

## Peer Review File

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### Reviewer A

This was a systematic literature review to assess differences in short- and long-term postoperative outcomes comparing anatomical and non-anatomical resections of lung metastases from colorectal cancer. Both RCTs and observational studies were considered. Out of 432 papers, three observational studies (1342 patients) were included.

This was an interesting and important research question.

**Comment 1:** The Introduction could be shortened. Perhaps some paragraphs could be moved to the Discussion instead.

**Reply 1:** We thank Reviewer A for his/her remark. We have shortened the Introduction and moved some paragraphs to the Discussion section.

**Changes in the text 1 (in red):** pages 11-12; lines 273-278, 292-305.

**Comment 2:** The first paragraph of the Discussion should summarize the main findings.

**Reply 2:** We thank Reviewer A for pointing out this issue. We have added a short paragraph at the beginning of the Discussion section.

**Changes in the text 2 (in red):** page 11; lines 267-272.

**Comment 3:** Please add a “Study limitations” subheading in the Discussion that clearly highlights the limitations of the current study.

**Reply 3:** We thank Reviewer A for his/her comment. We have added a subheading before discussing the limitations of the study.

**Changes in the text 3 (in red):** page 14; line 382.

### Reviewer B

This is a very well executed and written review on the significance of anatomical resections in colorectal cancer. All conclusions are bolstered by the presented data. Just two aspects which might be worth discussing:

**Comment 1:** I believe there is a risk for negative confounding when retrospectively comparing groups with different extents of resection for what is seemingly the same disease. Most likely there are clinical, non-measurable and thus not reported aspects which are influencing survival.

**Reply 1: We thank Reviewer B for pointing out this issue. We have added confounding to the limitations of the study.**

**Changes in the text 1 (in red): page 14; lines 385-387.**

Comment 2: In the light of JCOG0802: What is the actual significance of local tumor control for survival? In the JCOG trial sublobar resections result in more frequent recurrences but longer survival. CRC are relatively slow growing and local control rarely has any impact on survival in these patients.

Maybe you could add some of your thoughts about these aspects to the discussion.

**Reply 2: We thank Reviewer B for his/her suggestion. The JCOG0802 trial, however, compared segmentectomies and lobectomies for primary early-stage lung cancer. We believe it is not recommended, from a methodological point of view, to compare lung resection for primary early-stage lung cancer (stage I disease) with lung metastasectomy for stage IV CRC.**

**Changes in the text 2 (in red): none.**

### **Reviewer C**

This is a very well written systematic review on prognosis after pulmonary metastasectomy of CRC metastases. The focus is on the influence of the amount lung tissue resected on prognosis.

All aspects have been discussed. Unfortunately, only 3 reference publications have been found and therefore the results and conclusions are not so helpful for the readers.

**Comment 1:** As the whole paper is focused on the prognostic influence of anatomic vs. non-anatomic or sublobar resection, I think the title does not adequately reflect the topic. Please find a better solution. The running title seems to be more suitable...

**Reply 1: We thank Reviewer C for pointing out this issue. We have modified the title and running title accordingly.**

**Changes in the text 1 (in red): page 1; lines 2-4.**

**Comment 2:** The "purpose of this systematic review is to assess the differences in short- and long-term outcomes depending on the surgical extent of PM with curative intent." This purpose is not reflected in the conclusions sections, no answers are given to the initial questions.

**Reply 2: We thank Reviewer C for his/her suggestion. We have modified the Conclusions accordingly.**

**Changes in the text 2 (in red): page 15; lines 388-399.**

### **Reviewer D**

The article is a systematic review to try to establish if the type of resection of PM was associated with the survival.

They selected three retrospective studies and determined that anatomical resection was associated with an improved RFS. The article is well written and well designed. Unfortunately, the 3 selected available studies didn't allow to improve our knowledge on PM with a meta-analysis.

**Comment 1:** This review pointed out our ignorance and all that remains to be done (particularly on understanding the impact of genotype/phenotype of CRC metastasis on the extension of the disease, and so on the extension of the resection).

For me this review can not have this conclusion.

**Reply 1: We thank Reviewer D for his/her suggestion. We have modified the Conclusions accordingly.**

**Changes in the text 1 (in red): page 15; lines 388-399.**

## **Reviewer E**

**Comment 1:** I have some troubles qualifying the manuscript as a "systematic" review, it sometimes reads more like "a review of the literature". The full search strategy was not provided on Prospero and the manuscript only noted "pulmonary metastasis"[All fields], as the search term for pulmonary metastases. This is probably the reason why the authors only reviewed 431 articles.

