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## Platinum Priority – Editorial

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# Morbidity of Metastasectomy for Renal Cell Carcinoma: Emerging Evidence and Unmet Needs

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Metastatic renal cell carcinoma (mRCC) represents a complex clinical scenario owing to the heterogeneity of baseline patient and disease characteristics [1].

The dynamic changing paradigm induced by the introduction of targeted therapies has revolutionized the treatment philosophy, setting new challenges regarding the benefit and timing of cytoreductive nephrectomy and surgical metastasectomy (SM) in the context of multimodal approaches [2–4]. Current European Association of Urology (EAU) and European Society of Medical Oncology (ESMO) guidelines consistently state that no general recommendations can be made as to whether a patient should be referred for SM [5,6]. Nevertheless, the removal of all metastatic lesions, when technically feasible and clinically appropriate, provides the only potentially curative treatment for mRCC patients [3]. Indeed, a recent systemic review and meta-analysis showed that despite the low quality of evidence available, median overall survival ranged between 36.5 and 142 mo after complete SM, compared to 8.4–27 mo after incomplete SM. Incomplete SM cases had greater adjusted overall mortality, with a hazard ratio of 2.37 (95% confidence interval 2.03–2.87;  $p < 0.001$ ) [1]. The results of a previous systematic review also pointed towards a benefit of complete SM in terms of overall and cancer-specific survival, despite the substantial risk of selection bias and confounding in the studies included [3].

With all of this acknowledged, a relevant question arises. What is the price to pay for SM in mRCC patients? Assessing the morbidity of SM plays a key role in decision-making and in defining the best balance between benefits and harms of surgery in this complex patient group from urological, oncological, and public health perspectives. Unfortunately,

this topic has not been sufficiently addressed by the literature to date, and represents a critical unmet need.

In this issue of *European Urology*, Meyer et al [7] describe in-hospital complication rates after SM in a contemporary cohort of patients with mRCC. Using the National Inpatient Sample (NIS) database, they identified 45 279 patients diagnosed with mRCC between 2000 and 2011. The SM rate was 2.4%. SM was predominantly performed for lung, bone, and liver lesions. Overall and major (Clavien III–IV) complications occurred in 45.7% and 25.1% of patients, respectively. The in-hospital mortality rate was 2.4%.

On univariate analysis, age and hepatic metastases (compared to any other site) were independent predictors of overall complications, while a high comorbidity burden was an independent predictor of major complications. The authors also found a significantly lower likelihood of overall complications among pulmonary resections (compared to any other site) and of major complications among patients with private insurance.

The authors should be commended for their valuable efforts in addressing a complex research need in the rapidly changing scenario of mRCC. As the NIS represents the largest publicly available all-payer inpatient health care database in the USA, a major strength of the study is the possibility to provide reliable estimates of national rates of in-hospital complications after SM for RCC. Thus, the study represents a pioneering first step towards a more comprehensive evidence-based definition of perioperative morbidity of SM (and its predictors), opening new perspectives and research opportunities.

However, caution is needed in clinical interpretation of the results of this study because of many concerns regarding

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the study design and the analyses presented. Patients with mRCC might not have been observed for a sufficient time period to see the occurrence of the outcome. Since the data capture only in-hospital events, morbidity occurring after discharge could have not been assessed. Therefore, the rate of complications might have been underestimated owing to their possible occurrence outside the observational period. Moreover, a second problem with this scenario is that the rate of overall and major complications might have been significantly different among patients undergoing SM for different types of metastases only because of different lengths of hospital stay. Furthermore, the lack of a clear operative definition of overall complications could have led to the inclusion of complications potentially not related to SM.

Beyond these considerations, a major limitation associated with the statistical design of the study is the lack of a multivariate analysis to assess potential associations between patient-, hospital-, and disease-related characteristics and the occurrence of in-hospital complications after SM, which could have led to potentially spurious associations as those obtained with univariate logistic regression analysis.

Finally, the results presented also have inherent limitations related to the data sources, such as lack of knowledge on timing of cytoreductive nephrectomy; administration (and timing) of possible targeted therapy; number, site, size, and anatomic accessibility of metastases; synchronous or metachronous interventions; number of metastases resected at the time of surgery; patient performance status at surgery and prognostic risk group; intention to treat (radical vs palliative); type of surgery; and completeness of SM. These limitations, alongside the aforementioned sources of bias, inherently prevent any definitive conclusion regarding the predictors of in-hospital morbidity after SM, and therefore any guidance for patient counseling. Thus, we feel that the conclusions of the authors regarding potential associations between the occurrence of complications and patient- or hospital-related characteristics might be potentially inconsistent given the strength of evidence provided.

However, Meyer and colleagues should be praised for their pioneering efforts to fill the gap in knowledge in this field, providing reliable data on the rate of complications

after SM for RCC, opening new perspectives, and outlining the current unmet research needs.

Our view is that current knowledge on the perioperative morbidity of SM is, as for many other topics in renal cancer research, just the tip of an iceberg that we are now starting to realize. Although many unmet needs are likely to remain unsolved owing to the inherent difficulties in conducting studies of a high level of evidence in the setting of this complex disease, the urology community should strive to improve the quality of future trial design [8,9] with the aim of providing more granular and clinically meaningful answers to the current controversies.

*Conflicts of interest:* The authors have nothing to disclose.

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