Author’s response to reviews

Title: Adjuvant therapy for locally advanced renal cell cancer: A systematic review with meta-analysis

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Author’s response to reviews: see over
Reviewer #1:

Minor Essential Revisions:

1) The validity at first should be mentioned for pooling and analyzing patients treated with different therapies. The positive result if existing may be weakened by totalizing data from different therapies. Indeed we analyzed the trials individually, and then pooled them in subgroups, accordingly to the different therapies used. No subgroup analysis (immunotherapy, vaccines, biochemotherapy and hormone therapy) had relevant results.

2) It should be mentioned that some articles included patients with local stage T3 or T4 and others from T1 to T4. The trials used different staging systems, and it would be confusing aggregate the data in a table, for example. We preferred to state in the text the proportion of patients included in each stage. "Approximately 60% of patients had lymph node positive disease while 86% had pT2 or more advanced disease."

Reviewer #2:

Major concerns:

#1. Figure legends did not correspond to the actual figures. It was assumed that if the authors combined legends of Figure 2 and 3, it would correspond to Figure 1. Similarly a combined legend of Figure 4 and 5 would be suitable for Figure 2. Figure 1 legend should be corresponding to the Figure 3.

We adjusted the legends conform the figures.

#2. The word “Table” was severally described in this manuscript, however, no tables were included in this manuscript.

We inserted the tables in the manuscript file in order to be more precise.

#3. In Figure 1 for overall survival, values of hazard ratio and 95% CI for vaccine therapy and immunotherapy had discrepancy with those described in text.

We changed the text description of results:

Vaccines: (HR=1.02; 95% CI 0.75 to 1.39; P=0.89).
Immunotherapy: (HR=1.18; 95% CI 0.90 to 1.56; P=0.23)

Minor concerns:


We changed PFS to DSF (Disease Free Survival) to adequate the terms to the adjuvant setting. Some authors used the term Progression Free Survival, but we agree that it could be confusing.
Reviewer #3:

Major Compulsory Revisions:
Even though authors claimed that meta-analysis in this manuscript concluded that no clinical benefit for renal cancer patients, major conclusions have been reported in papers such as Clin Cancer Res. 2007(13):697s-702s and Nat Rev Urology 7, 327-338. 2010. Therefore, little of progress in this manuscript is achieved.
We undertook an aggregated data meta-analysis indeed. This is an already consolidated method in the evidence based medicine field. The specific question addressed in this systematic review is a matter of debate in several papers. The first paper (Clin Cancer Res. 2007(13):697s-702s) is a discursive review about multimodal approaches in locally advanced and metastatic renal cell carcinoma. The second paper is a discursive review about treatment of metastatic renal cell carcinoma.
We strongly believe this present meta-analysis adds information and represents the best current evidence about adjuvant therapy for locally advanced renal cell cancer.
Nothing changed in our article.

Reviewer #4:

- Discretionary Revisions;
P2, L4; Abstract; “adjuvant therapy setting in a renal cancer” is better?
We changed the text to “adjuvant therapy in renal cancer setting”.

L13, L4; I2 # I2
P8, L20 ; I2 # I2
We changed to I$^2$.

P9, L4 ; All three trials (1227 patients),
P9, L10 ; Eight trials (1910 patients)
-- same as P9, L20 ; All three trials (840 patients)
The trials are different. In the first case (P9, L4 - 1227 patients) the trials evaluated vaccines, and in the second case (P9, L20 - 840 patients) the trials evaluated immunotherapy.
As the explanation is in the text, we did not change it.

- Minor Essential Revisions;
For the discussion; “all types of drug” could lead misunderstandings.
This paper reviews most of the conventional adjuvant therapies other than molecular targeted therapy. And also, “adjuvant approaches studied are not improving” sounds like including all therapies such as molecular target therapy, even it states “studied”.
So I think it will be better to arrange this statement with adding a little more explanations, however, it is good to explain the recent expectations for molecular target therapy in the last paragraph.
Conclusion looks better, but it still sounds like too strong for this negative results.
We sought to identify all types of drug interventions studied. The studies with molecular targeted therapies are well described in the 6th paragraph. As some doctors extrapolate the data from metastatic disease
to adjuvant setting, we preferred to be emphatic with the results and recommendations, until publication of new data.

- Major Compulsory Revisions;
  P2, L18; For Abstract; It is true this met analysis showed no benefits. However, some of them had significant results in the individual data and it sounds too strong to say “no adjuvant therapy can be recommended.” So I recommend to state this conclusion in a more mild expression.
  Individual studies were discussed in the article. In fact there was only one with relative importance. It was discussed in the third paragraph: “Among the included trials, one deserves specific attention. Jocham et al[17] tested an autologous vaccine and was the only trial to present a positive PFS result. However, these results might have been compromised due to worrisome methodological issues discussed here and elsewhere.[22] All this justified the exclusion of the Jocham trial from PFS analysis.”
  One of the objectives of a systematic review is to evaluate and criticize all the evidence presented. Evaluating the presented data, we feel comfortable to indicate the absence of benefit of adjuvant treatment in patients with localized renal cancer.
  In order to be more open to new results, we changed the first phrase of last paragraph of discussion to: “This systematic review strengthens the evidence that no studied systemic therapy provides improvement in survival for patients who undergo surgical resection of renal cell cancer.”