

## Peer Review File

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### **Reviewers' comment:**

**Comment 1:** Introduction: Page 5, line 58 – consider defining the term “skip metastasis” in the introduction, rather than in the discussion section

**Reply 1:** Thanks for your comment. We added the definition of “skip metastasis” in the Introduction section and delete the definition part in the Discussion section.

**Changes in the text:** We added the definition in page 4, line 58 as advised: Skip metastasis in mediastinal lymph node is defined as positive N2 metastasis with the absence of N1 lymph node metastasis in hilar and intrapulmonary lymph nodes. The added parts were marked in red.

**Comment 2:** Methods: Data extraction – did the authors extract data on the method by which pathological diagnosis in the lymph nodes was made ie: surgical resection versus minimally invasive procedure such as endobronchial ultrasound? Differences in nodal sampling technique will yield differences in diagnostic yield and impact upon true diagnosis of skip metastasis or not

**Reply 2:** Thanks for your advice. It is important to differentiate surgical resection and minimally invasive procedure when assessing the pathological diagnosis as the reviewer mentioned. We included articles in which lymph nodes are obtained by surgical resection. We added the definition as you recommended in the manuscript.

**Changes in the text:** We added the method of pathological diagnosis in the Methods

section in Page 5, line 83 as follows: All the included articles assess the pathological diagnosis under surgical resection.

**Comment 3:** Statistical analysis – what variable have the authors used to weight the studies?

**Reply 3:** Thanks for your comment. When combining different results among studies,  $I^2$  was used to determine the effect model validated. Mild heterogeneity was defined as  $I^2 < 50\%$ , and a standard fixed-effect model (FE) test was used to validate outcome synthesis. The weight in the “inverse variance method” FE model is based on Woolf (Woolf 1955). The weights are equal to the inverse variance of each study’s effect estimator. Larger studies and studies with less random variation are given greater weight than smaller studies. For studies yielding  $I^2 > 50\%$ , the random effect model (RE) was applied to pool the data. Weighting within the RE model assumes two sources of variability in effects, one from sampling error and one from study level differences.

**Changes in the text:** We described the statistical analysis more clearly according to the comments in Page 6, line 106 as follows. Compared with fixed-effect model, weighting within the random-effect model assumes two sources of variability in effects, one from sampling error and one from study level differences.

**Comment 4:** Results: Article selection – report results for heterogeneity analysis

**Reply 4:** Thanks for your suggestion. We added the heterogeneity in each result we presented.

**Changes in the text:** The heterogeneity in each result was added in the Result section and were all marked in red.

**Comment 5:** Discussion: Page 12, line 212 – for those unfamiliar, include reference to nodal station anatomy

**Reply 5:** Thanks for your kind advice. We added the citation of nodal station anatomy when discussing the prevalence of skip node metastasis.

**Changes in the text:** Thus, mediastinal lymph node dissection would require additional care in the above stations under the nodal station anatomy even if no N1 station metastasis is found.

**Comment 6:** Page 12, line 227 – avoid informal phrasing “what’s more”. Consider “furthermore”

**Reply 6:** Thanks for your kind suggestion. We modified the expression according to your suggestion.

**Changes in the text:** Furthermore, our work validated the subclassification of N2 based on the newest IASLC staging.

**Comment 7:** The authors report significant publication bias. This needs to be discussed further in the limitation of this study, and the impact upon results discussed.

**Reply 7:** Thanks for the advice. It is important to discuss the publication bias in the Discussion section in order to improve the quality of our work.

**Changes in the text:** We added the comments in the Discussion section in Page 12,

line 230 as follows: Furthermore, the publication bias among the included articles should be noticed and studies based on large scale population should be conducted to ascertain the prognostic effect of skip metastasis.

**Comment 8:** Figure 1 – Formatting needs to be corrected as the headings on the left hand side of diagram and arrows have shifted. Need to list reasons for exclusion of articles.

**Reply 8:** Thanks for your advice. We rechecked the Figure 1 to make sure the format is correct. And reasons for exclusion of the articles were listed in Figure 1.

**Changes in the text:** Reasons for the exclusion of the articles were added in Figure 1.

**Comment 9:** Figure 2c – missing?

**Reply 9:** Sorry for causing the inconvenience in reading, the figure legend was amended in accordance with our manuscript.

**Changes in the text:** Figure legend was corrected in accordance with our manuscript.

**Comment 10:** Figure 3 – the quality of this figure is not consistent with the other figures ie: no labelling of axes, no I<sup>2</sup> / p value stated

**Reply 10:** Thanks for the comment. Sensitivity analysis was performed by sequential removal of each study. The consistency of results was assessed by evaluating whether each estimate effect size crosses the confidence interval (CI) of the initial result. The labelling of the axes shows the estimate effect size and corresponding CI of the initial result (solid line in the figure) and the range of removing each study. No p value or I<sup>2</sup>

was generated by the software we used (Stata V12). However, as we mentioned above, the result of this figure is easy to understand without p value presented. We are really sorry for not presenting p value or  $I^2$  due to the technical reason.

**Changes in the text:** We added a more detailed description in the Result section when reporting the sensitivity analysis for a better understanding of this figure.