Peer Review File

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Replies to Reviewer A

Method section

1. In lines 94-95, AJCC is the acronym of the American Joint Committee on Cancer. Please correct the manuscript.

Reply 1: We thank the reviewer for pointing this out. We are very sorry for such a simple mistake and have revised the text accordingly.

Changes in the text: We have modified our text as advised and is highlighted in red (see Page 5, lines 109-110).

Statistical section

2. In line 103 you need to enter the standard deviation and not just the standard. Please correct the manuscript.

Reply 2: Thank you for your thoughtful suggestion. We agree with your advice and have revised the text accordingly while highlighting it in red.

Changes in the text: We have modified our text as advised and is highlighted in red (see Page 5, line 118).

Results section

3. In line 129 TRAbs are indicated as thyroid peroxidase antibodies. TRAbs are thyrotropic receptor antibodies. Please correct the manuscript

Reply 3: We thank the reviewer for pointing this out. We are very sorry for such a simple mistake and have revised the text accordingly.

Changes in the text: We have modified our text as advised and is highlighted in red (see Page 6, lines 145).

4. The authors identify five significant risk factors for CLNM in patients with PTC. Do the authors have data on the extra thyroid tumor extension? Is this a significant risk factor for CLNM in your work?

Reply 4: We greatly appreciate the reviewer's suggestions, which are of significant guidance for enhancing the quality of our article. Considering the importance of extra thyroid tumor extension, we specifically retrieved the original data of the patient's preoperative ultrasound

images and invited experienced sonographers for evaluation to complete and include this critical data in our analysis. The analysis shows that extra thyroid tumor extension is one of the independent risk factors for ipsilateral central neck lymph node metastasis in PCT patients. We have thoroughly supplemented this finding in the methods, results, and discussion sections.

Changes in the text: In response to the reviewers' suggestions, we have incorporated additional data analysis and supplemented the relevant content in the Methods (see Page 5, lines 103-109), Results (see Page 7, lines 167-170,183,), and Discussion (see Page 8, lines 206-213) sections. Furthermore, we have highlighted these additions in red for easy identification. Furthermore, to maintain consistency, we have also made corresponding modifications to the content in the tables and figures.

5. Have the patients had Graves' disease in the past? Is this a significant risk factor for CLNM in your work?

Reply 5: We greatly appreciate the reviewer's suggestion and also believe this to be an important direction for research. However, as this study is a retrospective cohort study, there is a substantial lack of historical data on patients with Graves' disease, making it difficult to conduct an in-depth analysis. We have added a note regarding this limitation in the section on the limitations of our study.

However, prompted by the reviewer, we noted upon review of the data that the historical information regarding whether patients had Hashimoto's thyroiditis was complete. This aligns with the perspective reported in the literature that Hashimoto's thyroiditis is closely associated with papillary thyroid carcinoma(1).Through our detailed analysis, we indeed found that Hashimoto's thyroiditis is one of the independent risk factors for central cervical lymph node metastasis in patients with papillary thyroid carcinoma. To further explore this finding, we have provided detailed supplementary explanations in the methods, results, and discussion sections of our study.

Changes in the text: Due to the absence of data on whether patients had a concurrent history of Graves' disease, this point will be detailed in the limitations section of our study and highlighted in red font (see Page 11, lines 296-297).

Additionally, we have expanded our analysis of concurrent Hashimoto's thyroiditis in the Methods (see Page 5, line 100), Results (see Page 6-7, lines 137,157,161,165,182), and Discussion (see Pages 8-9, lines 222-235) sections, marking these enhancements in red for clarity. Furthermore, to maintain consistency, we have also made corresponding modifications to the content in the tables and figures.

Discussion section

6. In the limitations section it is necessary to insert that in all patients only ipsilateral lymph node dissection is performed. Therefore, the status of the contralateral lymph nodes is not known.

Reply 6: Thank you for your thoughtful suggestion. We agree with your advice and have revised the text accordingly.

