Dear Editors and Reviewers,

Thank you for your letter and comments concerning our manuscript entitled: “Imaging characteristics of orbital peripheral nerve sheath tumors: analysis of 34 cases (manuscript number: 76084)”. We are very grateful for your critical reading of our manuscript, and highly appreciate the recommendations for improvements. Your comments are all valuable and very helpful for revising and improving our paper, and important in add significance to our research. We have revised the manuscript according to the reviewers’ comments. Revised portion are marked in red in the paper. The main corrections in the paper and the response to the response to the reviewer’s comments are as follow:

Reviewer 1:

Introduction: 1. In 1910, neurinoma was histologically independent of neurofibromas and later named schwannoma later…” – Rephrase this. Maybe can use “after” confirming...

Response: We are grateful for your kind reminding, and apologize for confusion we brought to you. The second “later” should be “after”, and we have corrected it, marked it in red.

2. Include in the introduction, the most common tumor of the orbits? Incidence/prevalence of this tumor to be PNST unless otherwise?

Response: More than 95% of PNSTs are benign, and schwannoma is the most common benign PNST that appears heterogeneous because of its histologic composition. We added the relevant content to the introduction section according to

your suggestion.

3. Important to discuss: with the clinical characteristics and imaging alone, how would you differentiate this tumor as PNST compared to other tumors of the orbit. OR If PNSTs often occur in the Head and Neck, which is the most common location?

Response: Orbital PNSTs have a low incidence, accounting for only approximately 4% of all orbital tumors. They are thought to originate from sensory nerves, and have a frequent location of superior and medial orbital compartments. Although it is difficult to differentiate orbital masses based on imaging data, CT and MRI features could provide clues for diagnosis. Take neurofibromas for example, localized tumor on CT often demonstrates smoothly marginated, round, ovoid, homogenous density or lobulated.

4. Include a sentence or two, ideal TREATMENT of orbital PNSTs?

Response: Schwannomas, neurofibromas, and plexiform neurofibromas are benign tumors with favorable prognoses. Complete excision of these benign tumors with full effort to maintain the capsular integrity is the mainstay of treatment. However, for a patient whose documented serial imaging suggesting a solitary schwannoma or neurofibroma affecting the apex or where resection is not feasible, orbital decompression alone may be beneficial. In our study, all the 34 patients undertook the treatment of surgery and were followed up for one to six years, there was no tumor recurrence.

5. Can the authors include how the PNSTs in their study were treated? Surgical/Non-surgical? And Maybe their outcomes? – It is important esp. when you

can go ahead with treatment without biopsy, or is it safe to go to surgery or non-surgical therapy basing on clinical characteristics and imaging features alone.

Response: Dear reviewer, we have added the relevant content to the suggestion section according to your suggestion. In our study, complete gross resection was carried on for 33 patients based on their imaging manifestations, and the case of plexiform neurofibroma was performed partial resection. These patients were followed up for one to nine years, and there was no tumor recurrence.

6. Where histopathologic diagnosis based on final specimen extirpation or core needle biopsy?

Response: In our study, complete gross resection was carried on for 33 patients based on their imaging manifestations, and the case of plexiform neurofibroma was performed partial resection. Final diagnosis was clarified according to the pathology report of postoperative specimens.

7. DISCUSSION: In our study, none of the 21 schwannoma cases were accompanied by NF-1, although three neurofibroma cases (25.0%) and one plexiform neurofibroma case (100%) had NF-1. – May not put 100% for plexiform neurofibroma since it is only 1 case (not a sample population)

Response: Dear reviewer, we appreciate for your helpful comments, we have corrected this sentence as you request, and marked it in red.

