Peer Review File

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Reviewer Comments:

Comment 1: The title seems more one for a commentary rather than a literature review

Reply 1: Thank you for pointing this out. Originally, we were invited to submit a commentary but due to the restrictions on words and citations, we chose to transform the paper into a narrative review. We have made all the necessary changes to submit it as a narrative review, including changing the title (Page 1, Lines and 2) and adding a Methods section (Pages 4-5, Lines 77-90).

Changes in the text:
Page 1, Lines 1 and 2
Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma, the Ultimate Urologic 'Choosing Wisely' Campaign: a Narrative Review

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Comment 2: The abstract is not separated in the usual section of a scientific article.

Reply 2: In accordance with the Narrative Review Checklist Item Number 2, we have provided a an "unstructured summary" for our abstract.

Comment 3: The topic is not completely new and well-assessed by evidence. The authors should acknowledge what this review adds more to the previous ones.

Reply 3: This is an important point. We agree that while much of the narrative review focuses on the well-established idea that patient selection is key for CN, we describe multiple recently published studies supporting this theme, which prior reviews do not discuss. Moreover, our narrative review highlights the exciting new immuno-oncologic era with respect to CN, collating the most recent relevant trials. We have now made this explicit on Page 4, Lines 71-74.

Changes in the text:
Page 4, Lines 71-74
In this narrative review, we discuss how the role of CN has evolved alongside the development of TT, IO, and TT/IO combinations. We assess how to best utilize CN in contemporary practice with respect to timing of surgery and the use of systemic therapy, highlighting current clinical trials.

Comment 4: A section describing the methodology of the research and how and where the trials were selected should be included.

Reply 4: Thank you for pointing this out. We have added a Methods a section (Pages 4-5, Lines 77-90).

Changes in the text:
Pages 4-5, Lines 77-90
Methods

Using PubMed, Google Scholar, and Wiley Online Library, we performed a non-systematic review of articles between January 1993 and September 2020. Search terms included combinations of the following terms: "metastatic renal cell carcinoma", "cytoreductive nephrectomy", "systemic therapy", "targeted therapy", and "immunotherapy". Articles selected were required to be original articles published in English. News articles, editorials, and unpublished works were excluded.

Information on clinical trials was collected from www.clinicaltrials.gov, which was accessed in April 2020. Trials were selected by using combinations of the search terms "renal cell carcinoma", "systemic therapy", and "cytoreductive nephrectomy". Trials were classified as completed (Table 1) if their status was listed as "completed" on www.clinicaltrials.gov. Trials were classified as ongoing (Table 2) if their status was listed as "active", "recruiting", "active, not yet recruiting", "active, not recruiting", or "suspended". Trials were excluded if they were listed as "terminated" or "withdrawn".

Comment 5: Despite this review reports survival outcomes for CN and medical treatments for metastatic renal cell carcinoma, I suggest to provide a brief description of the surgical issues of metastatic renal carcinoma (10.1016/j.euo.2020.04.006).

Reply 5: We agree that such a section should be included. We have added a section regarding surgical issues surrounding CN and mRCC including a discussion on surgical approach and morbidity/mortality in which we have cited the aforementioned paper (Pages 6-7, Lines 105-131).

Changes in the text:
Pages 6-7, Lines 105-131
Surgical Considerations for CN

CN can be a complex operation associated with significant morbidity and mortality [12, 13]. In a retrospective multi-institutional analysis of 736 patients with mRCC undergoing CN, 10.9% of patients experienced intraoperative complications, the most common of which included bleeding (36%), splenic laceration (19%), and vascular injury (16%). Predictors of intraoperative complications included performing a thrombectomy or adjacent organ removal. 217 patients (29.5%) experienced postoperative complications, 6.1% of which were considered high grade (Clavien Dindo >3). Most common complications were vascular (30%), infectious (19%), and cardiopulmonary (17%). Estimated blood loss (OR 2.93; 95% CI 1.20–7.15; $p = 0.02$) and surgeon CN case volume (OR 0.13; 95% CI 0.03–0.59; $p = 0.009$) were identified as significant predictors of high grade complications [13].

Another study retrospectively evaluating 294 patients who underwent CN between 1990-2009 demonstrated a 12% early overall and 5% early major (Clavien Dindo >3) complication rate. The most common complications included wound infection (3%), acute renal failure (3%), pulmonary embolism (2%), and deep venous thrombosis (2%). 3 deaths (1%) were reported in the immediate 30-day postoperative period. While most patients did not experience complications, 61% of patients pre-determined to be candidates for systemic therapy did not receive it within 60 days of surgery [12].

