



# Prognostic significance of lymph nodes assessment during pulmonary metastasectomy: a systematic review and meta-analysis

Fabrizio Minervini<sup>1#^</sup>, Allen Li<sup>2#</sup>, Marianna Qu<sup>3</sup>, Henning Nilius<sup>4</sup>, Yaron Shargall<sup>5^</sup>

<sup>1</sup>Division of Thoracic Surgery, Cantonal Hospital Lucerne, Lucerne, Switzerland; <sup>2</sup>Faculty of Medicine & The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada; <sup>3</sup>School of Medicine, Queens University, Kingston, ON, Canada; <sup>4</sup>Department of Clinical Chemistry, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; <sup>5</sup>Division of Thoracic Surgery, Department of Surgery, McMaster University, Hamilton, ON, Canada

**Contributions:** (I) Conception and design: F Minervini; (II) Administrative support: F Minervini; (III) Provision of study materials or patients: A Li, M Qu; (IV) Collection and assembly of data: A Li, M Qu; (V) Data analysis and interpretation: A Li, F Minervini, H Nilius; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

<sup>#</sup>These authors contributed equally to this work.

**Correspondence to:** Fabrizio Minervini, MD, PhD. Division of Thoracic Surgery, Cantonal Hospital Lucerne, Spitalstrasse, 6000 Lucerne 16, Switzerland. Email: fabriziominervini@hotmail.com.

**Background:** Lung metastasectomy is an accepted treatment modality worldwide. Whether the addition of lymph node dissection to the procedure is useful remains, however, unknown.

**Methods:** We performed a systematic review of the literature analyzing MEDLINE, Embase, until 31st October 2021. We included all studies which met the inclusion criteria aiming to determine if the addition of lymph node tissue dissection/sampling to lung metastasectomy offers survival benefits when compared to patients who do not receive lymph node tissue dissection. Secondary outcomes were 3- and 5-year overall survival (OS) and disease-free survival (DFS). Each study was assessed for risk of bias. The data collected from the included studies were pooled using reconstruction of individual-level patient data and pooling of reported 5-year odds ratios (ORs). Interstudy heterogeneity was estimated with visual inspection of forest plots and calculation of the  $I^2$  inconsistency statistic.

**Results:** We found 11 eligible studies that included a total of 3,310 patients. The most common primary tumor type was colorectal cancer (1,740 patients) and the most commonly performed operative procedure was wedge resection (57%) followed by lobectomy (39%). When resection status was reported, R0 resection was achieved in 90% of the cases. Nine studies did not show a statistically significant effect of lymph nodes dissection or sampling on the 5-year OS with a pooled hazard ratio (HR) of 0.94 [95% confidence interval (CI): 0.82, 1.08;  $I^2=26%$ ; 95% prediction interval (PI): 0.70, 1.24]. Regarding DFS, the pooled HR 0.60 (95% CI: 0.44, 0.80;  $I^2=31%$ ; 95% PI: 0.12, 2.09).

**Conclusions:** The addition of lymph node tissue dissection during lung metastasectomy was not associated with a significant benefit in OS and showed a slight tendency towards a better DFS.

**Keywords:** Lung metastasectomy; lymphadenectomy; lung metastases

Submitted May 11, 2023. Accepted for publication Oct 25, 2023. Published online Dec 07, 2023.

doi: 10.21037/jtd-23-769

View this article at: <https://dx.doi.org/10.21037/jtd-23-769>

<sup>^</sup> ORCID: Fabrizio Minervini, 0000-0003-3595-7307; Yaron Shargall, 0000-0001-8585-0327.

## Introduction

Lung metastases are a frequent development in cancer patients. Historically, the presence of pulmonary metastases was synonymous with systemic disease and was commonly referred to as an incurable state and hence, if treated with chemotherapy, was with a palliative intent. In the modern day, however, isolated lung metastases are no longer considered as untreatable and local surgical resections are offered for selected patients. Several studies have shown a survival benefit associated with resection of lung metastases (1-3). Prognostic factors at the time of pulmonary metastasectomy (PM) have been retrospectively analyzed to identify and select patients who can potentially benefit from surgical resection of lung metastases. Histology of primary tumor, disease-free interval (DFI, namely the interval between resection of the primary tumor and detection of metastasis), control of the primary site of malignancy and number of metastases are usually considered valid prognostic indicators (1,4,5). Another prognostic factor is the presence or absence of local pulmonary lymph node metastases at the time of PM. Many studies have documented that the presence of metastatic lymph nodes is a sign of poor prognostic outcome (4,6,7). In the pre-operative assessment, a standard management is currently lacking because some authors rely on computed tomography (CT) whereas in several centers positron emission tomography (PET), endobronchial ultrasound (EBUS) or mediastinoscopy are part of the preoperative work-up.

Systematic lymph nodes dissection or sampling at the time of surgery for primary lung tumors has been established as the standard of care. This practice, however, remains to be validated when it comes to resection of secondary tumors.

### Highlight box

#### Key findings

- Lymphadenectomy during lung metastasectomy does not influence overall survival (OS) or disease-free survival (DFS).

#### What is known and what is new?

- There is a lacking of consensus if a lymph node dissection should be performed during pulmonary metastasectomy similarly to the standard of care for primary lung cancers.
- This meta-analysis shows no association between lymph node dissection and improved OS and a tendency towards a better DFS.

#### What is the implication, and what should change now?

- In the surgical treatment of pulmonary metastases, lung resection without lymph nodes dissection could be adequate.

