Original Article

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

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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 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

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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).

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 (≥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%, ≥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%, ≥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

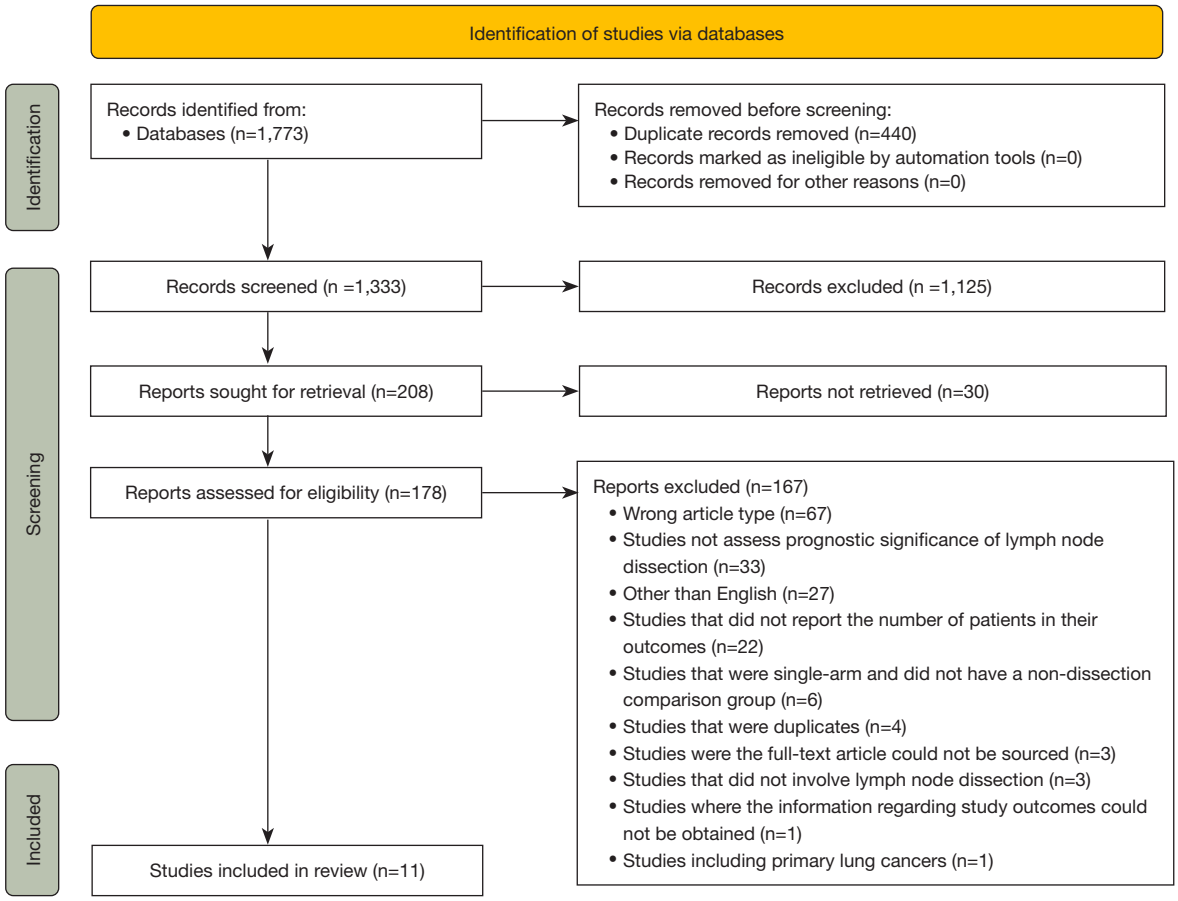

Figure 1 PRISMA 2020 flow diagram.

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		>1 pulmonary metastases	% 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	366	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	228	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	75	91	9	Colorectal [all]	Wedge resection [130], segmentectomy [17], lobectomy [29]	NR	NR
Li 2020, China	2011–2017	59	60%	106	161	NR	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	67	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	45	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
Pawełczyk 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.

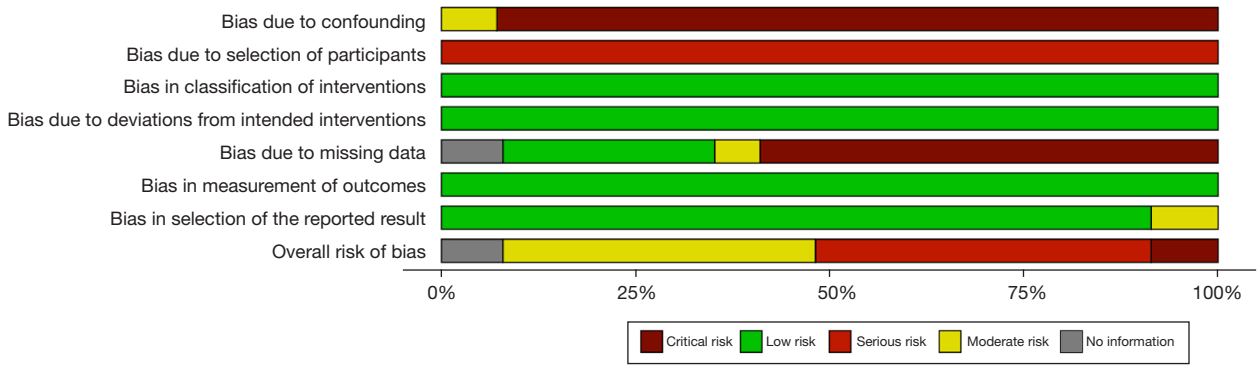

Figure 2 Summary of the risk of bias.

