

Peer Review File

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Reviewer A: The review article entitled “A meta-analysis of risk factors for lymph node posterior to the right recurrent laryngeal nerve metastasis in papillary thyroid carcinoma” enrolled 15 studies that investigated LN-prRLN metastasis and related risk factors in patients with PTC

The followings are my comments:

Comment 1. This study investigated an issue of clinical significance. The authors have done an amount of literature reviews, making the article attractive to readers.

Reply 1. I would like to express my gratitude to the editors and professors of Gland Surgery for reviewing the manuscript for pointing out the mistakes in my article in your busy time. As a young doctor who just has a glimpse into the field of head and neck Surgery, I feel honored to receive the advice of professors, and I also benefit a lot from the advice.

Comment 2. There are some key reasons that make this article to be largely revised before further review in many aspects. One of reference “Park YM, Lee SM, Kim DW, Shin SC, Lee BJ. Predictive factors of right paraesophageal lymph node metastasis in papillary thyroid carcinoma: Single center experience and meta-analysis. PLoS One. 2017;12(5):e0177956” is a meta-analysis study, which enrolled articles include Zhang (2016), Ito (2013), Kim (2012), Bae (2012). Excluding these double-counting patients, the analysis and Forest plot of the entire article should be all revised.

Reply 2. We reviewed the literatures and deleted Park Ym's research. Therefore, all the forest plots have been revised. The funnel chart, flowchart and tables have also been revised. After removing park et al research, it didn't have an impact on our findings.

Changes in the text: we have modified our text as advised (see Page 6-8, Risk Factors for LN-prRLN/Result; Page 15-20, Figure 1-11, Table1-2).

Comment 3. The reference number in the table is not the same as the actual number, it needs to be revised. Besides, the author of ref 16 is Lee BJ, which is mistaken as Byung in the article; the author of ref 18 is Kim YS, which is mistaken as King in the table.

Reply 3. Thank you for pointing out these errors. We have gone over the manuscript and corrected the errors. For example, Byung has been changed to Lee. B. J; Chang 2013 has been changed to Chang. H 2015. The corresponding forest plots have also been modified. The reference number already corresponds to the actual number.

Changes in the text: we have modified our text as advised (see Page 8, line 359-360; Page 16-20, Figure 3-11, Table1-2.)

Comment 4. In figure 3, males and females should be interchanged. Males have higher risk than females according to the results.

Reply 4. Males and females have been interchanged in the forest plot (Figure 3). According to the results, male sex is a risk factor for LN-prRLN metastases. Changes in the text: we have modified our text as advised (see Page 16, Figure 3)

Comment 5. In figure 4, the results of Chang et al should be included in this analysis.

Reply 5. we have added the study of Chang et al to the risk factors of age, and the results show that age ≤ 45 years is a risk factor of LN-prRLN metastasis. Changes in the text: we have modified our text as advised (see Page 6, line 159-164; Page 16, Figure 4)

Comment 6. The topics mentioned in this article do have clinical importance. However, while there are a large retrospective study with 5556 patients and a meta-analysis article with 6 articles and 1107 patients, the innovation and uniqueness of this article should be carefully considered.

Reply 6. Thanks to the professors for your recognition of our research. Firstly, to the best of our knowledge, this is the largest sample size to date addressing this topic. We identified several important risk factors with LN-prRLN metastasis for clinical practice and further research by performing this meta-analysis. Secondly, we tried to explore the sources of the heterogeneity via one-by-one elimination method and subgroup analysis to enhance the credibility of the results. Finally, we added a limited discussion of this study in the part of discussion. We expected that other indicators such as imaging omics could be included to evaluate LN-prRLN metastasis in the future. We also expect to include more prospective studies to improve the accuracy of the results.

Reviewer B

Comment 1. I think this meta-analysis is a well-performed study evaluating some risk factors related to LN posterior to the right recurrent laryngeal nerve. I raise some suggestions for revision.

Reply 1. I would like to express my gratitude to the editors and professors of Gland Surgery for reviewing my manuscript for pointing out the mistakes in my article in your busy time. I have modified it according to your suggestion.

Comment 2. Line 33. Nowadays, few guidelines recommend routine central lymph node dissection.

Reply 2. Thank you for your advice. After consulting relevant literatures, we found that there were defects in our previous expression. This paragraph has been amended to "Therefore, most guidelines for preoperative or intraoperative examination of the central lymph node positive recommend central Lymph node dissection (CLND) (3)." Corresponding references are also revised.

