

## Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-769>

### Reviewer A

I read your very interesting article titled “Prognostic significance of lymph nodes assessment during pulmonary metastasectomy: a Systematic Review and Meta-Analysis”. Thank you for the informative article. This is a well written manuscript addressing an important issue in pulmonary metastasectomy. This reports the first systematic review and meta-analysis of lymphadenectomy for metastatic lung tumors. Readers are eagerly awaiting this review.

There are some minor changes required:

In Figures 3, S3, S5, S6, S7, S8 and S9, "Shiono" is misspelled as "Shiano".

*Reply: Dear Reviewer,  
thank you for your kind comments. We have corrected the spelling mistakes*

### Reviewer B

The topic of the paper is interesting and potential useful for the daily surgical activity. The statistical analysis is very complex and this makes not simple to read the paper. The message of your study is clear. However, there are some points to debate. 1) It is not clear if the PM in the included studies was always considered complete or sometimes just for diagnosis; 2) it is not clear how many patients did adjuvant chemotherapy after resection (line 186 is not clear) 3) if the lymph node dissection could have a "curative" intent, surely the sampling doesn't have it; for this reason it is crucial to know postoperative cure.

At line 55 it misses a "not".

At line 71 The instead of the

At line 143 lymph node instead of lymphnode

At line 187 what means (<50%, >50% etc)

Figure S6 regimen instead of regiment

*Reply: Dear Reviewer,  
thanks a lot for your precious comments. Unfortunately, the definition of lymphadenectomy in all included papers (just like in a real-life scenario) was not clear nor well defined. As we stated in the discussion, we are aware that this is a big bias which can influence OS and DFS.  
Regarding the <50%, >50% comment: Thank you for spotting this. This means less than 50% of patients received chemotherapy in the study. We have made it clearer in the manuscript*

### Reviewer C

In total the authors are analyzing if a lymph node dissection in patients with lung metastases has an impact on survival or relapse free survival.

I have some remarks:

1. As the authors are mentioning in line 297, there is a big heterogeneity regarding the primary cancer in the analyzed studies. As we know that the prevalence of lymph node metastases differs between the tumor entities, this has a really big influence on the results. Especially sarcoma patients have a low number of lymph node metastases. The primary cancers should be the same tumor entity if you want to compare the results.
2. As this is a meta-analysis it would be important that the compared results had the same kind of lymph node dissection. It is not possible to compare a lymph node dissection with lymph node sampling. Were in all included studies the lymph node dissection reported and also reported how many stations/ lymph nodes were dissected?
3. Some of the included studies included patients with lymph node dissection and without. This is also a bias, because nobody would not do a lymph node dissection if lymph node metastases were suspected before or during the operation. Due to this reason, patients with lymph node metastases would more often have a lymph node dissection and this influences survival.
4. Regarding relapse free survival and overall survival it is important to know which kind of chemotherapies the patients had and if they had an additive chemotherapy after the metastasectomy. This is really difficult to analyze by the authors, but if you want to analyze these endpoints this is very important. And also here the heterogeneity of the primary cancer has a big influence.
5. Was there a big heterogeneity between single and multiple metastases and between preoperative lymph node metastases in the included studies?
6. How was the follow-up performed in the included studies? Was it equal in all studies? This has also an influence on the results.

*Reply: Dear Reviewer,  
thanks for your comments.*

*Giving the heterogeneity of lung metastases from different primary cancers we performed a subgroup analysis (Figures S8 and S9 in the supplementary material) in patients with pulmonary metastases from colorectal cancer or sarcoma but we did not analyze separately all the different primary tumors subgroups (for statistical reasons). Unfortunately, the papers included in our analysis even if they are representative of the actual level of evidence in the literature did not report any information about pre-operative lymph nodes status, how many stations or number of lymph nodes were dissected, type of follow-up and which regimens of chemotherapy were applied.*

*Regarding the number of metastases, thank you for raising this important point. We have added a subgroup analysis for the number of patients with multiple metastases. We only found a statistically significant different results for two studies that did not report the number of patients with multiple metastases.*

## **Reviewer D**

We appreciate the opportunity to review this work

And we would like to congratulate the authors on a fine systematic review  
Even though we realize that this manuscript must have taken a lot of time to perform  
We must admit that we lack the understanding what this systematic review adds to a recently performed systematic review on this topic, PMID: 34656390. This SR included several of the manuscripts that have been included in this review.  
The authors must have been aware of this publication, because they used the reference in the introduction.  
Also, the current systematic review adds a lot less articles even though it includes articles of different tumor types and the EJSO SR was prespecified for CRC..  
Two other questions come up, why no registration on Prospero? And why did you not decide to only select metastases of one tumor type.  
Lastly, and that is a bit of a detail, the 2008 ESTS survey was used in the discussion, but the 2023 ESTS survey was not referred to?