Even if the presence of lymph nodes metastases might have an adverse effect on survival, the real incidence of lymph node involvement is probably underestimated because a clear consensus on when to perform lymphadenectomy during a PM is still lacking (6-10). As such, this systematic review sought to analyze the prognostic significance of mediastinal lymphadenectomy at the time of PM. We present this article in accordance with the PRISMA reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-769/rc>) (11).

## Methods

A detailed description of the study rationale, objectives and methods is outlined in a prospectively published protocol registered on Open Science Framework ([osf.io/694jp](https://osf.io/694jp)).

### Information sources and search strategy

An extensive search was conducted using the online databases MEDLINE and EMBASE with the aid of a medical librarian at McMaster University. Databases were searched from the first available date until 31st October 2021. Medical Subject Heading (MeSH) keywords and terms were used to construct search filters, with key terms covering mediastinal lymph node assessment during PM. The reference lists of relevant review articles were hand-searched for additional articles. Studies were selected for inclusion based on predefined eligibility criteria listed below. The specific search strategy for each database can be found in the [Appendix 1](#).

### Study selection process

The studies captured in the initial search were screened independently by two investigators (A.L., M.Q.) using the Covidence Software (Melbourne, Victoria, Australia) for systematic reviews. The investigators first screened the titles and abstracts of each article. Then, the full texts of each citation, identified as potentially relevant from the initial search were subsequently reviewed independently by both investigators once again. Any disagreements were resolved through deliberation and consensus between both investigators with a third investigator (F.M.).

### Eligibility criteria

Studies were included if the following inclusion criteria

were met: (I) participants were adults ( $\geq 18$  years of age) undergoing PM; (II) results on the oncological value of lymph node tissue sampling versus no sampling were reported (III) the number of patients undergoing lymphadenectomy was reported; (IV) the article reported either overall survival (OS) or disease-free survival (DFS) up to at least 3 years; and (V) the article was a cohort or randomized study. Studies that analyzed primary lung cancers were excluded.

### Outcomes

The primary outcome of this study was to determine whether lymph node tissue dissection at the time of PM offers survival benefit when compared to patients who did not receive lymph node tissue dissection. Secondary outcomes included DFS, 3- and 5-year OS. Post-hoc subgroup analyses were done to assess the primary outcome in different populations.

### Data extraction and risk of bias assessment

Data from included studies were extracted by two investigators (A.L., M.Q.) independently using a standardized electronic data extraction spreadsheet on Microsoft Excel (Microsoft, Redmond, WA, USA). Disagreements were then resolved through deliberation between both investigators. Non-randomized studies were assessed with the ROBINS-I tool for non-randomized interventional studies (12). Disagreements were resolved through joint deliberation.

### Statistical analyses

The results of the studies were pooled utilizing two different methods: reconstruction of individual-level patient data and pooling of reported 5-year odds ratios (ORs). For the reconstruction of the individual-level patient data event counts for the primary and secondary endpoints were reverse-calculated using the methodology described by Liu *et al.* and Guyot *et al.* (13,14). Briefly, these are validated methods of estimating patient level data through digitalizing and reconstructing patient level data. The main advantage of the individual level patient data is that they allow survival analysis and pooling hazard ratios (HRs) to provide a comprehensive summary measure over time.

To meta-analyze the reconstructed patient level data, univariate Cox proportional-hazard models were then fitted

to the individual-level patient data of each study separately. The assumption of proportional hazards was checked by looking at the correlation of the scaled Schoenfeld residuals with time. The logarithmically transformed HRs and corresponding standard errors were pooled using a random-effects inverse variance model as implemented in the “meta” package for R (15).

The reported ORs for the 5-year OS and DFS were pooled using a random-effects Mantel-Haenszel estimator. This has the advantage that the ORs are often reported in primary studies and that they are not reliant on manual digitalization.

Interstudy heterogeneity was assessed through visual inspection of forest plots and calculation of the  $I^2$  inconsistency statistic. We considered  $I^2$  values  $>25\%$ ,  $>50\%$ , and  $>75\%$  to be considered low, moderate, and high levels of heterogeneity respectively.

A leave-one-out analysis was performed as a first sensitivity analysis and Cook's distance and the studentized residuals were calculated (16). Studies with a Cook's distance  $>50\%$  of the lower tail of a chi-square distribution with  $n$  degrees of freedom ( $n$  = number of model coefficients) or studentized residuals outside of  $-1$  and  $1$ , were marked as potentially influential outliers. Additionally, a graphic display of study heterogeneity (GOSH) plot was created (17).

