



## Platinum Priority – Editorial and Reply from Authors

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# Metastatic Renal Cell Carcinoma: An Invincible Enemy?

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Renal cell carcinoma (RCC) remains an important cause of cancer death, with a worldwide annual increase of 1.5–5.9% and an estimated 58 240 new cases and approximately 13 040 deaths in 2010 [1].

Despite the widespread application of cross-sectional imaging, approximately 30% of patients with RCC continue to present with metastases [2], whereas several studies report that between 14% and 29% of patients who are treated for clinically localized RCC subsequently develop recurrence of the disease [3,4]. Patients with untreated metastatic disease have a poor prognosis, with a 5-yr survival rate of <10% [2].

Metastatic RCC (mRCC) presents a particular therapeutic challenge for clinicians because of the resistance of kidney cancer to chemotherapy or radiotherapy and the limited response to immunotherapy [3]. Recently, the multitargeted tyrosine kinase inhibitors sunitinib and sorafenib have been assessed for patients with metastatic disease in randomized phase 3 clinical trials [5,6]. However, although an objective response rate of 47% was noted with sunitinib therapy, the majority of patients experienced partial responses or stabilization of disease, and only 11 of 375 patients (3%) demonstrated a complete response to treatment [5]. Moreover, although outcomes were improved significantly compared with patients who received interferon, the median overall survival for patients with mRCC who received sunitinib was still poor, at only slightly >2 yr (26.4 mo) [5].

From this perspective, the role of surgery and metastasectomy represents an important treatment for mRCC. Five-year survival rates of 30–45% have been reported in patients with mRCC after metastasectomy; in fact, the complete resection of all metastases has been associated with a two-fold decrease in the risk of death [2].

An interval from RCC diagnosis to occurrence of metastases >1 yr, a unique metastatic site, and age

<60 yr have been identified as favorable survival predictive factors following RCC metastases resection. In cases of pulmonary resection, delay from RCC diagnosis to metastases occurrence, complete resection, number of nodules to remove, and metastatic nodule size appear to be major prognostic factors. The 5-yr survival rate seems to be superior in cases of pulmonary resection (54%) than in cases of brain resection (18%). Pancreatic metastases are likely to occur late in the natural history of the metastatic disease and seem to have a good prognosis when surgical resection is feasible [7]. Nevertheless, if the efficacy of resection for RCC metastases has been demonstrated in the presence of solitary metastasis and/or disease in the lungs only [2], the utility of metastasectomy in patients with multiple metastases has been less well defined.

Recently, Alt et al. [8] investigated the survival of patients with multiple metastases from RCC who underwent complete surgical metastasectomy. The authors considered the importance of metastatic features, including disease site, timing and number of disease sites, and the impact of patient performance status, on outcomes after resection. Of 887 patients, 125 (14%) underwent complete surgical resection of all metastases. Complete metastasectomy was associated with a significant prolongation of median cancer-specific survival (CSS) (4.8 yr vs 1.3 yr;  $p < 0.001$ ). Patients who had lung-only metastases had a 5-yr CSS rate of 73.6% with complete resection versus 19% without complete resection. A survival advantage for complete metastasectomy also was observed among patients with multiple, non-lung-only metastases, who had a 5-yr CSS rate of 32.5% with complete resection versus 12.4% without complete resection ( $p < 0.001$ ). Complete resection remained predictive of improved CSS for patients who had three or more metastatic lesions and for patients who had synchronous and asynchronous

multiple metastases. According to their results, the authors could demonstrate that complete resection of multiple RCC metastases was associated with long-term survival and that it had to be considered, when technically feasible, in appropriate surgical candidates.

In this issue of *European Urology*, Tosco et al. [9] try to determine the impact of clinical prognostic factors on survival rate in patients affected by mRCC and suitable for resection of metastasis. Based on these factors, the authors elaborate a novel system, the Leuven-Udine classification, to predict the outcomes of surgically treated mRCC. They propose a stratification of patients according to their prognosis to create prognostic subgroups to be applied in the management of mRCC. The resulting 5-yr CSS rates were different for metastasis at different sites, with better outcomes for lung metastases, confirming the actual results reported in the literature [2,7,8]. Similarly, the authors could demonstrate improved CSS rates in patients with complete metastasectomy compared with patients with a single resection [9].

The outcomes after surgical resection for RCC metastases have been evaluated previously, and a survival benefit from complete resection was noted. For example, Kavolius et al. [10] reported a 5-yr overall survival rate of 44% in 141 patients who underwent complete surgical resection of RCC metastases compared with a 14% survival rate in patients who underwent incomplete surgery and an 11% survival rate in patients who were treated nonoperatively.

The most interesting and innovative aspect of the study performed by Tosco et al. [9] is represented by the elaboration of four demarcated prognostic subgroups (which the authors named Leuven-Udine prognostic groups) based on clinical variables that were shown to be independent predictors of survival. The importance of the Leuven-Udine classification is represented by the possibility of using it to stratify patients with mRCC at metastases outbreak, with the further advantage of providing CSS estimates for all patients affected by mRCC, not only for those with pulmonary metastases. In contrast, we have to consider that, in the future, the concept of tumor metastases resection could be revisited in the era of targeted therapy. We can hypothesize an increasing role of the multimodality treatment, combining surgical and medical therapy, and this would require the elaboration of new prognostic systems to predict survival for mRCC. Although the retrospective design and the inclusion of different metastatic sites represent some

important limitations that have been acknowledged by the same authors, this study deals with a disease that represents an invincible enemy, and we are still searching the appropriate weapons to oppose or defeat it.

Surgery for metastases still represents a very effective therapy for mRCC. Nevertheless, the battle has not concluded. Continuous research as well as the development of new strategies and tools, such as the Leuven-Udine classification, can support us on this long path and help us in the difficult treatment decision-making process for our patients affected by this life-threatening disease.

**Conflicts of interest:** The author has nothing to disclose.

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