Editorial Commentary

Re: Comparison of immediate *vs.* deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: the SURTIME randomized clinical trial

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Renal cell carcinoma (RCC) accounts for 3% of adult solid malignant tumors worldwide and is the third leading cause of mortality amongst urologic malignancies (1). Nearly 20% of patients diagnosed with RCC suffer from metastatic disease by the time of diagnosis and up to 40% of patients treated with radical nephrectomy for localized RCC will develop a metastatic disease (2). The last decade has been characterized by a profound evolution in the treatment of RCC due to the improvement of the understanding of biomarkers driving cancer growth. In this context, the role of cytoreductive nephrectomy (CN) has been extensively discussed in the light of the new evidence on systemic treatment.

Historically, in the pre-targeted therapy era, patients presenting with metastatic RCC (mRCC) showed a poor prognosis with an estimated 5-year overall survival (OS) of <5%. CN has been reinvigorated by the advent of cytokines, such as IFN-α, rIL-2, and combinations of these agents that showed objective clinical response in nearly 25% of the patients (3). In the pre-targeted therapy era, a combined analysis of two prospective randomized trials showed that patients treated with CN upfront to interferon alpha had a 31% decrease in cancer mortality and a 5.8-month increase in OS compared to those treated with interferon alpha alone (4). The exact pathophysiological mechanisms explaining the rationale of CN in mRCC are still unclear. The rationale of CN is the significant decrease in disease load and eventual spread of new metastasis: CN might be able to block the exogenous growth inhibitory and angiogenic factors produced by the primitive tumor and relieves immunological suppression with a positive effect on residual disease (5). Furthermore, a review of patient data from the surgical arm of one of the overmentioned trials suggested that kidney removal might result in an increase of azotemia and consequential low-grade systemic acidosis disrupting the tumor microenvironment and halting metastatic growth (6).

The understanding of the molecular bases of the VEGF and mTOR pathways in RCC led to the introduction of several novel target therapies showing longer progression-free survival (PFS) and higher response rate compared to cytokines (7,8). The CARMENA (Cancer du Rein Métastatique Néphrectomie et Antiangiogéniques) and SURTIME (Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer) trials are the two prospective studies on which the scientific community hope to draw the fate of CN in the management of patients with indication for targeted therapy. The CARMENA trial showed in the intention-to-treat analysis that sunitinib alone was noninferior to CN followed by sunitinib in terms of OS [hazard ratio (HR): 0.89, 95% CI: 0.71–1.10, 95% CI upper boundary for non-inferiority: ≤1.20] (9). Indeed, the Authors should be commended for their efforts as they were able to demonstrate with the higher level of evidence that sunitinib alone is not inferior to the combination therapy. However, these results could be influenced by: (I) the long accrual time possibly due to the unwilling to randomize patients with intermediate risk or large primary and small metastatic tumors; (II) the high percentage of patients who received nephrectomy in the

sunitinib-alone group, of which 17% receiving CN for local symptoms compared to 5% observed in the national inpatient sample data; (III) the non-negligible number of patients who did not receive sunitinib after CN; and (IV) the high number of poor-risk patients registered in the trial compared to those observed in the daily clinical practice (10). Indeed, the CARMENA trial emphasized the importance of the selection of patients undergoing CN on the basis of preoperative risk characteristics, tumor resectability and health status (11).

The National Cancer Research Institute Renal Clinical Studies Group/Wales Cancer Trial Unit (United Kingdom), and the Canadian Uro-Oncology Group jointly conducted the SURTIME trial, a randomized clinical trial comparing the upfront versus deferred treatment of CN in patients with synchronous mRCC undergoing sunitinib. Patients with previously untreated clear cell mRCC, with a resectable asymptomatic primary tumor and required therapy with sunitinib were included. Moreover, a World Health Organization (WHO) performance status of 0 or 1, a life expectancy greater than 3 months, and 3 or fewer surgical risk factors (12) were necessary eligibility criteria. PFS was the primary endpoint. However, due to poor accrual (99 versus a planned sample size of 458 patients in 5.7 years from 2010), it was decided to report the intention-to-treat progression-free rate at week 28 as primary outcome, which required 98 patients, instead of median PFS, which required 380 events to detect a 3-month increase (HR =0.75) compared to deferred CN with a 2-sided 5% log-rank test at 80% power. Further amendments on inclusion criteria and opening of additional sites were also undertaken previously to save the trial. In the immediate and deferred CN arm, 40/50 (80%) and 48/49 (98%) patients received sunitinib, respectively. No significant difference was observed between the immediate and the deferred CN arm in terms of progression-free rate (42% *vs.* 43%, respectively; P=0.61). The intention-to-treat OS was significantly higher in the deferred compared to the immediate CN arm (HR: 0.57, 95% CI: 0.34–0.95; P=0.03), with a median OS of 32.4 months in the deferred CN arm and of 15.0 months in the immediate CN arm. Indeed, the reduced accrual in this study, mainly affected by the unavailability of 2 European countries to participate to the study due to regulatory decisions and by the use of surgical risk factors for eligibility rather than WHO performance status, make these results being only exploratory. However, the restricted criteria for patients' inclusion led to a predominant selection of patients with predominantly intermediate risk and with the most suitable characteristics to undergo surgery. On the one hand, these results supported the finding from CARMENA that immediate CN does not provide an additional benefit in patients requiring sunitinib in patients with intermediate-high risk. On the other hand, these results suggest that deferred CN is a valid treatment for patients with intermediate-risk disease and with general clinical conditions at baseline amenable to undergo surgery.

Despite these findings, the clinical relevance of both CARMENA and SURTIME trials is limited by the fact that sunitinib is no longer the standard of care for mRCC, as it has been demonstrated the superiority of nivolumab and ipilimumab over sunitinib in terms of survival and quality of life in patients with intermediate- and poor-risk mRCC (13). CN likely still remains selective to patients with non-clear histology. Nevertheless the interim data of the KEYNOTE-427 (a phase 2 clinical trial) showed encouraging results for the check-point inhibition also in this setting (14) and it would be necessary to define the time setting of CN if these results will be demonstrated also in phase 3 randomized clinical trials.

CN is still needed in those patients requiring palliative treatment (i.e., for local pain or hematuria). Finally, patients with good performance status and low-volume metastatic disease may still benefit of CN. As such, the key question is 'which', and not 'if', patients can benefit from CN (15). In this view, both CARMENA and SURTIME do not clarify the potential benefit of CN in those patients for whom CN is most commonly considered. A deeper understanding and a systematic phenotyping of the genome characteristics of RCC may drive the clinical-decision making basing on the predicted risk of tumor metastasis spread and mortality. As the treatment paradigms for mRCC have significantly evolved since the introduction of VEGF inhibitors and combination therapies involving checkpoint inhibitors may become the next standard of care (16), proper integration of CN into current treatment strategies for metastatic RCC remains a key unmet clinical need. In light of the recent updated European Association of Urology (EAU) guidelines for CN in patients with synchronous metastatic clear-cell RCC (17) and of the evidence showing an association between higher facility volume and survival in patients being treated for mRCC (18,19), future clinical trials should evaluate the potential benefit and best timing of CN and surgical metastasectomy (20) in the setting of multidisciplinary teams at high-volume centres with longstanding experience in the treatment of kidney cancer.

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Footnote

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