### Subgroup analyses

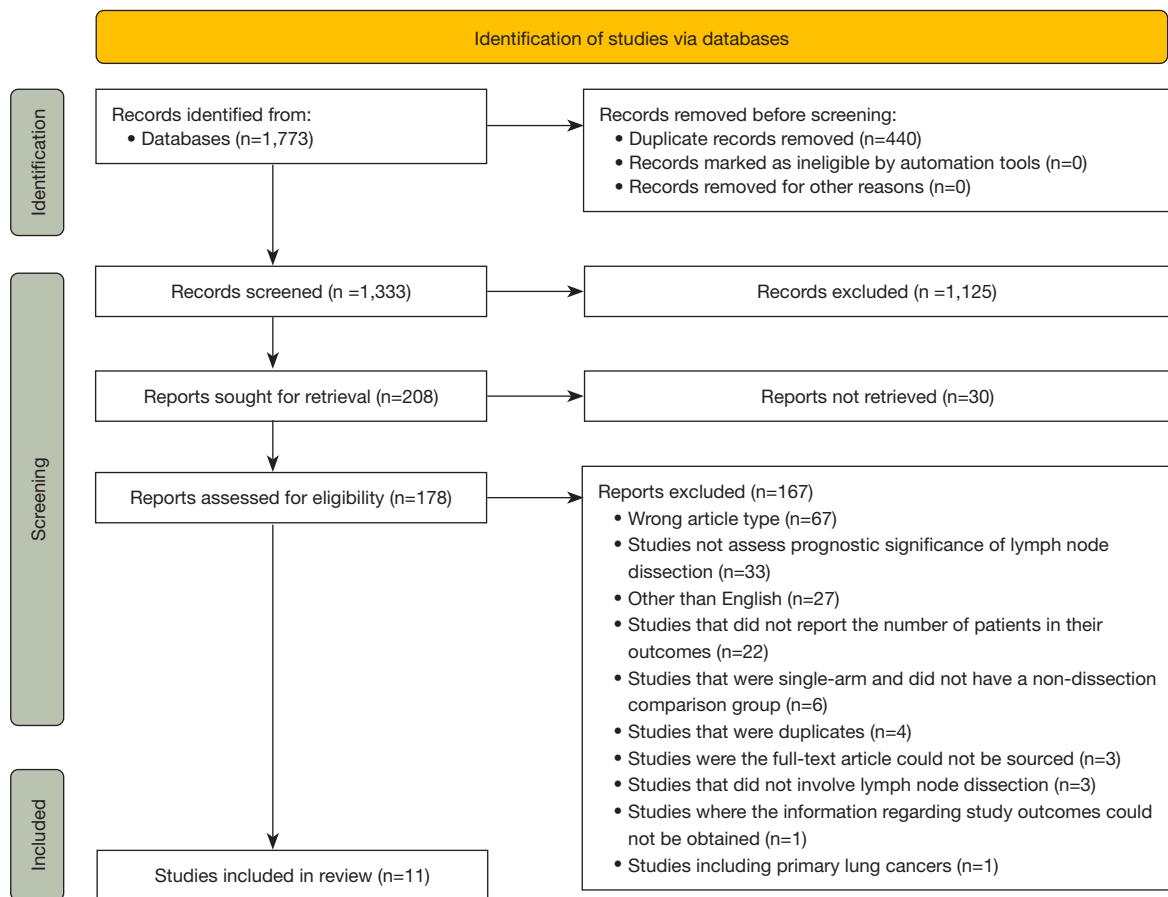
We performed subgroup analyses on the following groups: (I) percentage of patients receiving chemotherapy ( $<50\%$ ,  $\geq 50\%$ , not reported); (II) resection status (reported, not reported); (III) presence of colorectal cancer patients (only colorectal cancer patients; no colorectal cancer patients, mixed); (IV) presence of sarcoma patients (sarcoma patients present, no sarcoma patients present) and (V) percentage of patients with more than one metastasis ( $<50\%$ ,  $\geq 50\%$ , not reported).

Publication bias was checked using visual inspection of funnel plots and an Egger's test for asymmetry. All analysis was performed using the statistical software R version 4.1.2 (R Core team, Vienna, Austria).

## Results

### Study selection

Of the 1,773 studies captured in our search, a total of 11 non-randomized studies ( $n=3,310$  patients) were included



**Figure 1** PRISMA 2020 flow diagram.

for analysis (Figure 1).

### Characteristics of included studies

Characteristics of the included studies are summarized in Table 1. All studies were cohort studies with one being prospective and the remainder being retrospective. Data collected for the studies ranged from 1980 to 2017. Across the studies reporting the data, 61% of patients across nine studies had more than one pulmonary metastasis at the time of surgery with 15% across eight studies demonstrating thoracic lymph node involvement. The most common primary tumor type was colorectal cancer (n=1,740 patients) with five studies exclusively analyzing this tumor type (n=1,442 patients). The most commonly performed procedures were wedge resections (57%) and lobectomies (39%). Of the five studies that reported resection status, an R0 resection status was achieved 90% of the time.

### Risk of bias

Summary of the risk of bias analysis for the primary endpoint using the ROBINS-1 tool is shown in Figure 2. One study was rated to be at a critical risk to bias, three studies to be at a serious risk, and five studies to be at a moderate risk. The overall risk of bias for one study could not be evaluated due to criterion five (bias due to missing data) being indeterminant. Across all studies, however, bias regarding classification of intervention groups and reporting were the criteria least susceptible to bias (Figure S1). On the contrary, bias due to confounding and selection of participants were rated to be at the highest risk. Only one study employed methods to control for confounding factors (18).