Traditionally performed via an open approach, data on outcomes associated with minimally-invasive CN are sparse. Primary renal tumors in patients with mRCC may have adverse features such as IVC thrombi, significant bulky adenopathy, or invasion into local structures, making surgery technically challenging. A 2016 multi-institutional study reported on 120 patients across three high volume centers who underwent either laparoscopic (96.6%) or robotic (3.4%) CN between 2001 and 2013. 28 patients (23.3%) had postoperative classifications, nearly 30% of which were considered major (Clavien Dindo >3). 4 patients (3.3%) required conversion to open surgery [14]. At this time, no randomized control trials have investigated how minimally invasive approaches compare with open CN.

Comment 6: Recently Larcher et al. reported the implications for the guidelines of cytoreductive nephrectomy in metastatic patients with symptoms (10.1016/j.eururo.2020.05.014). The authors should discuss about that.

Reply 6: Thank you for bringing this new and pertinent article to our attention. We have added a discussion surrounding this topic to our paper (Pages 10-11, Lines 208-219).

Changes in the text:
Pages 10-11, Lines 208-219

Patient symptoms are another important aspect of selection for CN. 66% of patients with mRCC display symptoms with the most common being gross hematuria or flank pain from local tumor invasion, pain from bone metastasis, and dyspnea from lung metastasis [28]. To assess the tradeoff the morbidity of surgery and improvement in symptoms, Larcher et al. reported on 317 patients with symptomatic mRCC treated with CN between 1988 and 2019. They found that after CN, 43 and 71% had complete resolution or improvement in any symptoms related to their metastatic disease, respectively. With respect to local signs and symptoms, 91 and 95% demonstrated resolution and improvement, respectively. While the overall and major (Clavien Dindo >3) complication rates were 37 and 10%, respectively, the authors concluded that patients undergoing CN largely had a beneficial or mixed (symptom improvement/with complication or no improvement/resolution without complication) response. IMDC risk group was not predictive of complication risk [28]

Comment 7: What are the limitations of this review? This should be provided.

Reply 7: One major limitation is that this is a narrative review, which has inherent risks of bias. We agree with the reviewer and have added limitations to our discussion (Pages 17-18, Lines 372-378).

Changes in the text:
Pages 17-18, Lines 372-378

This narrative review has inherent limitations as it is non-systematic. As with all non-systematic reviews, there is a possibility for bias, as the evidence provided has not been systematically evaluated. However, our intention is to provide a comprehensive overview on various aspects of CN, place its evolution into historical context, and highlight up-and-coming research. Additionally, most of the studies cited were retrospective in nature, as there is still a paucity of level one evidence detailing the precise clinical role of CN. Randomized clinical trials will be critical for further understanding how to best use CN in practice.

Comment 8: "For patients interested in CN, doing so as part of a clinical trial should be encouraged." What do the authors mean with this sentence? Do they mean that being part of a clinical trial might help to better select the patients?

Reply 8: We are happy to clarify this statement. The choice and timing of systemic therapy with respect to CN remain controversial. Future clinical trials are important in determining the optimal therapy regimen and timing. Because of this uncertain role, we believe patients choosing CN should consider doing so in the context of a clinical trial. We have changed the wording in our conclusion (Page 18, Lines 383-385).

Changes in the text:
Page 18, Lines 383-385
Because many questions remain regarding the optimal systemic therapy regimen and timing of surgery, patients interested in CN should be encouraged to do so as part of a clinical trial.

Comment 9: Why is reported a figure regarding only one trial and no one for the others?

Reply 9: This is a great question. In the section entitled "The Immune Checkpoint Inhibitor Period and Future Directions," we discussed the future need for a clinical trial examining the administration of systemic immuno-oncologic agents and deferred CN. We chose to highlight Cyto-KIK, a new trial examining this issue, both in the text and through a figure demonstrating the trial schema.

Comment 10: Several typos are present along the article.

Reply 10: Thank you for your careful review. We have corrected the following typos listed below.

Changes in the text:

Page 10, Line 201: changed "and an neutrophil" to "and neutrophil"
Page 14, Line 305: changed "reported on data" to "reported data"