



BAISHIDENG PUBLISHING GROUP INC

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242 Fax: +1-925-223-8243

E-mail: bpgoffice@wjgnet.com <http://www.wjgnet.com>

Name of Journal: *World Journal of Radiology*

ESPS Manuscript NO: 22873

Manuscript Type: Retrospective Study

Response to Comments

Reviewer 1 Comments

1. I am not sure if the authors intend to submit this study as a case series or a research study since there seems to be an overlap in format. The reason it is important to differentiate this is because while a case series is less stringently evaluated, a research study needs to be more rigorous from a scientific study perspective. I believe this manuscript fits more easily as a case series than a research study.

We thank the Reviewer for their thoughtful comments. We would be happy to convert the format of this manuscript to a case series if so desired by the Editor.

2. Though the title and purpose seem to suggest that the authors have tried to study the imaging manifestation prior and after mTOR therapy, in fact the treatment received by the patients is a little more complex since the patients have received a combination of mTOR and embolization therapies. It would be naïve to suggest that the study only looked at the imaging effects of mTOR therapy.

We appreciate the Reviewer's comment. While all patients did indeed undergo both embolization and mTOR inhibition, the former intervention was separated in time from the latter. As such, for all patients we were able analyze imaging studies that could discretely characterize volumetric tumoral changes for each intervention.

3. The details provided in the methods and results section lack scientific precision and the authors use subjective terms to evaluate treatment response. Again, this is critical to differentiate between a case report and research study.

We disagree with the Reviewer that our Methods description lacks rigor. We have written this section with sufficient detail to allow replication by others; moreover, the image analysis methods are either conventionally accepted or based upon previously published techniques. The Results section text is not overburdened with numerical results as we believe these data are more elegantly expressed through Figures, particularly in the format afforded by this Journal which allows for full color images.

I. Abstract.

4. I am not sure if the format of abstract fits a case series. The authors might want to specify whether they would like this manuscript to be a case series or a research study as they are different.

We thank the Reviewer for their thoughtful comments. We would be happy to convert the format of this manuscript to a case series if so desired by the Editor.

II. Introduction

5. OK

III. Methods

6. Please provide more details about the CT scan technique such as protocol, contrast dose and injection rate etc.

This information has been added.

7. Please provide the details of the time period between the imaging studies, mTOR therapy and angiographic studies.

We have added three Tables (one for each patient) that detail the exact dates for imaging studies, mTOR therapy, and angiograms.

8. The method used to identify different tissue components is faulty. "Any tissue enhancing between 100-200 HU was considered to represent blood vessel" this statement is inaccurate since soft tissue tumors often enhance >200 HU depending on the contrast phase and iodine contrast dose.

While we agree with the Reviewer that our method for determining vascularity based on contrast-enhanced CT is not flawless, we believe that

the method used is the most accurate and based upon previously published literature (e.g., Planché, O., Correas, J.-M., Mader, B., Joly, D., Méjean, A., & Hélénon, O. (2011). Prophylactic embolization of renal angiomyolipomas: evaluation of therapeutic response using CT 3D volume calculation and density histograms. *Journal of Vascular and Interventional Radiology : JVIR*, 22(10), 1388–1395. <http://doi.org/10.1016/j.jvir.2011.05.016>). At our institution, a non-contrast phase is not routinely performed, particularly for pediatric patients, given the desire to minimize radiation exposure. On our evaluation, the thresholds used for the manuscript were the most accurate approximation for tumoral vascular content.

9. What method/thresholding was used to identify the soft tissue components?

The soft tissue component was calculated as the difference of the vascular and fatty components from the total volume.

10. What criteria were used to identify the blood vessels on MRI?

The arterial phase post-contrast subtraction masks were used to measure tumoral vascularity.

11. In which phase of contrast enhancement on CT or MRI did the authors measure the volume of soft tissue, blood vessels and fat?

For CT imaging, either one (nephrographic) or two (arterial and nephrographic) were available for analysis; for studies with two phases, vascularity and fat content were assessed on the earlier phase. On MRI, fat volume was calculated from “fat only” maps generated via the Dixon technique, and vascularity was calculated from the arterial phase subtraction mask.

12. For assessment of tumor vascularity on MRI, please provide details of the thresholding tool.

Given that the subtraction mask provided excellent delineation of tumor vascularity without any additional image manipulation, a simple thresholding tool could be applied to segment the vascularity.

13. The authors need to provide the exact details of the time line for mTOR therapy, embolization and imaging studies (CT and MRI). The details provided in the methods section lack sufficient information to allow one to understand the temporal sequence of events. It is also not clear how much time elapsed between the imaging study and start of mTOR therapy or the cessation of mTOR therapy and initiation of embolization and

CT/MR scans. Though the authors have tried to accomplish this in tables/figures exact details are missing.