### Individual-level meta-analysis

Individual-level patient data for the OS could be

**Table 1** Characteristics of included studies (18-28)

| Study, year, and country   | Recruitment period | Age | Male  | Whether receive lymphatic tissue resection |     | % receiving chemotherapy | Thoracic LN involvement | Primary tumor type  | Procedures done  | Resection extent |    |
|----------------------------|--------------------|-----|-------|--|-----|--------------------------|-------------------------|---|--|------------------|----|
|                            |                    |     |       | Yes  | No  |                          |                         |   |  | R0               | R1 |
| Casiraghi 2011, Italy      | 1998–2008          | 58  | 43%   | 353  | 137 | 50                       | 62                      | Breast [51], gastroduodenal [210], gynaecological [42], head and neck [43], thyroid/parathyroid [4], urogenital [86]  | Wedge resection [294], segmentectomy [58], lobectomy [132] pneumonectomy [6] | 490              | 85 |
| Hamaji 2012, United States | 1985–2009          | 62  | 61%   | 319  | 199 | NR                       | 40                      | Colorectal [all]  | Wedge resection [395], segmentectomy [31], lobectomy [85] pneumonectomy [4]  | NR               | NR |
| Ihn 2017, Korea            | 2003–2011          | 60  | 64.8% | 70   | 106 | 91                       | 9                       | Colorectal [all]  | Wedge resection [130], segmentectomy [17], lobectomy [29]                    | NR               | NR |
| Li 2020, China             | 2011–2017          | 59  | 60%   | 106  | 161 | 100                      | 13                      | Colorectal [all]  | Wedge resection [162], segmentectomy [12], lobectomy [93] pneumonectomy [0]  | NR               | NR |
| Lo Faso 2013, Italy        | 2000–2010          | 64  | 61%   | 117  | 49  | NR                       | 95                      | Breast [14], colorectal [99], gynaecological [2], head and neck [8], urogenital [3]   | Wedge resection [136], segmentectomy [22], lobectomy [53] pneumonectomy [1]  | 159              | 5  |
| Londero 2019, Italy        | 2005–2017          | 66  | 58%   | 86   | 95  | 64                       | NR                      | Breast [7], cutaneous [12] colorectal [76], gastroduodenal [1], gynaecological [5], head and neck [8], hepatobiliary or pancreatic [4], renal [25], thyroid/parathyroid [6], urogenital [1] | Wedge resection [110], segmentectomy [12], lobectomy [59] pneumonectomy [0]  | 174              | 7  |

**Table 1** (continued)

Table 1 (continued)

| Study, year, and country | Recruitment period | Age | Male | Whether receive lymphatic tissue resection |     | >1 pulmonary metastases | % receiving chemotherapy | Thoracic LN involvement | Primary tumor type   | Procedures done  | Resection extent |    |
|--------------------------|--------------------|-----|------|--|-----|-------------------------|--------------------------|-------------------------|--|--|------------------|----|
|                          |                    |     |      | Yes  | No  |                         |                          |                         |  |  | R0               | R1 |
| Pagès 2016, France       | 2005–2010          | 64  | 55%  | 161  | 156 | 250                     | 34.5                     | NR                      | Colorectal [all]   | Wedge resection [206], segmentectomy [27], lobectomy [116] pneumonectomy [5] | NR               | NR |
| Pawelczyk 2015, Poland   | 1996–2010          | NR  | 46%  | 50   | 195 | 250                     | 45.6                     | NR                      | Bone/soft tissue [1], breast [42], cutaneous [9], colorectal [65], gynaecological [30], head and neck [26], hepatobiliary or pancreatic [2] prostate [8], renal [46], urogenital [7] | Wedge resection [226], segmentectomy [9], lobectomy [15] pneumonectomy [0]   | NR               | NR |
| Riquet 2010, France      | 1985–2007          | 65  | 58%  | 82   | 35  | 42                      | 40                       | 13                      | Colorectal [all]   | Wedge resection/segmentectomy [125], lobectomy [81] pneumonectomy [17]       | NR               | NR |
| Shiono 2015, Japan       | 1980–2013          | 63  | 57%  | 545  | 67  | 392                     | NR                       | 108                     | Bone/soft tissue [1], colorectal [58], esophageal [1], gastroduodenal [2], gynaecological [11], head and neck [21], hepatobiliary or pancreatic [2], renal [8], urogenital [2]       | Wedge resection [0], segmentectomy [0], lobectomy [612] pneumonectomy [0]    | 556              | 56 |
| Winter 2010, Germany     | 1996–2009          | 60  | NR   | 110  | 111 | NR                      | NR                       | 38                      | Renal [all]  | Wedge resection [109], segmentectomy [30], lobectomy [13] pneumonectomy [4]  | 97               | 13 |

LN, lymph node; NR, not reported.

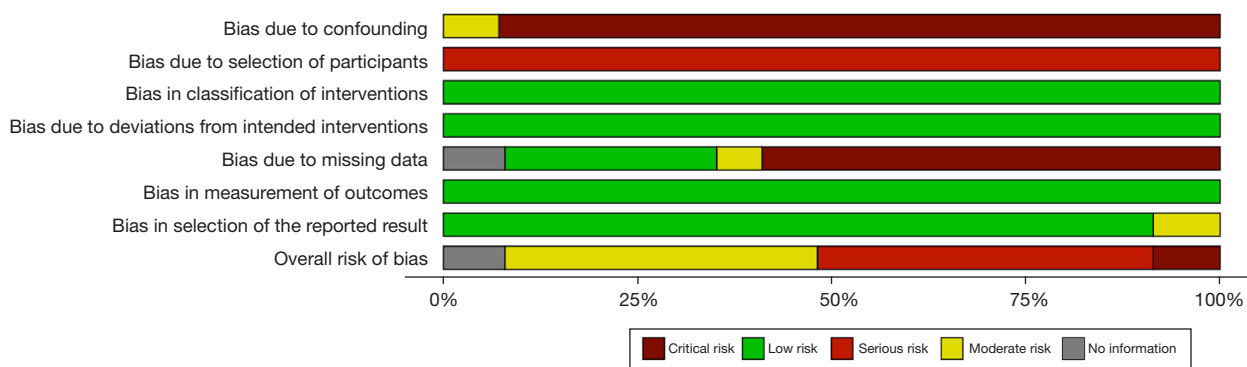


Figure 2 Summary of the risk of bias.

