

Peer Review File**Article Information: <https://dx.doi.org/10.21037/ajo-22-11>****Reviewer A**

Thank you for your submission. This work is a review of the literature regarding laryngeal paraganglioma. The main aim of the paper is to aid in the diagnostic workup and subsequent management of these rare lesions.

There is limited data regarding this rare entity in the available literature and this paper makes a contribution to that available data.

Reply: None

Reviewer B

This paper is exactly what the title states: A systematic review of a rare subset (multicentric) of a rare condition (laryngeal paraganglioma). It is unlikely that most Otolaryngologists will come across this presentation in their career, however, having a reference to turn to if one does come across this lesion is helpful.

Overall, well researched and written.

Reply: None

Editorial Comments

First of all, regarding the type of this article, there is a crucial issue to be addressed. As authors identified this manuscript as a systematic review in the Title, we fail to see the study risk of bias assessment, which is an important component of the systematic review. The statement in Methods, “The risk of bias was assessed using a standardized tool developed for observational studies”, is inappropriate since the included studies are all case reports. Also, the reason, “Because the studies were case reports or series, the risk of bias in whether the authors included them in the systematic review is low, as the case findings are not open to interpretation”, cannot account for lack of assessment. Thus, authors need to add this part if the article type remain unchanged. And there is a reference for assessing the case report/ series (<https://jbi.global/critical-appraisal-tools>).

The following are the comments regarding the PRISMA 2020 for Abstract checklist:

1. Please specify the inclusion and exclusion criteria for the review. The eligibility criteria are not equivalent to the search strategy. Authors should present the subject, the dates of coverage, and the type of articles included.

Reply: we have included in the methods section of the Abstract that “The authors included all article types within the published literature from 1975 to 2022, without exclusion based on language, that reported on laryngeal paraganglioma with multifocal disease.”

2. The date when each database was last searched also should be specified.

Reply: we specified in the Methods section of the main manuscript that the search was performed on 27th September 2021, however as requested by the editors in points 7-9, the search strategy was updated on 22nd September 2022 to include EMBASE and SCOPUS databases.

Changes in text: we have specified the above in the Methods section to include the date and to include the new databases entered into the search

3. As stated at the beginning, please specify the methods used to assess risk of bias in the included studies.

Reply: we have updated the risk of bias assessment and used the JBI checklist for case reports and case series. This is provided in the supplementary files.

Changes in text: In the Methods section we have written that the JBI checklist was used and provided the risk of bias summary in the supplementary files.

The following paragraph was added to the Results section: The bias of the included studies was low, with all studies documenting the demographic and clinical characteristics of the patient, the symptomatology of the LP or synchronous lesion, the investigative modalities used, and the type of management for both lesions. One study in a Radiology journal did not mention the management of either the LP or synchronous carotid body tumor. Most studies either did not adequately document follow up or had a short follow up duration.

4. We suggest removing the statement “All reported cases of multicentric LP were identified, to the best of our knowledge” in Abstract-Methods, which is irrelevant to the study methods.

Reply: The following statement was removed.

5. It is great that authors provided the inclusion and exclusion criteria. But some aspects still need to be clarified, such as the study design, year of dissemination, and report status (for example, whether unpublished manuscripts and conference abstracts were eligible for inclusion).

Reply: all article types within the published literature from 1975 to 2022 were eligible for the study. We did not include unpublished literature

Changes in text: “All article types within the published literature between 1975 and 2022 were eligible for inclusion. Studies were excluded if they described head and neck paragangliomas without larynx involvement. Studies were not excluded based on language and 1 study from the non-English literature was included in the analysis” - has been included in the Methods section

6. To our knowledge, the PubMed database covers the content of MEDLINE. Therefore, as a systematic review, the number of selected databases in this study was somewhat small. Why

not use Web of Science, Scopus, Embase, etc.?

Reply and Changes in Text: We have included Scopus and EMBASE to broaden the database search and updated our PRISMA diagram accordingly. No additional reports of LP with synchronous or multifocal disease were found, and a large overlap between the databases was noted. The majority of studies were related to non-laryngeal head and neck paragangliomas or did not include LP with a synchronous lesion.

