Author's response to reviews

Title: Treatment of Renal Angiomyolipoma: Pooled Analysis of Individual Patient Data

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Author's response to reviews: see over
Dear Editor-in-Chief:

Thank you very much informing us about the status of our manuscript and for providing us the comments from the reviewers. We have revised the manuscript according to the comments from the reviewers. Below please find our replies to the reviewers’ comments. We hope the manuscript will now be suitable for publication in *BMC Urology*.

This manuscript has not been published or presented elsewhere in part or in entirety, and is not under consideration by another journal. All the authors have approved the manuscript and agree with submission to your esteemed journal. Conflict of interest for Markku Vaarala: Consultant: Amgen, Astellas, Janssen. Speaker Honorarium: Amgen, Astellas, Novartis. Trial participation: Amgen, Aragon Pharmaceuticals, Astellas, AstraZeneca, Pfizer, Orexo, Millenium Pharmaceuticals, Janssen. The other authors declare that they have no conflict of interest.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,

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Changes made have been highlighted in the manuscript. Linguistic corrections are visible in a supplementary file containing tracked language corrections made by Edanzediting.

Reviewer: Ahmed Ghaith (Editor)
Reviewer's report:
Line 50: Why you excluded tuberous sclerosis complex and epithelioid AML from the study?

**R1. The purpose of the study was to evaluate sporadic AMLs. Tuberous sclerosis complex is progressive disease with completely different clinical course compared with sporadic AML. Epitheloid AMLs are potentially malignant mesenchymal neoplasms with reported metastasis in approximately one-third of the cases. So epitheloid AMLs should be treated like renal carcinomas.**

Line 82: What do you mean by individual patient data were obtained from the authors of two studies and from the Oulu University Hospital (7 patients)?
R2. In addition to patient data retrieved from publications, detailed data was obtained from two previously published studies with high number of patients added with cases from our patient registry.

Is the multiplicity not considered as an independent predictor for re-intervention?

R3. Re-intervention means repeat intervention to the same tumor, not to the same kidney or to the same patient. The multiplicity was not an independent predictor for re-intervention.

I think your main target of this study is to evaluate the embolization as a treatment method for angiomyolipoma. Your data about other lines of treatment are deficient.

R4. Our study is based on extensive literature search. Published data on other lines of treatment is deficient and does not facilitate reliable comparison to the embolization.

The discussion is poor and needs re-evaluation.

R5. Unfortunately, the Reviewer gives no clues how to improve the discussion. We suggest keeping the discussion as it is as the other reviewers did not rise any specific issues.

There are many linguistic mistakes.

R6. The revised manuscript has been language edited by Edanzediting.

Quality of written English: Needs some language corrections before being published

Reviewer: Giacomo Maria Pirola

Reviewer's report:

Discretionary Revisions

The aim of this work is evaluation of sporadic renal angiomyolipoma treatment. Authors followed the “canonic” rules for the construction of Methods, that I believe it’s the most important part of this review.

The idea of demanding individual patient data from other Authors of case series it’s original by my personal knowledge, and I think gives more value at the presentation of the case series of the Institution to which the authors belong, even if limited (7 cases).

I feel the construction of the Article it’s original, it analyses different Center casistic experience and seeks to define certain criteria of treatment with a valid statistical analysis.

I wonder if the authors have deliberately avoided to describe the possibility of performing a biopsy of the lesion in case of doubt with a carcinoma or because they didn’t find consistent Literature. Also the risk of neoplastic foci of angiomyosarcoma in large size AML has not been stated.

R7. According to the Reviewer’s suggestions, the following sentence has been added to the Background (lines 36-37): Biopsy may guide the treatment decisions for lesions with unusual growth and imaging characteristics [3].

We believe the risk of angiomyosarcoma in large size AML is very rare and we do not suggest specifically mention that entity.

At the end of “discussion” section, Authors describes study limitations, that are clear and true (limited casistic with relatively short follow-up).

However, I think this work can help readers to focus on this still debated renal tumor. Methods and analysis are well conducted.

I believe the work it’s interesting and publishable.
Reviewer: Angelo Territo
Reviewer's report:
MAJOR COMPULSORY REVISION
The manuscript is interesting and shows a good literature researchs about surgical and minimally invasive (embolization) management of renal angiomyolipoma, a relative rare mesenchymal tumor.

As written, a large number of studies suggested that the risk of bleeding is related to the vascularity and size of this tumour, of course.

- It’s important to underline that, among treatment methods, embolization was associated with a significantly higher risk of re-intervention than a partial nephrectomy. A large series in literature reported enucleation or partial nephrectomy as recommended treatment for renal angiomyolipoma. Than, embolization is considered like a second choice (for example in case of comorbidities that controindicate a surgical treatment), specially in case of large tumors.

R8. We have stated in discussion: “Among treatment methods, embolization was associated with a significantly higher risk of reintervention.” to point out this issue. According to European Association of Urology guidelines, “Selective arterial embolisation (SAE) seems to be the first-line option used for active treatment (reference #10 in the manuscript). Thus we kindly disagree with the Reviewer with the first-line treatment modality and suggest keeping the text as it is.

- Moreover, the authors didn’t report that angiomyolipoma is a rare mesenchymal tumor arising mainly in the kidney that can potentially behave aggressively. In fact, angiomyolipoma can often resemble sarcomatoid renal cell carcinoma, high grade renal carcinoma or sarcoma. This aspect confirms the importance of to extirpate the neoplasm completely with a surgical approach in particular in case tumor with large size (> 4 cm).

R9. We agree with the reviewer that in cases with aggressive growth or atypical radiological findings, follow-up is not first-line option and tumor removal should be considered. We believe that surgical removal of suspected malignancy is the first-line treatment option among surgeons and urologists making treatment decisions, so we do not suggest specifically point out this issue. However, radiologically diagnosed AML may be treated without surgery according to the current guidelines (reference #10 in the manuscript).