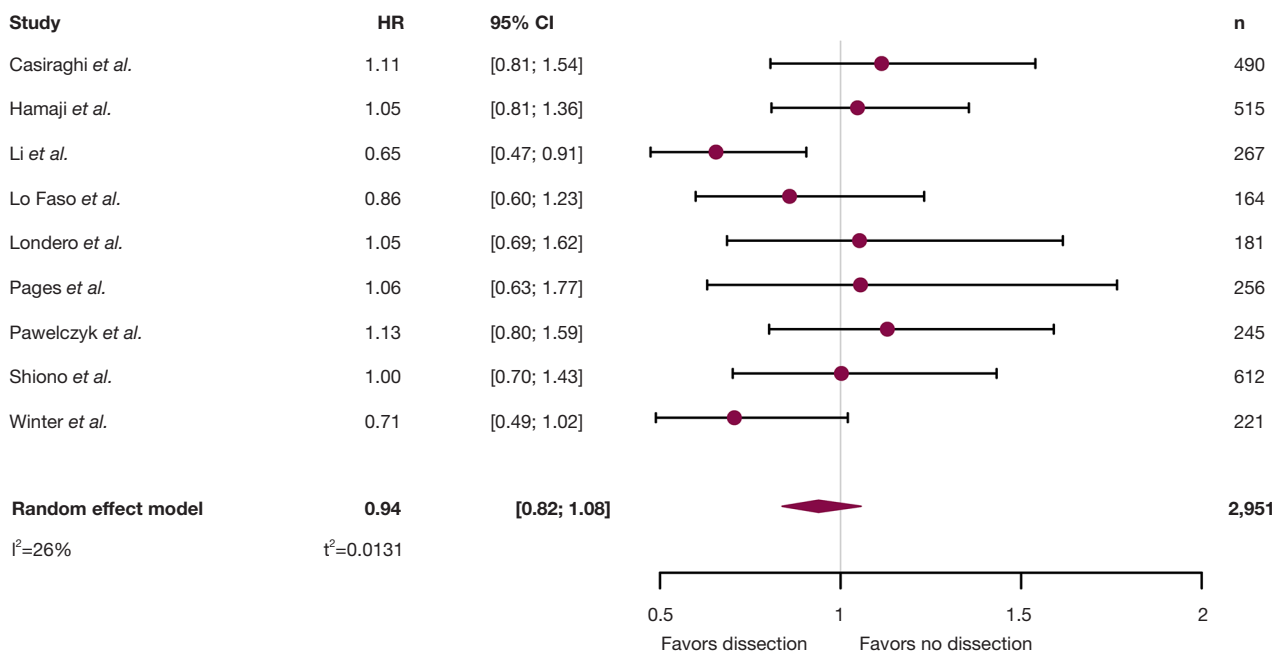
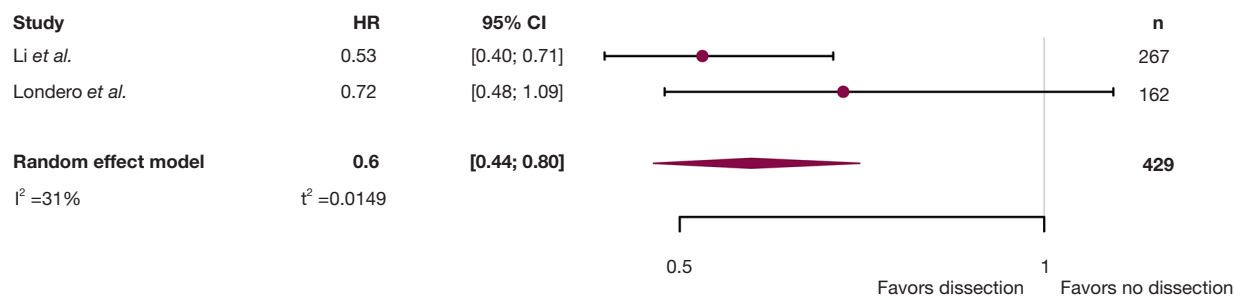


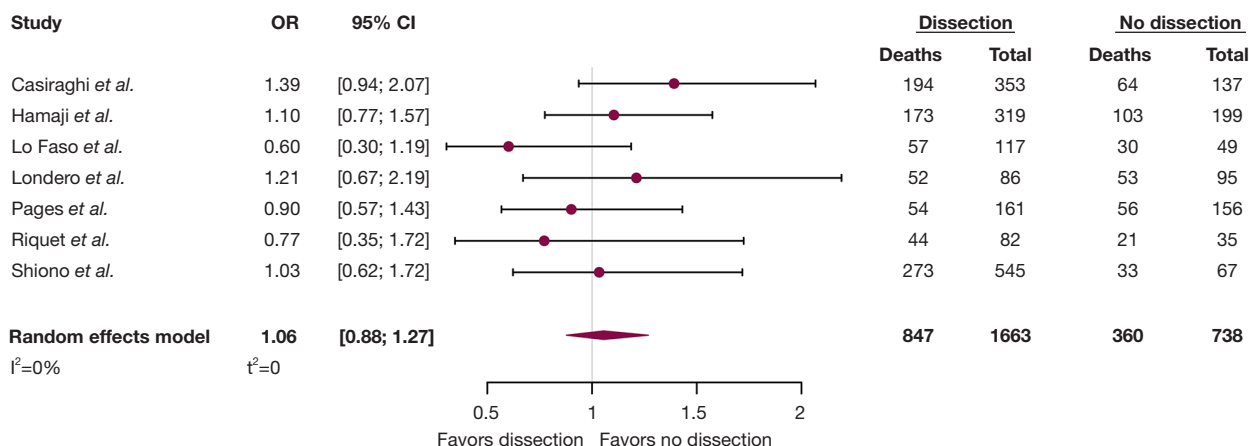
Figure 3 Forest plot of the overall survival after lymph node dissection based on reconstructed individual-level patient data. Univariate Cox proportional-hazard models (no dissection *vs.* dissection) were fitted to the data separately. The logarithmically transformed hazard ratios were then pooled using an inverse variance method. HR, hazard ratio; 95% CI, 95% confidence interval.