7. It seems that search records would include many other diseases in accordance with the search strategy in Methods. We try to search the PubMed using the search strategy of this study, and it shows 3290 records.

Reply and Changes in Text: The search strategy has been reviewed in the Methods section as we can see how some confusion has arisen – we did not combine the search term paraganglioma with OR with larynx/head and neck. We have updated it accordingly.

For example, the search was (larynx) AND (paraganglioma) AND (multicentric OR metachronous OR synchronous), which yielded 49 results on Medline, then (head and neck) AND (paraganglioma) AND (multicentric OR metachronous OR synchronous), which yielded 48 results. Similarly, the same was done in PubMed.

We have updated the search strategy to include Embase and Scopus as requested, and updated the PRISMA diagram to reflect this new search more accurately. A total of 331 articles with 138 duplicates was found between the four databases, with 8 articles included which reported on LP with multifocal disease. A further 3 articles were found from reference lists of the included articles.

8. Authors claimed that “Articles were either case reports or case series, as previous literature or systematic reviews covering this topic have not been performed” in Methods. However, it appears that we then discover several observational studies about laryngeal paragangliomas (<https://pubmed.ncbi.nlm.nih.gov/31626927/>, <https://pubmed.ncbi.nlm.nih.gov/23520216/>). A reliable result relies on the rigor methodology. Therefore, search and screening of studies are important for the systematic review. Please recheck the search strategy and records accurately.

Reply: The observational studies are describing head and neck paragangliomas and not laryngeal paragangliomas (LPs). Most of the literature focusses on carotid body tumours and glomus vagale, glomus tympanicum, and glomus jugulare, as these are the most commonly affected subsites. Both the articles referenced by the editors are not specific to LPs – the former is specific to carotid body tumours. The latter is referenced in our manuscript on the role of imaging modalities in diagnosing paragangliomas – it is general to head and neck paragangliomas, and mentions one case of LP which was unilateral and solitary. The literature on LPs is minimal and limited to case reports and case series, which is where we obtain the data from the table. We have used information from observational studies related to head and neck paragangliomas in general to guide our discussion especially with regards to diagnosis and management, as paradigms in clinical care should be similar. As suggested the authors have expanded the database search to include EMBASE and SCOPUS,

and no studies beyond case reports/series are found that are specifically related to laryngeal paraganglioma, whilst a few are available related to head and neck paragangliomas (which we have included some in our discussion and references).

Changes in Text: An additional section 4.5 Limitations has been created which touches on the paucity of literature with respect to LPs, with most evidence coming from case reports and series – this is due to the rarity of this disease in clinical practice. We mention that evidence from studies on head and neck paragangliomas has to be extrapolated to the management of multicentric LPs.

9. The description, “The search results were reviewed for eligibility by a single reviewer (as the inclusion criteria was objective) based on the title and abstract of the article”, is not enough for the selection process. Only one reviewer is prone to selection bias. If it could not be avoided, please present this potential bias in the Limitation.

Reply: The statement “as the inclusion criteria was objective” has been removed. Single-author screening has been used in systematic reviews previously. Where uncertainty arose the expertise of a consultant head and neck surgeon was sought. As data extraction for this systematic review is focused on whether the paper described a laryngeal paraganglioma with a multifocal lesion it is unlikely to have had significant bias from single author screening compared to a topic where there is more ambiguity in whether a study meets the author’s selection criteria (e.g. the value of post operative radiotherapy in oral cavity SCC).

Changes in Text: We have included that the expertise of a panel of consultant head and neck surgeons was available where any uncertainty arose. A new section called 4.5 Limitations has been added which comments on the potential limitations of the review including single author screening as a potential source of bias

10. The analysis, “Possible limitations arise in ... which can limit comparisons being made”, in Methods might be more suitable for Discussion.

Reply: this part has been moved to the Discussion

Changes in Text: A new section called 4.5 Limitations has been added which comments on the potential limitations of the review.

11. We strongly recommend authors to follow the PRISMA 2020 flow diagram for new systematic reviews (<https://www.prisma-statement.org//PRISMAStatement/FlowDiagram>). Authors should indicate the number and reasons of excluded studies in EVERY step.

Reply and Change in Text: We have updated to the PRISMA 2020 flow diagram and included the updated search strategy with EMBASE and SCOPUS included.