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Benefit of cytoreductive nephrectomy in metastatic RCC: do we learn from retrospective studies and small prospective studies?

The benefit of cytoreductive nephrectomy in metastatic renal cell carcinoma (mRCC) has been demonstrated in patients treated with interferon [1, 2]. Because of that demonstration, cytoreductive nephrectomy has become the standard of care in most institutions. However, one should realize that the benefit has been demonstrated mainly in patients with good performance status (PS) and lung metastases, although in clinical practice, urologists are now used to remove the primary tumor on every mRCC. Whether this statement remains true in the era of targeted therapy is controversial, and two large randomized trials have been launched to answer this question, the Carmena trial (NCT00930033) and the European Organisation for Research and Treatment of Cancer (EORTC) trial (NCT01099423). Both trials ask the question of cytoreductive nephrectomy in mRCC. The Carmena trial will compare nephrectomy followed by sunitinib versus sunitinib alone, whereas the EORTC trial will compare upfront or delayed nephrectomy with sunitinib. In this issue of *Annals of Oncology*, two articles present data, which seem to approach this question, but may induce misleading interpretation.

The MD Anderson (MDA) experience with targeted agents and the primary tumor *in situ* is very interesting to analyze [3]. In this large retrospective study, 188 consecutive patients who received targeted therapy and never underwent cytoreductive nephrectomy are reported. The median survival for this group is 10.4 months, far beyond the observed survivals in the large phase III of sunitinib, bevacizumab, or recently pazopanib, which range from 22 to 26 months. Although the authors recognize the limitations of this study, and the benefit of targeted therapy in mRCC without cytoreductive nephrectomy, they conclude that this study 'may aid in the design of randomized clinical trials to determine the role of cytoreductive nephrectomy in the era of targeted therapy'. I strongly disagree with this conclusion. This study is not only biased by the retrospective aspect of the study, the single-center experience, but also by the reasons recorded as noneligibility criteria for surgery. Obviously, the size and local extent of the tumor were not the reasons in the majority of patients, with 58% of the tumor being T1-2 and 3a, which in the hands of the MDA surgeons will never be a reason for not carrying out nephrectomy. The reasons for this noneligibility, drawn from Table 1, were poor PS (35.2%), brain metastases (11.7%), and likely progression on treatment started as neoadjuvant therapy. In none of these patients, cytoreductive nephrectomy was indicated in the basis of the randomized studies [1, 2], and probably all these patients have poor prognosis. As did the authors, I would conclude that this study strongly suggests that targeted therapy has activity in mRCC without cytoreductive nephrectomy but, also in opposite to them, that the data do not help to design randomized trials because most of the patients analyzed here are not the patients for which the question of cytoreductive nephrectomy is of value. Furthermore, the survival observed in this group of patients should not be compared with any of the pivotal phase III of targeted therapy in mRCC because the patient populations are dramatically different.

A second article in this issue indirectly raises the question of cytoreductive nephrectomy [4]. This article reports the safety and efficacy of upfront sunitinib before nephrectomy. Two separate studies are reported together, as 'a prelude to the randomised trial investigating interval nephrectomy'. Overall, 52 patients (19 and 33 in each study) received two or three cycles of sunitinib before nephrectomy, and surgery was carried out either 1 or 14 days after treatment interruption. I strongly disagree with the authors that 'this allows assessment of the optimal number of cycles prior to surgery and optimal treatment free interval'. Thus, the conclusion that 'only one day off treatment is optimal' is highly questionable. Similarly, the safety of such neoadjuvant approach is uncertain, with 30% of the patients finally not operated and 27% of the patients with surgical complications. Based on these data, one should caution a large phase III study comparing initial with delayed nephrectomy as planned in the EORTC study. Obviously, the results might be biased if 30% (or more in a multicentric setting) of the patients finally do not undergo nephrectomy.

These two studies provide to the readers some interesting information on the efficacy of targeted agents in mRCC patients with primary tumor *in situ*. However, the conclusions from both studies tend to suggest that nephrectomy should be carried out in this patient population, even though some retrospective studies also suggest that efficacy of tyrosine kinase inibitors is greater in nephrectomized mRCC [5]. Biases are very common in retrospective studies, and one should remember that there is currently no evidence that this statement is true, and I strongly support to first demonstrate, in a well-designed randomized trial, whether nephrectomy should remain the standard of care in mRCC with primary tumor *in situ*. This question is in my view the most pertinent one, and hopefully, the Carmena trial will answer it.

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disclosure

The authors declare no conflict of interest.

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