reconstructed from Kaplan-Meier curves in 9 studies. Univariate Cox proportional-hazards models were fitted to the data for each of the studies separately. All models did not violate the constant hazard assumption. Eight studies did not show a statistically significant effect of dissection on the OS (18-25). However, the study by Li *et al.* displayed a statistically significant lower hazard for the dissection group (26). The pooled HR was 0.94 [95% confidence interval (CI): 0.82, 1.08;  $I^2=26%$ ;

95% prediction interval (PI): 0.70, 1.24]. A forest plot displaying the results is shown in Figure 3. For the DFS, Kaplan-Meier curves were available in two studies only. Both studies found a lower hazard of disease recurrence, however, one was not statistically significant (22,26). The pooled HR was 0.60 (95% CI: 0.44, 0.80;  $I^2=31%$ ). The forest plot is shown in Figure 4. Visual inspection of the funnel plot and Egger's test do not indicate the presence of publication bias for the main analysis (Figure S2).



**Figure 4** Forest plot of the disease-free survival after lymph node dissection based on reconstructed individual-level patient data. Univariate Cox proportional-hazard models (no dissection *vs.* dissection) were fitted to the data separately. The logarithmically transformed hazard ratios were then pooled using an inverse variance method. HR, hazard ratio; 95% CI, 95% confidence interval.



**Figure 5** Forest plot of the overall survival after lymph node dissection based on reported odds ratios. Logarithmically transformed odds ratios were pooled using the Mantel-Haenszel estimator. OR, odds ratio; 95% CI, 95% confidence interval.

### Meta-analysis of reported ORs

Seven studies reported the information to calculate OR for the OS after 5 years (Figure 5). All studies did not find a statistically significant effect of dissection on the 5-year OS (19-23,25,27). The pooled OR was 1.06 (95% CI: 0.88, 1.27;  $I^2 = 0\%$ ; 95% PI: 0.83, 1.34).

Five-year ORs for DFS were available in four studies (Figure 6). Three studies (22,23,26) reported decreased odds of an event in the dissection group, and one study (28) reported no statistically significant difference. The pooled OR was 0.52 (95% CI: 0.34, 0.78;  $I^2 = 36\%$ ; 95% PI: 0.12, 2.09).

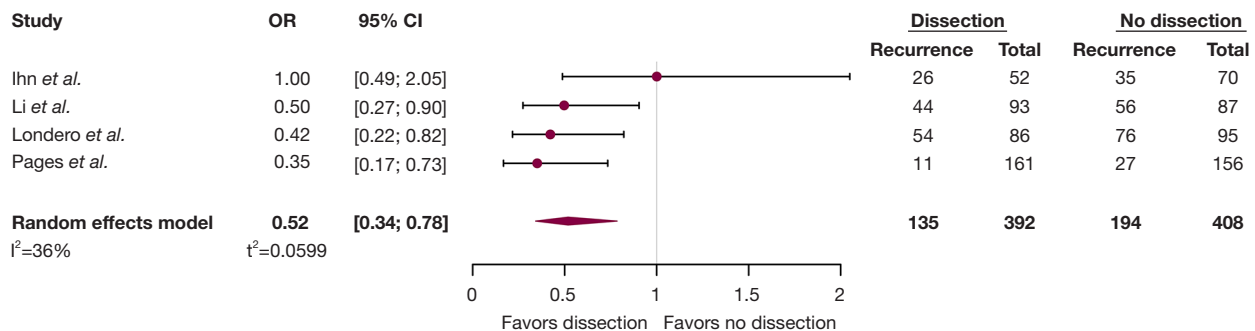
### Subgroup analysis

We performed multiple subgroup analyses based on

the individual-level data for the OS. As a first step, we performed a leave-one-out analysis and a GOSH analysis to identify potentially influential outliers (Figures S3,S4). The study by Li *et al.* was identified and after removing it the pooled HR was 0.99 (95% CI: 0.88, 1.12), and the  $I^2$  reduced to 0% (26) (Figure S5).

Focusing on the percentage of patients undergoing chemotherapy the HR was 1.11 (95% CI: 0.83, 1.47) if less than 50% of patients received chemotherapy, 0.91 (95% CI: 0.64, 1.28) if more than 50% of patients received chemotherapy and 0.92 (95% CI: 0.77, 1.09) if it was not reported (Figure S6). Pooling studies that reported the resection status the HR was 1.00 (95% CI: 0.84, 1.20), and in studies that did not report the resection status, the HR was 0.89 (95% CI: 0.71, 1.12) (Figure S7). In studies that only included colorectal cancer patients, the HR was





**Figure 6** Forest plot of the disease-free survival after lymph node dissection based on reported odds ratios. Logarithmically transformed odds ratios were pooled using the Mantel-Haenszel estimator. OR, odds ratio; 95% CI, 95% confidence interval.

0.89 (95% CI: 0.64, 1.23), in studies that did not include colorectal patients, the HR also was 0.89 (95% CI: 0.57, 1.40) and in studies that included colorectal cancer patients as well as other cancer patients the HR was 1.01 (95%: 0.84, 1.21) (Figure S8). Considering studies that included sarcoma patients the HR was 1.04 (95% CI: 0.87, 1.24) and in studies that did not include sarcoma patients, the HR was 0.87 (95% CI: 0.70, 1.08) (Figure S9). Regarding multiple metastases studies with less than 50% of patients presenting with multiple metastases, the HR was 1.08 (95% CI: 0.91, 1.27). with more than 50% 0.98 (95% CI: 0.79, 1.21). If not reported, the HR was 0.68 (95% CI: 0.54, 0.86) (Figure S10).