The full details for each patients' timelines have been added in three Tables.

14. Who performed the image analysis?

Image analysis was provided by the first author, a Board-certified radiologist with subspecialty training in abdominal imaging.

15. Please provide details of the mTOR therapy? What was the dose? How frequently was it administered? What were its side effects?

Results

16. How did the authors determine that none of the AMLs in patient 1 have substantial fatty component? How can one quantify "substantial" - is it <50% or >50%?

Patient 1's tumoral fat content was < 5%.

17. How was the dramatic decrease in tumor volume after Mtor therapy in patient 1 determined? What does dramatic mean?

We have added percent change values in the Results section to provide a greater degree of quantitation to the data.

18. The details of treatment and assessment of treatment response to embolization for patient 1 is too confusing particularly regarding the treatment regimen for the multiple lesions.

We have added timelines for all the patients to clarify treatment regimens and imaging schedules.

19. Similar comments for patient 2 and 3. The authors use very vague terms to describe treatment response - "sizeable fat" "significant decrease" "mirrored across". How did the authors determine this scale of response? Was a p-value calculated to determine significance?

We have added percent change values in the Results section to provide a greater degree of quantitation to the data.

20. The authors need to provide details of the volumetric evaluation they describe in the methods section. How much did the soft tissue component change or fat component change?

We have added percent change values in the Results section to provide a greater degree of quantitation to the data.

Discussion.

21. I do not think there is sufficient information in this series to suggest what the authors conclude that tumor volume reduction impacts all three tissue components of the tumor.

We believe that our conclusions are well substantiated. Although the total number of patients is small, we have demonstrated that the vascular, soft tissue, and fatty components all decrease in size following mTOR inhibition. The patients in this series had both lipomatous and non-lipomatous AMLs, and we believe that the results in this manuscript are generalizable to the broader TSC population.

V. References

22. OK

VI. Tables and Figures

22. Figure 1 and 5. Please include if possible figures after endovascular intervention showing changes in dimensions of soft tissue and fat component of tumors.

The changes in tumoral volume, particularly individual tissue compartments, were relatively small for these patients after embolization (hence the initiation of mTOR inhibitors), and so a Figure trying to highlight these changes would be challenging and potentially misleading.

Reviewer 2 Comments

This is a retrospective report including only three patients. The observations are interesting but the data and design are insufficient. The aims of the study should be more clear in the text like it is in the abstract. Also the potential hypothesis and end-points should be more well defined. Nothing is said about further treatment of the patients after demonstration of rebound growth of the AMLs. What was the follow-up time and why was mTOR inhibitor therapy stopped in

each case as it seems to have had good clinical effect? Were there any side effects of this treatment? What is the cost price? It is said that all three patients underwent MR imaging, but one patient also CT imaging - why? Were the volumetric analyses performed with MR in all cases? Which role did CT play, and why only in one of the patients - please explain. Tumor vascularity was based on angiography and classified into 3 grades. Was this classification subjective? In patient #2 is said that embolization was performed in 2006 because of size of the tumor - which size? Were the volumes in this patient based on CT at all times? Fig. 5A is not referred to in the text The limitations of this study should be more clearly explained in the text in a separate paragraph. It is impossible to conclude much based on three cases. There is no statistics included in the report. There are no suggestions for clinical implications of these findings or for further studies.

We thank the Reviewer for their thoughtful comments. We have clarified the aim of the manuscript along the lines of the Abstract in the Introduction. We have no further data on subsequent treatment for these patients, as the manuscript brings each patient's history to the present time. We have added why mTOR inhibition was stopped for all the patients. We have also added statements regarding side effects for this therapy. We are unable to obtain pricing data for mTOR inhibition, as each patient's insurance was different; for Patient 2, the drug was administered through a clinical trial and was therefore given at no cost to the patient. CT imaging was initially performed in Patient 2 because in 2003, when she first presented, that was the standard of care. The other patients presented more recently, and as Table 2 demonstrates, Patient 2's subsequent imaging was performed with MRI. Tumor vascularity was based on a previously published semi-quantitative grading system for AMLs (Rimon, U., Duvdevani, M., Garniek, A., Golan, G., Bensaid, P., Ramon, J., & Morag, B. (2006). Large renal angiomyolipomas: digital subtraction angiographic grading and presentation with bleeding. *Clinical Radiology*, 61(6), 520-526. <http://doi.org/10.1016/j.crad.2006.02.003>). We have added a paragraph acknowledging multiple limitations.

Reviewer 3 Comments

nice article with clinical significance and within the scope of the journal