

Peer Review File

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Review Comments (Round 1)

Comment 1:

Page 4

1. In line 2: “meningiomas represent 37.6% primary central nervous system (CNS) tumors”. The word “of” should be added between “37.6%” and “primary”.
2. In line 5: a sentence cannot start with “And”. The sentence needs to be revised.
3. In line 8: add “et al.” to “Solero” so it becomes “Solero et al.”

Reply 1: We thank the reviewer for pointing this out, and we have modified our text and updated some data as advised.

Comment 2:

Page 4

4. I seem to find more than 6 studies mentioning anaplastic spinal meningiomas. Please find four other references you may add and that include at least 1 anaplastic spinal meningioma:

1. DOI: 10.3171/2021.2.FOCUS20977
2. DOI: <https://doi.org/10.1016/j.jocn.2019.11.020>
3. DOI: 10.1093/neuros/nyw092
4. DOI: 10.1007/s11060-021-03771-1

Reply 2: We are grateful that the reviewers found some published results that we neglected. We previously set the searching date in April 2021. We again checked the searching strategy and added two extra cases to our literature review **table 3**. Also, we excluded the article published by Sade in 2007, because it provided no information about PSAM.

Comment 3:

Page 4

5. In line 9: the sentence starting with “another...” needs English revision.
6. In line 15: “It jeopardizes our patients hugely”. This sentence can be removed.
7. I strongly advise the authors to consider thoroughly going through their introduction with an intent to improve the text linguistically and grammatically, in order to meet the writing standards of scientific publication.

Reply 3: We thank the reviewers for giving advice on our text and wording. We rewrote the introduction as advised and made it more readable.

Comment 4:

Page 5:

1. In line 2-3: I find the 3rd criteria to be interesting. Since you have reviewed the literature, my question to you is if there have been any reported cases of anaplastic meningiomas from the brain metastasizing to the spinal cord? If so, you may consider adding something about that in your introduction.

Reply 4: We agree with the reviewer that metastasis from intracranial meningioma is an interesting topic, which might differ a lot from the PSAM to many levels. We hereby added one sentence to introduction, stating that 15.2% of the distant metastasis happened intraspinally. However, our focus was on PSAM, a malignant subtype that develops and progresses originally within the spinal canal.

Comment 5:

Page 5:

2. In line 6: Since the Simpson grading scheme is the standard reference for extent of tumor resection in meningiomas of both spine and brain, the authors may consider adding information about that, instead of only alluding to GTR and STR.

Reply 5: We agree with the reviewer that Simpson Grading is well recognized in meningioma resection. We changed the previous GTR and STR into Simpson Grading from I to V after double-checking the surgical charts.

Comment 6:

Page 5:

3. In line 11-12: It is worth noting that there are no specific recommendations as to the use of IONM for extradural extramedullary tumors, and that the recommendations referred to by the authors mainly targets intra- and juxtamedullary tumors. In fact, minimal to no benefits were shown by previous studies researching the benefits of IONM on operation of these tumors (DOI: 10.1007/s10143-017-0815-2 DOI: 10.14245/ns.2143186.593). Since most of the tumors presented were indeed purely extramedullary, it may be warranted to delete the following: “a general recommendation for intraspinal pathologies” (line 11).

Reply 6: We are grateful that the reviewers pointed this out that IONM might not actually offer evidenced benefits to extramedullary tumor resection. We deleted the sentence mentioning recommendation as advised.

Comment 7:

Page 5:

4. In the methods section you may consider featuring the mean or median length of follow-up across patients.

Reply 7: We agree with the reviewer that the feature of follow-up should be clearly stated. We added the median follow-up of 8.5 months with extrema as advised.

Comment 8:

Page 6

1. Line 7: typo “inthe” instead of “in the”.
2. Line 9: add duration “of symptoms” for clarity, provided that it is what is meant.

Reply 8: We have modified our text as advised.

Comment 9:

Page 7

1. Line 2: each of the three available Ki-67 value can be reported separately or consider including the mean/median value.

Reply 9: We performed the ki-67 staining and H-E staining again and we provided the ki-67 values and pictures as advised.

Comment 10:

Page 7

2. Line 17-19: The two sentences require English revision.

Reply 10: We revised the paragraph as advised.

Comment 11:

Page 7

3. Line 19-20: Why only provide detailed description of two of the deceased patients (Cases 3 and 1)? In my opinion, either all should be described in detail or none. Only describing two may be confusing to the readers.