## Discussion

In this systematic review of the literature, we analyzed 11 eligible studies including 3,310 patients. The 5-year OS rate was not different between patients who underwent lymph node tissue assessment (n=1,929) and patients who did not receive any lymph node tissue sampling (n=1,205) during PM. A slight difference between the two groups, according to our analysis, was found regarding the DFS.

Further, sub-analyses performed on several subgroups did not show any benefit of lymph nodes tissue sampling on OS and DFS.

Historically, cornerstones of lung metastases surgical management have been a complete resection along with parenchyma sparing procedures. While sampling/dissecting hilar and mediastinal lymph nodes slightly prolong operative time and might be associated with a minimal complications rate, the rationale of performing it is, to date, not fully established.

Moreover, even though the prevalence of lymph nodes metastases varies from 5% to 66.3% (25,29-31), no

consensus exists if lymph node tissue sampling should be carried out during lung metastasectomy. A survey conducted in 2023 among members of the European Society Thoracic Surgery (ESTS) showed that, similarly to a survey from 2008, at the time of metastasectomy, 33% performed no nodal assessment at all (32).

Some authors recognized the importance of a pre-operative negative lymph node status in order to exclude from surgery patients who can not undergo curative treatment. In addition, they recommended a lymph node tissue assessment during PM due to the prognostic significance of lymph node metastases, but no clear guidelines exist (29).

In 2019, the Society of Thoracic Surgeons expert consensus recommended performing lymph node sampling or dissection during PM, considering the prognostic significance of lymph nodes' involvement (33).

A systematic lymph node dissection is also suggested by the German Cancer Society in case of resection of lung metastases from renal cell carcinoma (recommendation grade B, level of evidence 3) (34).

No other clear statements from societies regarding lymph node assessment during PM exist in current guidelines.

Several retrospective studies indeed highlighted the presence of nodal involvement as a worse prognostic factor in patients with lung metastases (6,7,20,35). Therefore, a logical effect should be that lymph node tissue sampling will potentially positively affect survival (assuming that patients diagnosed with lymph nodes metastases will be treated further following their metastasectomy). As a matter of fact, conflicting results have been published and our systematic review of current literature demonstrates that OS was not influenced by lymph nodes tissue assessment during PM and

DFS (reported only in four studies) was slightly influenced. However, the interpretation of the results should be prudent due to the limitations present in our analysis.

First, given the lack of prospective studies, we were able to include in our analysis solely retrospective studies where often the populations were too heterogeneous with several confounding biases (small peripheral nodule grouped with central metastases requiring a more extensive resection, different primary tumors) and with several missing data (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). Specific analyses were performed in patients with pulmonary metastases from colorectal cancer or sarcoma but we did not analyze separately all the different primary tumors subgroups.

Second, the definition of “lymphadenectomy” in the included papers, exactly in line with the current daily practice, was nebulous and mostly not well defined. Nevertheless, the extent of lymph nodes tissue sampling can represent a serious bias influencing OS and DFS.

Furthermore, DFS was reported only in four of the eleven studies included in our analysis.

However, our study holds some strengths. To our knowledge, this is the first systematic review and meta-analysis that analyze the impact of lymph nodes assessment on OS and DFS in patients who undergo pulmonary resection of metastases resulting from different primary tumors. Furthermore, our analysis summarizes and evaluates all available and relevant data on the significance of lymph nodes' dissection in patients with lung metastases.

Relying on the current analyses, we are unable to recommend a systematic lymph nodes sampling/dissection while performing PM. However, we do recognize the relatively low level of evidence in the existing studies included in the analyses and hence the need for prospective studies (preferably randomized controlled trials like the one currently ongoing in Denmark) to assess some of the points suggested in our paper. In addition, in our opinion, an internationally standardized pre-operative assessment can provide a potential tool to help define which subgroup of patients should undergo lymph node tissue assessment during metastasectomy (36).

## Conclusions

Based on the current literature, lymph nodes dissection/sampling, performed at the time of PM, does not impact

significantly OS, but might impact DFS. Further research possibly based on multicenter databases analysis may provide future evidence.

## Acknowledgments

The manuscript was presented as an oral presentation during the ESTS Annual conference on Monday 5<sup>th</sup> June 2023 in Milan (Miscellaneous I Session III).

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-769/rc>

*Peer Review File:* Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-769/prf>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-769/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

*Open Access Statement:* This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

## References

1. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg* 1997;113:37-49.
2. Lee WS, Yun SH, Chun HK, et al. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. *Int J Colorectal Dis* 2007;22:699-704.