8. Sentence or two on differentiating benign PNSTs to malignant ones.

Response: Malignant PNSTs account for an extremely low proportion, have a special gross appearance of fusiform, fleshy, white mass with arears of degeneration and

secondary hemorrhage. More than 95% of PNSTs are benign, and schwannoma is the most common benign PNST that appears heterogeneous because of its histologic composition. Unlike malignant PNST, which has a peak incidence in the seventh decade, benign orbital PNSTs are considered tumors of adulthood, except plexiform neurofibromas, of which approximately 50% are diagnosed in early childhood. We added the relevant content to the parts of introduction and discussion according to your suggestion.

9. What is the recommended imaging MRI or CT scan when suspecting for an orbital PNST? Can all the imaging variables be seen with one imaging modality? – Based on your institutional experience, would you suggest both CT and MRI be ordered? - Include in discussion evidence on Workup of orbital PNSTs.

Response: MR multi directions imaging displays individual structures of the tumors, while CT can make users observe the details of the involvement of adjacent orbital bone better. Since one imaging modality cannot see all the imaging variables, it is recommended to use MRI plain and enhanced scan as the main examination method, and CT scanning as an important supplementary means. We have added the relevant content to the conclusion part.

10. In table 1, suggest to fuse Plexiform to the “Neurofibroma” group for comparison. And just state it in the Methodology. Not statistically sound to compare 1 patient to groups with multiple patients. In table 2, please provide the (%) in both groups.

Response: Dear reviewer, we have modified the Tables and the section of Materials and Methods according to your suggestion.

11. Please discuss your findings, Clinical Presentation and Imaging Variables (Location, Intramuscular, Extrapyramidal, Morphology, Bone involvement, Homogenousity) in contrast to available literature/data. Were your findings similar to available data?

Response: There are few studies on the characteristics of orbital PNSTs imaging features. In the study of Young SM, they analyzed the imaging characteristics of 13 patients with histologically proven schwannoma of the orbital frontal nerve. Data showed that all front nerve schwannomas were located extraconally, 10 of 13 patients had bone remodeling on CT and 1 had calcification on pre-contrast CT. On pre-contrast CT, most were heterogeneously isodense to hypodense. On post-contrast CT, all had heterogeneous mild to moderate contrast enhancement. On T1-weighted MRI, most were heterogeneously iso- to hypointense, while on T2-weighted MRI, all were heterogeneously iso- to hyperintense, with portions of hypointensity within the tumor. In comparison of our results, their data supported an obviously high rate of bone involvement ang a low rate of homogeneous density/ signal intensity, this may be attributed to single orbital nerve type. We have added the relevant content to the part of discussion according to your suggestion.

12. Please include Limitations of your study. Orbital PNSTs are rare tumors. Your work provides preoperative basis of diagnosing these tumors so to help early on in treatment planning. Would suggest to include at least, what treatment modalities including adjuvant tx the patients underwent and their outcomes if data is available.

Response: The limitation of our study is relatively sample size, especially only one case in the sample of plexiform neurofibroma. We believe that our results will encourage further studies using large sample sizes and help elucidate the imaging characteristics of all types of orbital PNSTs. In our study, complete gross resection was carried on for 33 patients based on their imaging manifestations, and the case of plexiform neurofibroma was performed partial resection. Final diagnosis was clarified according to the pathology report of postoperative specimens. These patients were followed up for one to nine years, and there was no tumor recurrence.

Reviewer 2:

This paper was well written and does have scientific merits for publication. My only comment is that the actual p values should be used in Table 1.

Response: Dear reviewer, thanks for affirming of the study achievement. We have listed the actual p values, modified the Table 1 according to your suggestion.

Editor:

1. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author’s intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the

reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is ‘original’, the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response: Dear editor, according to your request, we have provided the original pictures using PowerPoint and uploaded them to the system, please check.

2. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Response: Dear editor, thanks very much for your suggestion about the Tables. We modified the tables according to your suggestion.

We deeply admire your rigorous academic attitude; please do not hesitate to contact us for any further query.

Thanking you in anticipation.

Best wishes

Sincerely

Dong Wang

25th April 2022