Reply 11: We apologize for the ambiguity. We summarized the recurrence, metastasis, and mortality at the beginning of this paragraph. For Line 19-20, we described metastases which occurred to two patients. We afterwards stated the mortality cause, which was respiratory failure with lung infection due to confinement to bed.

Comment 12:

Page 8

1. Line 2: In the text, it is mentioned that the first surviving patient witnessed recurrence at 11years. However, according to Table 2, the patient had recurrence at 11 months. Which is correct?

Reply 12: We apologize for the mistake. Case 2 had recurrence at 11 years after initial diagnosis. Eleven months in Table 2 was mistakenly put, and eleven years was correct. We revised the sentence as demanded.

Comment 13:

Page 8

2. Line 3: I think the wrong terminology has been used, as patients can obviously not self-diagnose themselves with a tumor regrowth. As such, the status of the patient is either clinically stable without evidence of regrowth, radiologically stable without evidence of regrowth or recurrence, or the status can merely be unknown.

Reply 13: The patient went to local hospital and got MRI scan routinely as we recommended. We intended to describe the status of the patient. He was clinically and radiologically stable without evidence of recurrence. We made modifications as advised.

Comment 14:

Page 8

3. The illustrative case part requires minor English adjustments.

Reply 14: According to your comment, the manuscript has been edited for proper English language, grammar, punctuation, spelling, and overall style by a native English speaker. We hope it will meet with your approval.

Comment 15:

Page 8

4. Case 2: it would be nice to write that the MRI-detected lesion at 11 years follow-up was in fact a recurrence.

Reply 15: We agree with the reviewer that it should be defined as recurrence, and we revised the illustrative case as advised.

Comment 16:

Page 8

5. Case 3: In this patient, it would be worth mentioning to the readers why biopsy without excision was considered in the first place instead of aiming for GTR and later analyzing the specimen.

Reply 16: Case 3 achieved biopsy at another hospital. The patient decided to come to our hospital for a radical resection after the first trial.

Comment 17:

Page 9

1. The discussion part also requires English language adjustments.

Reply 17: According to your comment, the manuscript has been edited for proper English language, grammar, punctuation, spelling, and overall style by a native English speaker. We hope it will meet with your approval.

Comment 18:

Page 9

2. Line 10: I suggest you write only three cases were “analyzed in depth” instead of “detailed”, as it may be misleading.

Reply 18: We have modified our text as advised.

Comment 19:

Page 9

3. Authors are advised to use “seem to” or “may” in sentences reflecting interpretation of findings, as a way to soften conclusions. Example, in lines 19-20, the authors may use PSAMs “seem to” occur more frequently in... This is because, inherently, the nature of the study, its design and sample size do not allow for hard conclusions to be drawn. Please apply this all over in your discussion section.

Reply 19: We agree with the reviewer that some wording should be softened through using “maybe” or “seem to”. We believe that a retrospective study like ours should not be written with confirmative tones due to its inherent limitations. Therefore, we made adjustments as advised.

Comment 20:

Page 10

1. Line 10-11: there is no grounds provided by the study to conclude that a correlation between radiological features and spinal meningioma grading may be present. Hence, the sentence is to be removed.

Reply 20: We agree with the reviewer that we should not conclude anything confirmative concerning radiological features. We added “Further study on the correlation between the tumor morphology and intratumoral heterogeneity might assist in differential diagnosis of spinal meningiomas of different WHO grading.” instead.

Comment 21:

Page 10

2. Line 16-17: the sentence starting with ”Despite...” is seemingly unclear and should be removed if not clarified.

Reply 21: We have modified our text as advised.

Comment 22:

Page 10

3. Line 18-19: the sentence seems incomplete: where is screening recommended?

Reply 22: We apologize for the ambiguity. TERT mutation surveillance was suggested to be performed by Mirian et al (2020). We rewrote the whole paragraph.

Comment 23:

Page 11

1. Line 5: the suggestion proposed by the authors, although probably useful, does not relate to their manuscript, data, and findings. It should hence be removed.

Reply 23: We have modified our text as advised.

Comment 24:

Page 11

2. Line 9: the sentence starting with “We can consider” is unclear and should either be clarified or deleted.

Reply 24: We have modified our text as advised.

Comment 25:

Page 11

3. Line 12: Again, strongly affirming the role of IONM in this setting is questionable (see previous comment). The sentence may be removed.

Reply 25: We have modified our text as advised.

Comment 26:

Page 11

4. Line 17-18: It may be worth mentioning that the study referenced concerns intracranial anaplastic meningiomas, as it may be misleadingly mistaken for a study addressing spinal ones.

