

Peer Review File

Article information: <http://dx.doi.org/10.21037/amj-20-79>.

Comments to the authors:

Thank you for the opportunity to review this peer-reviewed manuscript on the review of locally advanced renal cell carcinoma. I have minor suggestions for revisions.

Thank you so much for these thoughtful suggestions. They have been added to the paper.

Comment 1. In line 33 and 34, I would suggest that the authors re-phrase the comment about cytoreductive nephrectomy not being “mainstay of treatment.” I would simply state that cytoreductive nephrectomy remains uncertain in the current immunotherapy era in the sequence of treatment and may offer benefit in some patients with good-risk features.

Reply: Edits on lines 56-58.

Comment 2. I would suggest that the authors revise the introduction section by having the objectives put at the end (rather stating each after a couple of brief statements).

Reply: Edit on lines 58-61.

Comment 3. Please change the section of “Background and History” to Background. *Line 68.* In this section, I would also add a comment and citation of the incidence of locally advanced, lymphadenopathy and caval thrombus for renal cell carcinoma in this section. Between lines 97 – 108, I would also brief comments of immunotherapy and cite the highly relevant studies and rapidly changing clinical landscape for locally advanced renal cell carcinoma.

Reply: See lines 138-140

Comment 4. In the lymphadenectomy section (Lines 128 – 130), I would also add comments about the low event rate of lymph node metastasis as well as providing some information about the study (number enrolled and target, number of lymph node metastasis detected) as well as the primary outcome.

Reply: See lines 162-174

Comment 5. For the section about Cytoreductive nephrectomy (Line 196), I would change the title to the “Evolving role of cytoreductive nephrectomy.” This section also needs to be somewhat softened in the moving away from cytoreductive nephrectomy, since one could plausibly argue that this area remains uncertain. For example, there

are no clinical trials that inform the ideal treatment for good-risk metastatic RCC. Moreover, the CARMENA trial had significant heterogeneity in patients accrued, along with metastatic renal cell carcinoma presentation. For instance, patients with some isolated pulmonary metastasis or small pulmonary nodules where the bulk of the disease in kidney may in fact benefit from cytoreductive nephrectomy. Lastly, there needs to be a discussion about the possible postoperative complications after cytoreductive nephrectomy following systemic therapy. I would mention and highlight the recent study by Rousell et al (Rates and Predictors of Perioperative Complications in Cytoreductive Nephrectomy Eur Urol Onc 2020). I would also conclude this section by saying cytoreductive nephrectomy is evolving and the next areas of research should focus on identifying which clinical and pathologic factors that can better select patients for the sequence of multimodal therapy.

Reply: This comment was very informative—thank you. Please see highlighted text from lines 261-291 for edits.

Comment 6. In the Surgical Indications and Preoperative Considerations, the pre-operative renal artery embolization is an area of some controversy for locally advanced renal masses. I would suggest adding a statement that the clinical trial mentioned for pre-operative renal artery embolization was largely negative. Moreover, I would also mention this study showing renal artery embolization was largely negative (Subramanian et al. Utility of preoperative renal artery embolization for management of renal tumors with IVC thrombi. Urology 2009). I would also add a comment the possible complications of renal artery embolization as well.

Reply: Please see lines 387-395

Comment 7. In the section of the adrenalectomy (line 429), I would add a comment that routine adrenalectomy is not necessarily indicated. Furthermore, I would add a statement about indications of routine adrenalectomy being upper pole tumors or direct invasion as well as citing the following studies about the reasoning behind this:

- Weight et al. The role of adrenalectomy in renal carcinoma. Eur Urol 2016
- Weight et al. Routine adrenalectomy in patients with locally advanced renal cell carcinoma does not offer oncologic benefit and places a significant portion of patients at risk for an asynchronous metastasis in solitary adrenal gland. Eur Urol 2011.

Reply: Please see lines 496-500

Comment 8. In the tumor thrombus section, the authors need to add the need and indications for IVC graft placement (tumor thrombus invasion into IVC wall) and techniques.

Reply: See lines 522-526 and 712-734.