



When should surgery be used to supplement systemic therapy in metastatic renal cell cancer?

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Comment on: Le UT, Passlick B, Schmid S. Surgery for thoracic oligoprogression in metastatic renal cell cancer in the era of new systemic therapies. *J Thorac Dis* 2023;15:1133-41.

Keywords: Renal cell; metastasis; surgery

Submitted Mar 21, 2023. Accepted for publication May 26, 2023. Published online Jun 05, 2023.

doi: 10.21037/jtd-23-457

View this article at: <https://dx.doi.org/10.21037/jtd-23-457>

Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults in the US. Treatment of metastatic renal cell cancer depends on multiple factors including the subtype type of RCC (both pathologic and genetic), location and resectability of the metastases, and patient comorbid conditions (1). In addition, environmental factors such as the experience of the treating facility in which care was provided can affect outcomes (2). In treating metastatic RCC, a multidisciplinary approach is used and is comprised of chemotherapy, radiotherapy, immunotherapy, biologics, cryotherapy, other targeted therapy, and even sometimes surgery (3-6). While contrary to the management of metastatic cancer, including RCC, the question arises of whether surgery for metastatic renal cell cancer can provide some meaningful benefit in patient outcomes?

In the paper by Le and colleagues, the authors conclude that resection of oligoprogressive lesions, specifically of the lungs or thoracic cavity/chest wall, in systemically treated metastatic RCC may lead to sustained overall disease control (7). They suggest that with effective local surgical treatment the patient may be spared from side effects of systemic therapy. Other potential advantages of surgical resection include reserving future treatment options by not committing to a systemic modality and the possibility of histopathological and molecular/genetic analysis from resection, which may lead to further tailoring of treatment for these patients.

Indeed, metastasectomy may have advantages for a highly selected subset of patients. The same concept has been applied to other cancers in addition to RCC, including breast cancer, colon cancer, and melanoma. For example, Lasithiotakis *et al.* reported that complete resection of all melanoma metastases when feasible offered the high survival rates (8). Nesbit *et al.* reported that oligometastatic breast cancer may benefit from aggressive ablative therapy that included a combination of surgical excision, radiofrequency ablation, and hypofractionated image-guided radiotherapy (HIGRT). Relative to our discussion here, they concluded that HIGRT may synergize with immunotherapy by releasing cytokines that increase immune surveillance to help overcome resistance to therapy (9). With regard to colon cancer, Kang *et al.* presented evidence supporting metastasectomy in select patients using a retrospective cohort study queried from the National Cancer Database (NCDB), comprised of patients with stage IVA colon cancer with isolated liver metastasis. They found that the variables of higher income patients, those receiving chemotherapy, and those presenting to an academic/research hospital were more likely to undergo metastasectomy. Factors positively impacting survival included receipt of chemotherapy, presenting to an academic/research institution, and undergoing metastasectomy (10).

Findings such as these and those from Le *et al.* support the consideration of metastasectomy in highly selected

patients with various malignancies. Key to the success of metastasectomy has been the progression-free interval of the non-responding lesions. In general, the longer the duration of the progression-free interval, the more reasonable it is to consider surgery, which is consistent with the authors' cohort of patients, reporting a mean time from initial diagnosis to oligoprogressive disease of 65 months.

Certainly, there are limitations to this study, which the authors acknowledge. The small cohort of ten patients is insufficient to endorse widespread conclusions. Because there is a male predominance in the study cohort (8 male and 2 female), the generalizability of results is also limited. In addition, lifestyle and comorbid data such as obesity and hypertension would be useful in the analysis of the study conclusions, as these factors are known to have significant impact on the outcome of the disease (11,12). Lastly, while this study was quite comprehensive in the treatment history and course of progression, little is known about the genetic/molecular profiles of these patients. Responses to the different systemic therapies [tyrosine kinase inhibitor (TKI), mammalian target of rapamycin (mTOR), etc.] that were used may be related to known or unknown RCC biomarkers. Thus, it is very challenging to draw a general conclusion about the effectiveness of metastasectomy in the setting of all these systemic therapies. Perhaps in the future, computational solutions may provide more insight into the potential benefit of surgery in metastatic RCC (13).

Nonetheless, the authors provide a detailed analysis contributing to the ever-growing body of evidence that metastasectomy for metastatic RCC may be of benefit for highly selected patients. As new discoveries and tools take hold for RCC (and indeed many other cancers), the role of surgery in metastatic disease will hopefully become clearer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Thoracic Disease*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-457/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Hardman M, Gabriel E. When should surgery be used to supplement systemic therapy in metastatic renal cell cancer? *J Thorac Dis* 2023;15(6):2896-2898. doi: 10.21037/jtd-23-457