Changes in the text: We have modified our text as advised and is highlighted in red (see Page 10, lines 290-293).

Replies to Reviewer B

1. The novelty of this paper is in the prediction of CLNM in patients suitable for lobectomy and ipsilateral central neck dissection. This should be emphasised in the Abstract and elaborated in the Introduction of the manuscript.

Reply 1: Thank you for your thoughtful suggestion. We agree with your advice and have revised the text accordingly.

Changes in the text: We have modified our text as advised and is highlighted in red (see Page 2, lines 24-26, Pages 3-4, lines 56-67).

2. The variable "multifocal nodule" is not significant in univariate analysis, but is included in the multivariate analysis. This is discordant with the method described in line 142 of the manuscript. Moreover, are the multiple nodules proven to be malignant on histology? If there is only one malignant nodule on histopathology, the other nodules, even if present, probably would not cause an increased risk of CLNM. This should be carefully analysed.

Reply 2: We appreciate the suggestions from the reviewers. In this study, the variables included in the multivariate analysis were not solely based on the results of the univariate analysis; we also considered clinical relevance and findings from previous literature for variable selection. According to the literature we reviewed, "multifocality" has been identified as an independent risk factor for lymph node metastasis in papillary thyroid carcinoma (PTC) across numerous studies(2-6). Therefore, "multifocality" was also included as a factor in our multivariate analysis. Following another reviewer's suggestion, during the revision process, we added two variables: Hashimoto's thyroiditis and extrathyroidal extension. Upon reanalysis, we discovered that multifocality no longer serves as an independent risk factor for central neck lymph node metastasis in papillary thyroid carcinoma. Furthermore, as you pointed out, we reviewed the original data and indeed found it challenging to determine the proportion of malignancy within multiple nodules. Given the retrospective design of our study, we were unable to perform an in-depth analysis of these data. Therefore, we have explicitly described this limitation in the results and discussion sections of our study. We look forward to further exploring this issue through prospective studies in the future.

Changes in the text: Following the reviewers' recommendations, we have made the corresponding revisions in the Discussion section (see Pages 9-10, lines 257-262, Pages 10, lines 293-295), highlighted in red font for clarity. Furthermore, to maintain consistency, we have also made corresponding modifications to the content in the tables and figures.

3. Suggest change nodule characteristics to characteristics of the cancerous nodule if histology can be matched to sonography. Please describe the method of matching as this is a retrospective study.

Reply 3: We greatly appreciate the reviewer's suggestions. We have made corresponding revisions based on the reviewer's comments and provided matching explanations in the Methods section.

Changes in the text: We have modified our text as advised and is highlighted in red (see Page 5, lines 104-107, Page 6, line 158). Furthermore, to maintain consistency, we have also made corresponding modifications to the content in the tables and figures.

4. Enlarged lymph nodes: are they in the central neck or lateral neck? Please indicate clearly.

Reply 4: Thank you for the reviewer's suggestion. "Enlarged lymph nodes" refer to the lymph nodes in the central region of the neck. We have made corresponding clarifications and revisions in the text.

Changes in the text: We have modified our text as advised and is highlighted in red (see Page 2, line 35, Page 5, line 108, Page 6, lines 151,159, Page 7, lines 161,168,182, Page 8, line 220, Page 11, lines 304). Furthermore, to maintain consistency, we have also made corresponding modifications to the content in the tables and figures.

5. Osteoporosis: the rationale for checking this pre-operatively is unclear. If it is to detect bone mets, why performing a bone density scan for osteoporosis instead of skeletal survey, bone scan, or other dedicated whole body bone imaging?

