot be automatically translated to the mRCC setting.

As the treatment paradigms for mRCC have significantly evolved, proper integration of cytoreductive PN into current

treatment strategies remains a key unmet clinical need. Currently, the indication for cytoreductive PN remains undefined and is mainly set by the individual surgeon's expertise and preference. Although tumor size per se is not a limit for nephron-sparing surgery, careful evaluation of the tumor burden and recognition of conditions that require radical treatment are of utmost importance to avoid exposing patients to potentially unnecessary risks or compromising oncological radicality. However, if grounded on proper patient selection, it seems that cytoreductive PN might achieve equivalent cancer control to RN, with the additional benefit of better preservation of renal function and greater patient ability to tolerate future systemic therapies. However, patient selection is key. Taking all these observations together, it is evident that only a few select cases might be amenable to cytoreductive PN, mostly tumors of cT1 stage and a limited metastatic tumor burden. Randomized clinical trials in high-volume centers with longstanding experience in RCC treatment are warranted to evaluate the best timing for cytoreductive PN and to better assess its potential benefits for survival outcomes.

Conflicts of interest: The authors have nothing to disclose.

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