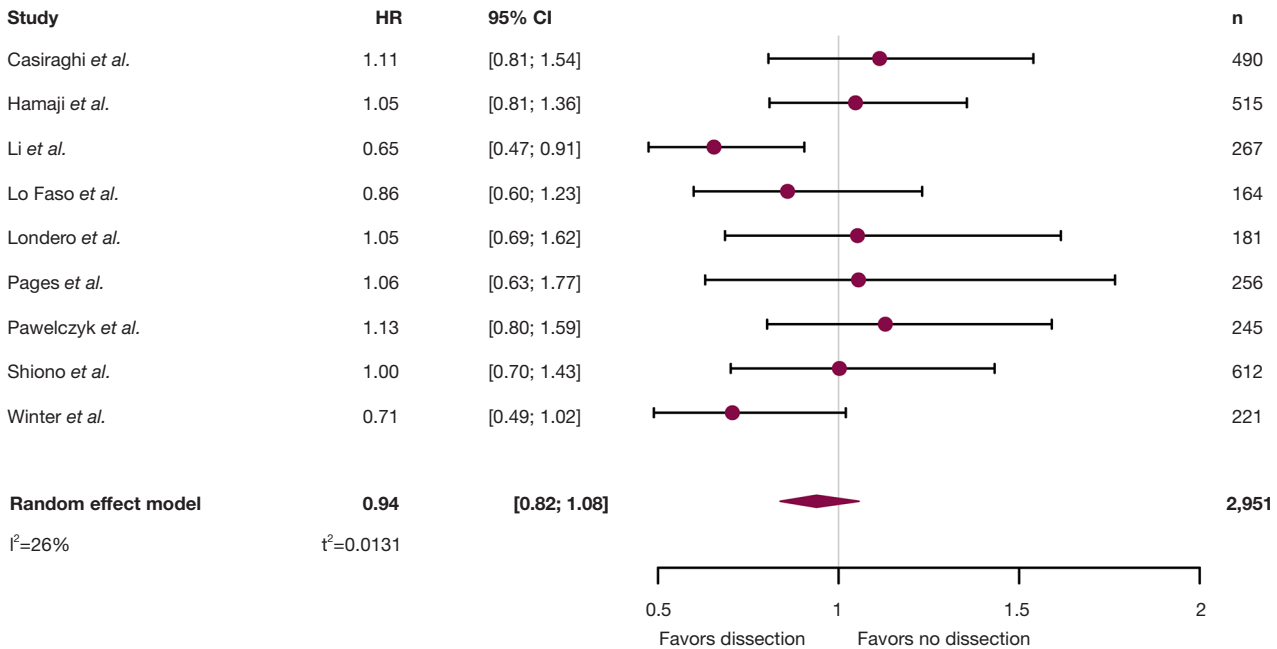

Figure 3 Forest plot of the overall survival after lymph node dissection based on reconstructed individual-level patient data. Univariate Cox proportional-hazard models (no dissection *vs.* dissection) were fitted to the data separately. The logarithmically transformed hazard ratios were then pooled 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).

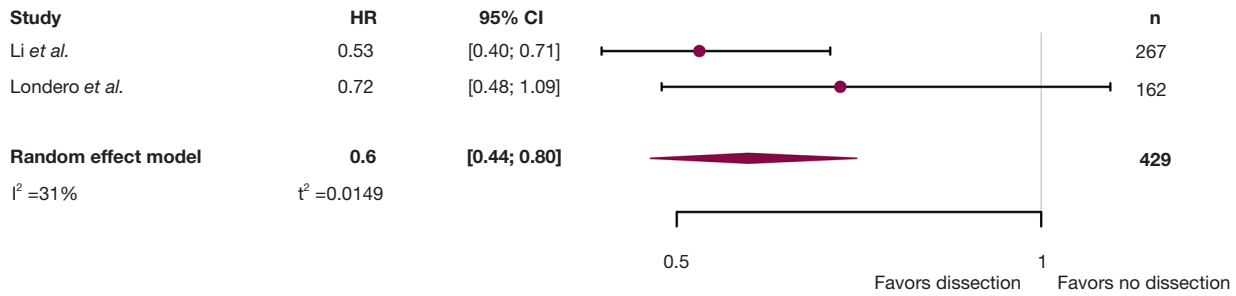

Figure 4 Forest plot of the disease-free survival after lymph node dissection based on reconstructed individual-level patient data. Univariate Cox proportional-hazard models (no dissection *vs.* dissection) were fitted to the data separately. The logarithmically transformed hazard ratios were then pooled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