Reply 5: We are very grateful to the reviewer for pointing this out. The purpose of conducting bone density tests was not to determine the presence of bone metastasis. This was done because patients post-thyroidectomy may require thyroid hormone supplementation or replacement therapy, which has a significant impact on bone metabolism. Additionally, excessive thyroid hormones, can accelerate bone metabolism, leading to bone loss and potentially increasing the risk of osteoporosis and fractures. Hence, to facilitate postoperative follow-up and management, we assessed the preoperative bone density of patients undergoing thyroid lobectomy. Our study unexpectedly found that osteoporosis is an important risk factor for cervical lymph node metastasis in patients with PTC, a point rarely reported in previous studies. However, the specific mechanism between osteoporosis and cervical lymph node metastasis in thyroid cancer remains unclear, which also indicates a potential direction for our future research.

6. Smoking: is this variable denoting current smoking or ex-smoker? Is the pack-years of smoking possible to ascertain? If this means history of smoking as the authors alluded to, it is difficult to measure, apply in practice, and probably not able to independently influence the CLNM rates.

Reply 6: Thank you for your thoughtful suggestion. In this study, smoking is defined as current smokers, that is, individuals currently using one or more types of tobacco products. Non-

smokers in this study include two scenarios: first, lifetime quitters, individuals who have smoked no more than 20 grams in their lifetime; second, former smokers, those who have quit smoking for 365 days or more. Due to the retrospective nature of this study, we were unable to determine the pack-years of smoking for patients. We agree with the reviewer's comment that the definition of smoking history in this study is vague and difficult to quantify. Therefore, we have excluded the factor of smoking history from our study. Similarly, we have also excluded the factor of drinking history. We have made corresponding modifications to the sections of the paper.

Changes in the text: In accordance with the reviewers' suggestions, we have removed the sections pertaining to smoking and drinking history. Furthermore, to maintain consistency, we have also made corresponding modifications to the content in the tables and figures.

7. Have the authors done a different multivariate logistic regression by excluding history of smoking and osteoporosis to see if variables such as size of the cancer become significant? If established risk factors for the recurrence of PTC, such as size, are not significant in this study, an explanation is required.

Reply 7: We thank the reviewer for pointing this out. Following the reviewers' suggestions and after excluding histories of smoking and osteoporosis, tumor size still was not an independent risk factor for central cervical lymph node metastasis in thyroid cancer. Upon reviewing the literature, we considered that the size of thyroid nodules indeed affects the determination of their benign or malignant nature, and we have conducted corresponding analyses in the Discussion section.

Changes in the text: Based on the reviewers' suggestions, we have modified our text as advised and is highlighted in red (see Pages 9-10, lines 256-278).

8. The limitation of this study should also include the lack of external validation.

Reply 6: Thank you for your thoughtful suggestion. We agree with your advice and have revised the text accordingly.

Changes in the text: We have modified our text as advised and is highlighted in red (see Page 11, line 300).

References

1. Xu J, Ding K, Mu L, et al. Hashimoto's Thyroiditis: A "Double-Edged Sword" in Thyroid Carcinoma. Front Endocrinol (Lausanne) 2022;13:801925.

2. Xu S, Huang H, Huang Y, et al. Comparison of Lobectomy vs Total Thyroidectomy for Intermediate-Risk Papillary Thyroid Carcinoma With Lymph Node Metastasis. JAMA Surg 2023;158:73-9.

3. Wang Z, Gui Z, Wang Z, et al. Clinical and ultrasonic risk factors for high-volume central lymph node metastasis in cN0 papillary thyroid microcarcinoma: A retrospective study and meta-analysis. Clin Endocrinol (Oxf) 2023;98:609-21.

4. Cui L, Feng D, Zhu C, et al. Clinical outcomes of multifocal papillary thyroid cancer: A systematic review and meta-analysis. Laryngoscope Investig Otolaryngol 2022;7:1224-34.

5. Chang Q, Zhang J, Wang Y, et al. Nomogram model based on preoperative serum thyroglobulin and clinical characteristics of papillary thyroid carcinoma to predict cervical lymph node metastasis. Front Endocrinol (Lausanne) 2022;13:937049.

6. Feng Y, Min Y, Chen H, et al. Construction and validation of a nomogram for predicting cervical lymph node metastasis in classic papillary thyroid carcinoma. J Endocrinol Invest 2021;44:2203-11.