*Reply: Dear Reviewer,*

*thanks a lot for your time reviewing our paper and thanks for your comments. We are aware of the cited systematic reviews on colorectal cancer metastases but given the lack of a meta analysis including **all histology subgroups** of lung metastases (from different primaries rather than only colorectal) we believe it was justified to perform this new one, which includes all types of quoted primaries. Moreover, we did perform a sub analysis based on specific primary subtypes, hence assessing each one of them separately. That, we believe, gives a more accurate and all-inclusive analyses of the role of lymph nodes assessment in metastatic diseases to the lung, the purpose of the current analysis (our manuscript)..*

*We worked on this paper during covid pandemic, so Prospero was not accepting new registration. For this reason, we decided to register the metanalysis on Open Science Framework.*

*Finally, We agree with you regarding including the 2023 ESTS survey and we apologize for the shortcoming, Accordingly, we updated the citation of the recent contemporary Survey, and added it to the discussion, even though the percentage of surgeons who are not performing mediastinal lymph nodes assessment remained the same.*

## **Reviewer E**

I would like to congratulate for your effort to determine the utility of lymph node dissection during pulmonary metastasectomy. You included only 11 studies and heterogeneity was high to make clear conclusion.

I have observed that you didn't include the Spanish prospective studies (Call et al. Surgery Today 2015). They reported that lymph node dissection was associated with better DFS and OS during pulmonary metastasectomy for colorectal cancer patients. Can you comment?

In addition you mention the ESTS survey of 2008. This survey has been updated recently and should be mentioned (Metastasectomy for colorectal pulmonary metastases: a survey among members of the European Society of Thoracic Surgeons. van Dorp M, Gonzalez M, Daddi N, Batirel HF, Brunelli A, Schreurs WH. Interdiscip Cardiovasc Thorac Surg. 2023 Feb 6;36(2):ivad002)

You did not mention that there is an ongoing RCT (NCT03113318)

(No lymph node dissection versus systemic mediastinal lymph node dissection during pulmonary metastasectomy for CRC) in Denmark. This study will probably give important informations.

*Reply: Dear Reviewer,*

*thanks a for your comment. We did not include the study written by Call and coll because the study compared survival rates between patients that had positive vs negative vs unknown (non-sampled LNs) LN metastases. Unfortunately, the outcome data/survival curves that separated patients based on dissection/sampling vs non dissection/sampling was not reported, and as such, could not be included in a systematic review process. While there are many articles on the subject, only those who would fulfill our inclusion criteria could be included in the analyses.*

*We updated the citation of the 2023 ESTS survey (see comment to previous reviewer), updated the discussion to reflect it and we cited in the discussion the ongoing trial from Denmark.*

*Thank you for helping us improving the quality of the manuscript.*

## **Reviewer F**

Dear authors,

I was allowed to review your manuscript. You deal with an interesting and important topic, as the role of thoracic lymph node dissection remains unclear. Your manuscript is well written. The meta-analysis is also presented in a well-structured way, although this should still be checked by a statistician. I understand the difficulty of this questioning/analysis, but I have a few comments/questions:

- In your meta-analysis, do you have information on the number of lung metastases and their impact on prognosis?
- Do you have information on the preoperative lymph node status in the imaging/staging? This could also influence the decision for lymph node dissection.
- Are patients included with bilateral lung metastases?
- Do the publications provide further data on the extent of lymph node dissection (systemic versus sampling)? When sampling and when systemic lymph node dissection?

There is still a very heterogeneous patient population with lung metastases from different primary tumours. In my opinion, thoracic lymph node dissection as well as the prognosis of patients is influenced by numerous parameters: preoperative thoracic lymph node status, location and number of lung metastases, histology and tumour stage of the primary tumour.

In summary, the role of thoracic lymph node dissection remains unclear. However, several other prognostic factors for survival must also be considered. This should be discussed further in the debate.

*Reply: Dear Reviewer, thank you for your important comments. We completely agree with you. Several prognostic factors should be kept in mind and, unfortunately, the papers included in our analysis, even if they are representative of the actual level of evidence in the literature, did not report any information about pre-operative lymph nodes status, localization of the metastases, how many stations or number of lymph nodes were dissected, type of follow-up and which regimens of chemotherapy were applied and imaging methods used prior to surgical intervention to determine or exclude the existence of lymph nodes metastases. As is commonly the case with a research question where the level of evidence is low, and the quality of existing publications is limited, the process of systematic review and meta-analysis has to rely on those publications, with all their limitations, as reflected by the relatively low number of articles which were analyzed in the final analysis, amid a very large number of publications on the subject (see figure 1). We added few comments in the discussion to reflect on your comment. Thanks for helping us improving the quality*

*of the paper.*

## **Reviewer G**

I read with great interest your manuscript reporting a pooled analysis of studies involving patient undergoing pulmonary metastasectomy with/without associated lymphadenectomy. The methodology is solid and well-described and the risk of biases across and within studies is elegantly reported with adequate graphs. Figures and tables are well-designed. Based on the nature of the included studies, the analysis intrinsically bears several limitations, that are clearly highlighted. I do not have major observations on this manuscript and I would therefore accept it in the present form. I only suggest a English language editing for some minor imperfections.