3. Park JS, Kim HK, Choi YS, et al. Outcomes after repeated resection for recurrent pulmonary metastases from colorectal cancer. *Ann Oncol* 2010;21:1285-9.
4. Zhao Y, Li J, Li C, et al. Prognostic factors for overall survival after lung metastasectomy in renal cell cancer patients: A systematic review and meta-analysis. *Int J Surg* 2017;41:70-7.
5. Ambrogi V, Tamburrini A, Tajé R. Results of redo pulmonary metastasectomy. *J Thorac Dis* 2021;13:2669-85.
6. Ercan S, Nichols FC 3rd, Trastek VF, et al. Prognostic significance of lymph node metastasis found during pulmonary metastasectomy for extrapulmonary carcinoma. *Ann Thorac Surg* 2004;77:1786-91.
7. Welter S, Jacobs J, Krbek T, et al. Prognostic impact of lymph node involvement in pulmonary metastases from colorectal cancer. *Eur J Cardiothorac Surg* 2007;31:167-72.
8. Renaud S, Alifano M, Falcoz PE, et al. Does nodal status influence survival? Results of a 19-year systematic lymphadenectomy experience during lung metastasectomy of colorectal cancer. *Interact Cardiovasc Thorac Surg* 2014;18:482-7.
9. Welter S, Gupta V, Kyritsis I. Lymphadenectomy in pulmonary metastasectomy. *J Thorac Dis* 2021;13:2611-7.
10. van Dorp M, Bousema JE, Torensmas B, et al. Pulmonary metastasectomy with lymphadenectomy for colorectal pulmonary metastases: A systematic review. *Eur J Surg Oncol* 2022;48:253-60.
11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
12. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
13. Liu N, Zhou Y, Lee JJ. IPDfromKM: reconstruct individual patient data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2021;21:111.
14. Guyot P, Ades AE, Ouwens MJ, et al. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9.
15. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019;22:153-60.
16. Harrer M, Cuijpers P, Furukawa T, et al. dmetar: Companion R Package For The Guide 'Doing Meta-Analysis in R'. R package version 0.0.9000. 2019. Available online: <http://dmetar.protectlab.org/>
17. Olkin I, Dahabreh IJ, Trikalinos TA. GOSH - a graphical display of study heterogeneity. *Res Synth Methods* 2012;3:214-23.
18. Winter H, Meimarakis G, Angele MK, et al. Tumor infiltrated hilar and mediastinal lymph nodes are an independent prognostic factor for decreased survival after pulmonary metastasectomy in patients with renal cell carcinoma. *J Urol* 2010;184:1888-94.
19. Casiraghi M, De Pas T, Maisonneuve P, et al. A 10-year single-center experience on 708 lung metastasectomies: the evidence of the "international registry of lung metastases". *J Thorac Oncol* 2011;6:1373-8.
20. Hamaji M, Cassivi SD, Shen KR, et al. Is lymph node dissection required in pulmonary metastasectomy for colorectal adenocarcinoma? *Ann Thorac Surg* 2012;94:1796-800.
21. Lo Faso F, Solaini L, Lembo R, et al. Thoracoscopic lung metastasectomies: a 10-year, single-center experience. *Surg Endosc* 2013;27:1938-44.
22. Londero F, Morelli A, Parise O, et al. Lymphadenectomy during pulmonary metastasectomy: Impact on survival and recurrence. *J Surg Oncol* 2019;120:768-78.
23. Pagès PB, Serayssol C, Brioude G, et al. Risk factors for survival and recurrence after lung metastasectomy. *J Surg Res* 2016;203:293-300.
24. Pawełczyk K, Marciniak M, Błasiak P, et al. Evaluation of prognostic factors in the surgical treatment of pulmonary metastases. *Contemp Oncol (Pozn)* 2015;19:378-84.
25. Shiono S, Matsutani N, Okumura S, et al. The prognostic impact of lymph-node dissection on lobectomy for pulmonary metastasis. *Eur J Cardiothorac Surg* 2015;48:616-21; discussion 621.
26. Li H, Hu H, Li B, et al. What is the appropriate surgical strategy for pulmonary metastasis of colorectal cancer? *Medicine (Baltimore)* 2020;99:e21368.
27. Riquet M, Foucault C, Cazes A, et al. Pulmonary resection for metastases of colorectal adenocarcinoma. *Ann Thorac Surg* 2010;89:375-80.
28. Ihn MH, Kim DW, Cho S, et al. Curative Resection for Metachronous Pulmonary Metastases from Colorectal Cancer: Analysis of Survival Rates and Prognostic Factors. *Cancer Res Treat* 2017;49:104-15.
29. García-Yuste M, Cassivi S, Paleru C. Thoracic lymphatic involvement in patients having pulmonary metastasectomy: incidence and the effect on prognosis. *J Thorac Oncol* 2010;5:S166-9.
30. Loehle F, Kobinger S, Hatz RA, et al. Value of systematic

- mediastinal lymph node dissection during pulmonary metastasectomy. *Ann Thorac Surg* 2001;72:225-9.
31. Veronesi G, Petrella F, Leo F, et al. Prognostic role of lymph node involvement in lung metastasectomy. *J Thorac Cardiovasc Surg* 2007;133:967-72.
  32. van Dorp M, Gonzalez M, Daddi N, et al. Metastasectomy for colorectal pulmonary metastases: a survey among members of the European Society of Thoracic Surgeons. *Interdiscip Cardiovasc Thorac Surg* 2023;36:ivad002.
  33. Handy JR, Bremner RM, Crocenzi TS, et al. Expert Consensus Document on Pulmonary Metastasectomy. *Ann Thorac Surg* 2019;107:631-49.
  34. Leitlinienprogramm Onkologie. Konsultationsfassung S3-Leitlinie Diagnostik, Therapie und Nachsorge des Nierenzellkarzinoms. Version 4.01. Jun 2022.
  35. Pfannschmidt J, Klode J, Muley T, et al. Nodal involvement at the time of pulmonary metastasectomy: experiences in 245 patients. *Ann Thorac Surg* 2006;81:448-54.
  36. Mediastinal Lymph Node Dissection in Conjunction With Pulmonary Metastasectomy From Colorectal Cancer. NCT03113318. Available online: <https://classic.clinicaltrials.gov/ct2/show/NCT03113318>

**Cite this article as:** Minervini F, Li A, Qu M, Nilus H, Shargall Y. Prognostic significance of lymph nodes assessment during pulmonary metastasectomy: a systematic review and meta-analysis. *J Thorac Dis* 2023;15(12):6447-6458. doi: 10.21037/jtd-23-769