Changes in the text: we have modified our text as advised (see Page 2, line 60-61; Page 13, line 508-513).

Comment 3. Adding some discussion on the effect size of the risk factors will help readers understand the importance of each risk factor.

Reply 3. According to your opinion, we have increased the effect size of the risk factors in the discussion part, such as demographic factors, lymph node metastasis. At the same time, the significance of OR value of each risk factor was described in the result section for readers to understand the importance of each risk factor.

Changes in the text: we have modified our text as advised (see Page 9, line 423-425; Page 9, line 434-437; Page 10, line 456-459).

Comment 4. Adding some discussion on the limitations of this study such as the sample size, heterogeneity of the selected studies and so on.

Reply 4. According to your suggestion, we have added limitations of our study in the part of discussion. Meanwhile, we also performed publication bias analysis and heterogeneity analysis in the part of results. Heterogeneity analysis was conducted by one-by-one elimination method and subgroup analysis.

Changes in the text: we have modified our text as advised (see Page 5, line 131-132; Page 7, line 301-303; Page 9, line 422-424; Page 10, line 155-158; Page 11, line 476-481)

Reviewer C

Comment 1. Zhou et al. conducted a meta-analysis of risk factors for LN-prRLN metastasis in PTC. Although this is a well-written paper, I have some concerns.

Reply 1. I would like to express my gratitude to the editors and professors of Gland Surgery for reviewing my manuscript for pointing out the mistakes in my article in your busy time. I have modified it according to your suggestion.

Major

Comment 2. Unmet need of this study is not clear. Most of the previous studies showed similar risk factors including tumor size, extrathyroidal extension, and central LN metastasis. There is a little controversy, if any, about the risk factors of LN-prRLN metastasis.

Reply 2. Thanks to the professors for your recognition of our research. Firstly, to the best of our knowledge, this is the largest sample size to date addressing this topic. We identified several important risk factors with LN-prRLN metastasis for clinical practice and further research by performing this meta-analysis. Secondly, we tried to explore the sources of the heterogeneity via one-by-one elimination method and subgroup analysis to enhance the credibility of the results. Finally, we added a limited discussion of this study in the part of discussion. We expected that other indicators such as imaging omics could be included to evaluate LN-PRRLN metastasis in the future. We also expect to include more prospective studies to improve the accuracy of the results.

Comment 3. The latest 2016 American Thyroid Association guideline has indicated that routine central LN dissection is not recommended in patients without clinically evident LN metastasis.

Reply 3. Thank you for your advice. After consulting relevant literatures, we found that there were defects in our previous expression. This paragraph has been amended to "Therefore, most guidelines for preoperative or intraoperative examination of the central lymph node positive recommend central Lymph node dissection (CLND) (3)." Corresponding references are also revised.

Changes in the text: we have modified our text as advised (see Page 2, line 60-61; Page 13, line 508-513).

Comment 4. There is no description about Figure 7. (Forest plot according to multifocality by subgroup analysis). Also, the figure numbers in the main manuscript are not correct (numbers 7-10 -> 8-11).

Reply 4. We reviewed the literatures included, and the forest plots were redone (Figure6-7). We further performed subgroup analysis based on regional factors to find the source of heterogeneity of multifocality to LN-prRLN metastasis in the results section. Then the relationship between regional factors and multifocality was discussed in the discussion section.

Changes in the text: we have modified our text as advised (see Page6-7, line171-291; Page9, line 434-437; Figure6-7)

Comment 5. More detailed description is needed about the limitations of the study & potential sources of biases.

Reply 5. According to your suggestion, we have added limitations of our study in the part of discussion. Meanwhile, we also performed publication bias analysis and heterogeneity analysis in the part of results. Heterogeneity analysis was conducted by one-by-one elimination method and subgroup analysis.

Changes in the text: we have modified our text as advised (see Page 5, line 131-132; Page 7, line 301-303; Page 9, line 422-424; Page 10, line 155-158; Page 11, line 476-481)

Minor

Comment 6. There were some typographical errors. For example, ref. 16 should be referred to Lee, not Byung. Also, in figure 3, Chang 2013 should be changed to Chang 2015.

Reply 6. Thank you for pointing out these errors. I have gone over the manuscript and corrected the errors. For example, Byung has been changed to Lee. B. J; Chang 2013 has been changed to Chang. H 2015. The corresponding forest plots have also been modified.

Changes in the text: we have modified our text as advised (see Page 8, line 359-360; Page 16-20, Figure 3-11, Table1-2.)