*Reply: Dear Reviewer, thanks a lot for your comments and your time spent on reviewing our paper. We carefully checked the manuscripts and corrected all grammatical issues, when appropriate*

## **Reviewer H**

An interesting article on a topic of importance in the space of pulmonary metastasectomy.

Good use of analysing both grouped and patient level data and well-selected subgroup analyses. It appears that the PRISMA checklist was accurately adhered to. Limitations are accurately mentioned and conclusions are supported by the evidence.

*Reply: Dear Reviewer, thanks a lot for your comments and your time spent on reviewing our paper.*

## **Reviewer I**

The Meta-analysis investigates a very interesting aspect of the pulmonary metastasectomy. As the authors report in their manuscript the studies that are familiar with the aspect are limited. However, as it was expected, lymph node sampling did not influence overall survival.

The authors should report how many of the patients had lymph node metastases and if this fact influences survival. If it is mentioned in the included studies the rates of preoperative suspicious lymph nodes should be included. As many of these aspects could be missing from the included studies as alternative could be a mention in the limitations section. I think that these adds would make the manuscript more interesting.

*Reply: Dear Reviewer, thanks a lot for your comments. We fully agree with you. Actually,, the papers included in our analysis, even if they are representative of the actual level of evidence in the literature, did not report several important factors, such as pre-operative lymph nodes status, type of imaging methods used to detect lymph nodes metastases **pre** operatively, localization of the metastases, how many stations or number of lymph nodes were dissected, type of follow-up and which regimens of chemotherapy were applied. We updated the discussion to reflect those short comings. Thank you for helping us improving the quality of the paper.*

## Reviewer J

The prognostic significance of lymph node dissection in lung resection for metastatic lung tumors, although clinically important, has only been studied in small retrospective studies. It is worthwhile to conduct a meta-analysis on this issue. The analysis is carefully conducted and fully addresses the biases that the original studies contained. The conclusions are reasonable and acceptable.

Li. et al's HR for OS is 0.65 in Figure 3, while it is 1.35 in Figure 5. It is necessary to explain how such a marked difference can be caused simply by a change in the analysis method.

*Reply: Dear Reviewer: thank you very much for bringing this to our attention. We regret that an oversight occurred in our original manuscript. In the previous version of the manuscript, we inadvertently included outdated versions of Figure 5 and Figure 6. In the previous version of the figures, we had included odds ratios 5-year survival rates extracted for Kaplan-Meier curves, for studies where this information was not explicitly provided. This affected 3 studies: Li et al., Pawelczyk et al., and Winter et al. We abandoned this approach because it combines the disadvantages of both analyses methods. In the new version of the figures, we have rectified this and excluded those studies. Additionally, this old version still pools risk ratios instead of odds ratios. This was also rectified in the new version, as seen in the final manuscript attached.*

Page 10, line 224

It should be noted what HR, CI and PI stand for.

The authors use both hazard ratio and odds ratio throughout the Manuscript, which term is correct?

*Thank you for your comment. In our manuscript, we conducted two separate meta-analyses using different analysis techniques. The first meta-analysis focused on survival analysis and utilized reconstructed individual patient data. The outcome measure for this analysis was the hazard ratio (HR). One of the main advantages of this method is that the HR provides a comprehensive summary measure over time and that it can handle censored data (e.g. loss-to-follow up). However, it does require manual reconstruction of the Kaplan-Meier curve. The second meta-analysis examined the 5-year survival odds ratios. This particular measure has the advantage of being frequently reported in the primary studies. However, it only captures information from a single time point. In order to address these different aspects, we included a paragraph in the manuscript explaining why we employed both specific techniques.*

Numerous errors in notation as follows

Page 4, line 71

the addition >> The addition

Page 7, line 143

lymphnode >> lymph node

Page 7, line 151

DSF >> DFS

Page 12, line 266

DSF >> DFS

Page 13, line 293

DFI >> DFS

Page 14, line 306

DFI >> DFS

Figure 3 etc.

Shiano >> Shiono

*Thank you, all corrected*