I would suggest the following search bloc for pulmonary metastases in Medline:

(Pulmonary Metasta\*[Tiab] OR Lung Metasta\*[Tiab] OR "Lung Neoplasms/Secondary"[MeSH] OR Metastasectomy[Mesh] OR Metastasectomy[Tiab] OR Metastasectomies[Tiab]).

Also, the initial search strategy on Prospero does not match the content of the manuscript: "Outcomes of typical segmentectomy versus atypical segmentectomy versus lobectomy in the surgical treatment of lung metastasis from colorectal cancer", was the title on Prospero. This title suggests a deliberate search for articles on 'colorectal' metastases. The manuscript states that "the search design did not exclude any primary tumour histology", however the authors included three studies for review that all included pulmonary metastases from colorectal cancer patients. This is a bit confusing to me.

**Reply 1: We thank the Reviewer for his remarks. As regards registration on PROSPERO, we reported the search strategy that was initially submitted. In order to enable PROSPERO to focus on COVID-19 registrations during the 2020 pandemic, our systematic review's registration record was automatically published exactly as submitted. Afterwards, we have updated the search protocol, but it has not been reviewed by the PROSPERO team.**

**The full search strategy was similar to the one you suggested:**

**Pulmonary Metastasis[Tiab] OR Lung Metastasis[Tiab] OR "Lung**

**Neoplasms/Secondary"[MeSH] OR Metastasectomy[Mesh] OR Metastasectomy[Tiab] OR Metastastomies[Tiab]**

**Changes in the text 2: none.**

**Comment 2:** In the results section, the outcome of three individual studies is presented without presenting comparisons between these studies. Several comparisons are presented in the discussion section, however comparing the outcome of included studies in a systematic review should be presented as the results of your study. Even without performing a meta-analysis, the outcome of a systematic review is the comparison of the included studies.

All three included studies present different groups. The Hernandez study compares major to lesser resections, the Shiono study compares wedge to segmentectomy and the Li study compares lobectomy to sublobar resections. Including three studies with different grouping complicates comparative analyses.

**Reply 2: We thank Reviewer E for pointing out this issue. We have added a final paragraph in the Results section to summarize and compare the outcomes of the three included studies. We agree that analysing studies with different grouping is problematic and would not be methodologically appropriate, which is one of the reasons why a meta-analysis was not possible.**

**Changes in the text 3 (in red): page 10; lines 249-264.**

**Comment 3:** On several occasions throughout the manuscript colorectal pulmonary metastases are referred to as 'lesions'. Personally, I would refrain from using this term. These are pathologically proven colorectal metastases.

**Reply 3: We thank Reviewer E for his remark. We have modified the text accordingly.**

**Changes in the text 4 (in red): pages 1, 4, 8; lines 49, 104, 182; Table 1.**

**Comment 4:** A disadvantage of the current concept of the study is a relatively vague research question. The reader is sometimes left in doubt which resections are compared to each other. Just mentioning anatomical resections, limits the applicability of the current study. The authors describe correctly in the discussion section, that it is more likely that minor resections are performed for peripheral metastases, while central metastases often require an anatomical resection.

Personally, I would prefer to compare two comparable resections when performing a systematic review on this topic, and compare wedge resection to segmentectomy for colorectal pulmonary metastases. This way, many more articles can be included for comparative analysis. Especially comparing the local (staple line) recurrence rate between both type of resection would be of interest.

**Reply 4: We thank Reviewer E for pointing out this issue. We acknowledge the limitations of our systematic review concerning non-measurable data (peripheral vs hilar vs central metastases, respiratory function, etc.). However, our intents in comparing anatomical and non-anatomical resections for lung metastasectomy were:**

- to cover the broad and diversified spectrum of the current surgical practice

- for lung metastases: in some centres only wedge resections or lobectomies are performed, while segmentectomies find little applicability
- to include a higher number of studies: a quick search on PubMed (performed on 12/04/2022) using the following string ("wedge resection"[All Fields] AND ("segmentectomy"[All Fields]) AND ("metastasectomy"[All Fields]) only identified 29 results
  - to assess the difference in radicality between non-anatomical resections (which solely imply sectioning the lung parenchyma) and anatomical resections (which also require vascular and bronchial suturing, and are more commonly associated with lymph node dissection)

**Changes in the text 5: none.**

**Comment 5:** I fully concur with the final conclusion of the article that there is a knowledge gap in the field of pulmonary metastasectomy which should be addressed.