Reply 26: We agree with the reviewer that we should mention that the references were borrowed from intracranial anaplastic meningiomas.

Comment 27:

Page 12

1. Line 4-6: there lack references for these intriguing statements about the effect of chemotherapy in the management of meningiomas.

Reply 27: We apologize for the ambiguity and careless mistakes. We added the references as advised.

Comment 28:

Page 12

2. Line 7: the word “remedy” is to be replaced.

Reply 28: We have modified our text as advised.

Comment 29:

Page 12

3. Line 18-19: the last sentence is unclear and requires revision or, preferably, deletion.

Reply 29: We have deleted the sentence as advised.

Comment 30:

Page 12

4. The limitation section requires English revision.

Reply 30: According to your comment, the manuscript has been edited for proper English language, grammar, punctuation, spelling, and overall style by a native English speaker. We hope it will meet with your approval.

Comment 31:

Page 13

1. Line 1: the sentence starting with “Additionally...” does not fit the Limitation section and should hence be removed.

Reply 31: We have deleted the sentence as advised.

Comment 32:

Page 13

2. Line 5: in the author’s manuscript, there is no evidence supporting the fact that “the radiological features, pathological findings and biological behaviors of PSAM all indicate poor outcomes”. In other words there is no correlation between these factors and outcomes. The sentence ought to be modified. The authors may simply refer to what is known: that the tumors have poor outcomes and a high mortality compared to other spinal meningiomas.

Reply 32: We agree with the reviewer that we basically could not conclude anything confirmative due to the limited sample size, and we rewrote the conclusion as advised.

Comment 33:

Page 13

3. The conclusion should feature the main findings of the manuscript: high mortality, recurrence, and metastasis rates, aggressivity of this tumor subtype, and quick summary of the literature review.

Reply 33: We agree with the reviewer that we basically could not conclude anything confirmative due to the limited sample size, and we rewrote the conclusion as advised.

Comment 34:

Page 13

4. The conclusion also requires English language modifications.

Reply 34: According to your comment, the manuscript has been edited for proper English language, grammar, punctuation, spelling, and overall style by a native English speaker. We hope it will meet with your approval.

Comment 35:

Figures:

The authors are commended for their thorough documentation of both histological and radiological data for each and every patient.

Reply 35: We thank the reviewer for this. We added Ki-67 of all six patients for further reference.

Comment 36:

Tables:

Table 3: add the additional studies previously suggested, if possible (see previous comment).

Reply 36: We did another full search and added the relevant studies as demand.

Review Comments (Round 2)

Comment 1: The discussion should include a brief section regarding the 2 survivors. Why do u think they survived but not the others? Was there any age difference? Difference in the extent of resection? In the KI-67? I understand that the resulting reflection would only be based on speculations but it may still be interesting if appropriately proclaimed as such.

Response: This comment was very informative. We are also very interested in the survival of the two patients. As said by the reviewer, only some bold speculations could be made, and no confirmative conclusions should be given. We modified the last paragraph of Discussion section as advised.

Comment 2: I would recommend the authors to expand their conclusions, as it is too short as is right now.

For the conclusion: what are the main take-aways from this manuscript? In my opinion, what is most important is that "PSAMs are a rare entity, there is limited evidence as to the management of these lesions, they may metastasize or recur and are associated with a high mortality rates (poor prognosis). You may expand on that.

Response: We are grateful that the reviewer pointed this out. We modified the conclusion as advised. We changed it to "PSAMs are a rare disease, and there is limited evidence as to the

management of these lesions. They may metastasize, recur, and portend a poor prognosis. A close follow-up and further investigation are therefore necessary.”

Comment 3: The word remedy may be replaced with "treatment", "management", "therapy", "care strategy"... Remedy does not fit well within the context of a scientific article, at least in my opinion.

Response: We agree with the reviewer on that, and we modified the wording as advised.

Comment 4: I recommend the authors to have a read at the following manuscripts as they may act as a solid base for several of the statements, and answer questions especially regarding epidemiology, risk factors of malignant spinal meningiomas, extent of resection and the risk of recurrence:

- DOI: 10.3390/cancers14246251

- DOI: 10.3390/cancers14246221

Response: We are grateful that the reviewer pointed this out. We found the articles very informative concerning the current knowledge of spinal meningiomas. We made a few modifications to our revised manuscript in Discussion (Page 10 line 9, 12-14; Page 13 line 4-7; Page 14 line 6-10).