

Subject: Revision and resubmission of manuscript ID: 02907848

Characteristics of clear cell renal cell carcinoma metastases to the thyroid gland: A systematic review

Dear Editor in chief and reviewers,

Thank you for your letter and useful comments on our manuscript entitled “Characteristics of clear cell renal cell carcinoma metastases to the thyroid gland: A systematic review”.

We have now revised the manuscript taking into consideration the comments raised by the reviewers and hope that it is now improved and suitable for publication in your journal.

Please see below a point-to-point reply to the reviewers’ comments. The changes in the manuscript are marked in red and cross-out is indicated in blue font.

The revision has been approved by all authors and I have again been chosen as the corresponding author.

Thank you for your consideration of our manuscript.

Sincerely,

Karam Khaddour, MD

Reviewer Comments, Author Responses and Manuscript Changes

Reviewer 1

Interesting literature review. In the Methods section, the authors should list the keywords used for the systematic research.

Response: The keywords used for the systematic research are now included in the Methods section, **page 3, line 50-52**

Reviewer 2

Comment 1: Add and discuss some significant published papers on in this topic such as: Survival after renal cell carcinoma metastasis to the thyroid: single center experience and systematic review of the literature. Beutner U, Leowardi C, Bork U, Lüthi C, Tarantino I, Pahernik S, Wente MN, Büchler MW, Schmied BM, Müller SA. *Thyroid*. 2015 Mar;25(3):314-24. Metastases to the thyroid gland from renal cancer. Cesaretti M, Trotta M, Varaldo E, Ansaldi G, Leale I, Borgonovo G. *Tumori*. 2013 May-Jun;99(3):e107-10. Thyroid metastases from clear cell renal carcinoma 18 years after nephrectomy. Sindoni A et al. *Ann Endocrinol (Paris)*. 2010 Mar;71(2):127-30. Thyroid metastases from renal cell carcinoma: review of the literature. Sindoni A et al. *ScientificWorldJournal*. 2010 Apr 1;10:590-602.

Response: We thank the reviewer for the input and the valuable additional resources provided in the comment. The study by Beutner U et al. was already included in the previous version of the manuscript. The most important key notes from the study are included in our discussion including the observation that there was no significant survival benefit between patients who underwent complete thyroidectomy compared to partial thyroidectomy. Also, we mentioned that this study noticed the significant survival difference between female and male groups who underwent total thyroidectomy.

We have now included the other references as suggested by the reviewer and added a relevant comment in the epidemiology and pathophysiology section. The study of Cesaretti et al. showed that the frequency of metastatic disease from kidney cancer to

the thyroid was very low which was highlighted in our discussion section (highlighted in red), **page 10 line** 245-249 . Moreover, our data analysis replicated similar findings in the study of Sindoni et al which showed slight female to male preponderance which also was mentioned and cited in text (highlighted in red), **page 10 line** 249-250

Comment 2: Improve the quality of histological image (lower and higher magnification) and if possible introduce any histological image with positive immunohistochemical markers for renal cell carcinoma.

Response: The authors have included a separate file with high resolution images with the submitted manuscript. Unfortunately, no other immunohistochemical stain other than TTF1 and thyroglobulin were applied as the H&E architecture was consistent with clear cell renal cell carcinoma.

Comment 3: check the few spelling grammatical errors.

Response: Done, the manuscript has been carefully reviewed for grammar and style and edited accordingly.

Other responses to comments on the style of the of the manuscript from editor were included in the revision document.

Sincerely,

Karam Khaddour, M.D.