**Reply 5:** We thank Reviewer E for his valuable comment.

**Changes in the text 6: none.**

#### **Reviewer F**

This is the systematic review for outcomes of pulmonary metastasectomy for colorectal cancer metastasis.

I have two questions for authors.

**Comment 1:** First, what is the primary outcome you want to reveal in this review? There were only three reports matched to inclusion criteria, showed Table1, but I could not find the main implication you gained in these reports. I think it is important to briefly state the common content between these reports even if meta-analysis was not feasible.

**Reply 1:** We thank Reviewer F for pointing out this issue. We have added a final paragraph in the Results section to summarize and compare the outcomes of the three included studies.

**Changes in the text 1 (in red): page 10; lines 249-264.**

**Comment 2:** Second, what are the novelty and strength in this report ? it is important to mention about the value of your report. I think this is valuable review in terms of providing an alert that there has not been enough evidence to PM.

**Reply 2:** We thank Reviewer F for his/her valuable comment. We have modified the Conclusion section describing the novelty and strengths of our work.

**Changes in the text 2 (in red): page 15; lines 391-392, 395-396.**

#### **Reviewer G**

This is an interesting and generally well-written paper. The authors present their results of a systematic literature review regarding a comparison of anatomical versus non-anatomical resection of lung metastases. Lung metastasectomy is a frequently used therapeutic option with promising results lacking randomized data mainly due to ethical reasons. Therefore, this paper covers a relevant clinical problem.

Only 3 retrospective non-randomised studies (out of 432 papers) with 1.342 patients were appropriate for the systematic review.

There are a few areas in which I believe the manuscript could be modestly improved:

**Comment 1:** The authors should comment on the relevance of laser resection for lung metastasectomy. It is a wellknown fact that, despite histologically proven free resection margins, local recurrences close to the stapler line occur. Therefore, laser resection is recommended by many authors. One could hypothesize, that laser resection would lead to similar results regarding resection-margin recurrences and RFS as compared to anatomical resections.

**Reply 1: We thank Reviewer G for his/her valuable suggestion. We have added a paragraph focusing on laser resection in the Discussion section.**

**Changes in the text 1 (in red): pages 13-14; lines 354-365.**

**Comment 2:** The authors should clarify the details of technique which have been compared (anatomical vs. non-anatomical or major vs. lesser resections). Anatomical segmentectomies represent adequate anatomical resections even discussed as state-of-the-art procedures for early stage lung cancers.

Line 39: “Methods: A systematic literature review of studies comparing anatomical and non-anatomical resections of 40 lung metastases was performed”

Results line 191: Study by Hernandez: “104 major resections (19.9%; 192 100 lobectomies and 4 pneumonectomies) and 418 lesser resections (80.1%; 394 wedge resections, 19 193 anatomical segmentectomies and 5 atypical resections).”

**Reply 2: We thank Reviewer G for pointing out this issue. Indeed, our aim was to compare anatomical vs non-anatomical resections. Also, we agree on the value of segmentectomies as established anatomical resections. Our systematic search included an extremely small number of papers, therefore, after conferring, we decided to select the paper by Hernández et al. (as in the major resection group only anatomical resections, lobectomies and pneumonectomies, are included). Of course, we took this bias into account when describing the limitations of our systematic review (see page 14; lines 383-385).**

**Changes in the text 2: none.**

**Comment 3:** The conclusion should determine, that the extent of resection depends mainly on the location, size and number of metastases.

**Reply 3: We thank Reviewer G for his/her valuable comment. We have modified the Conclusion section accordingly.**

**Changes in the text 3 (in red): page 15; lines 397-398.**

**Reviewer H**

**Comment:** This systematic review article for pulmonary metastasectomy from colorectal carcinoma has quite important and practical information. Anatomical resection might contribute to improve the postoperative outcome.

The manuscript is well written and could be considered for high priority for publication.

**Reply: We would like to express our gratitude to Reviewer H for his/her comment.**

**Changes in the text: none.**