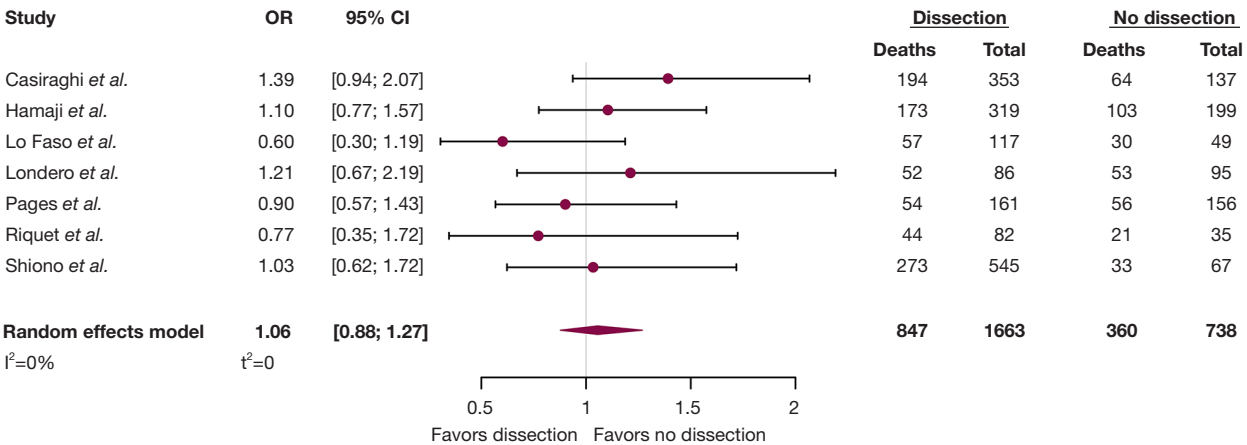

Figure 5 Forest plot of the overall survival after lymph node dissection based on reported odds ratios. Logarithmically transformed odds ratios were pooled using the Mantel-Haenszel estimator. OR, odds ratio; 95% CI, 95% confidence interval.

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

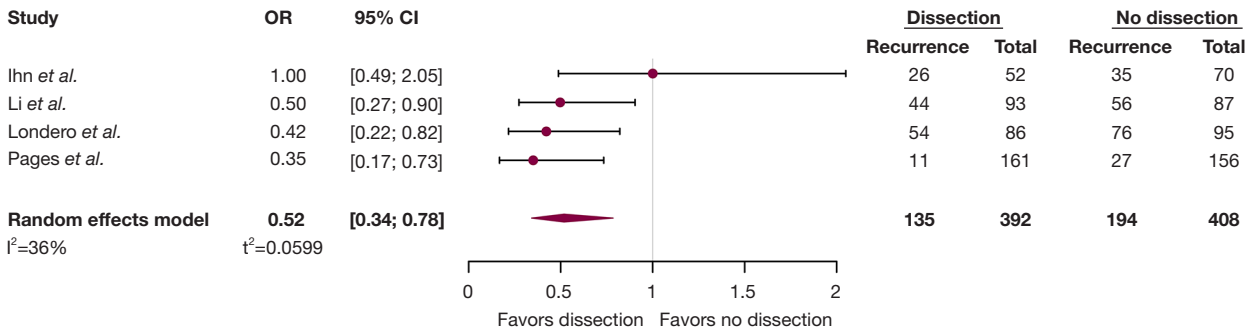

Figure 6 Forest plot of the disease-free survival after lymph node dissection based on reported odds ratios. Logarithmically transformed odds ratios were pooled using the Mantel-Haenszel estimator. OR, odds ratio; 95% CI, 95% confidence interval.

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 heterogenous 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.

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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.

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Supplementary

Appendix 1 Search strategy for MEDLINE and Embase

1. lung neoplasm.mp. or exp Lung Neoplasms/
2. (lung adj3 metastas*).mp.
3. (pulmonary adj3 metastas*).mp.
4. pulmonary neoplasm.mp.
5. lung cancer.mp.
6. pulmonary cancer.mp.
7. 1 or 2 or 3 or 4 or 5 or 6
8. metastasectomy.mp. or Metastasectomy/
9. (pneumonectomy adj3 metastas*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. (lobectomy adj3 metastas*).mp.
11. (metastas* adj3 resection).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12. (metastas* adj3 surg* resection).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13. 8 or 11 or 12
14. 7 and 13
15. lymph node.mp. or Lymph Nodes/
16. Lymphatic Metastasis/
17. Lymphatic Metastasis.mp.
18. lymph node excision.mp. or Lymph Node Excision/
19. Sentinel Lymph Node Biopsy/11929
20. Sentinel Lymph Node Biopsy.mp.
21. (lymph* adj2 metastas*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating subheading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
22. 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 14 and 22
24. 9 or 10 or 23

https://dx.doi.org/10.21037/jtd-23-769

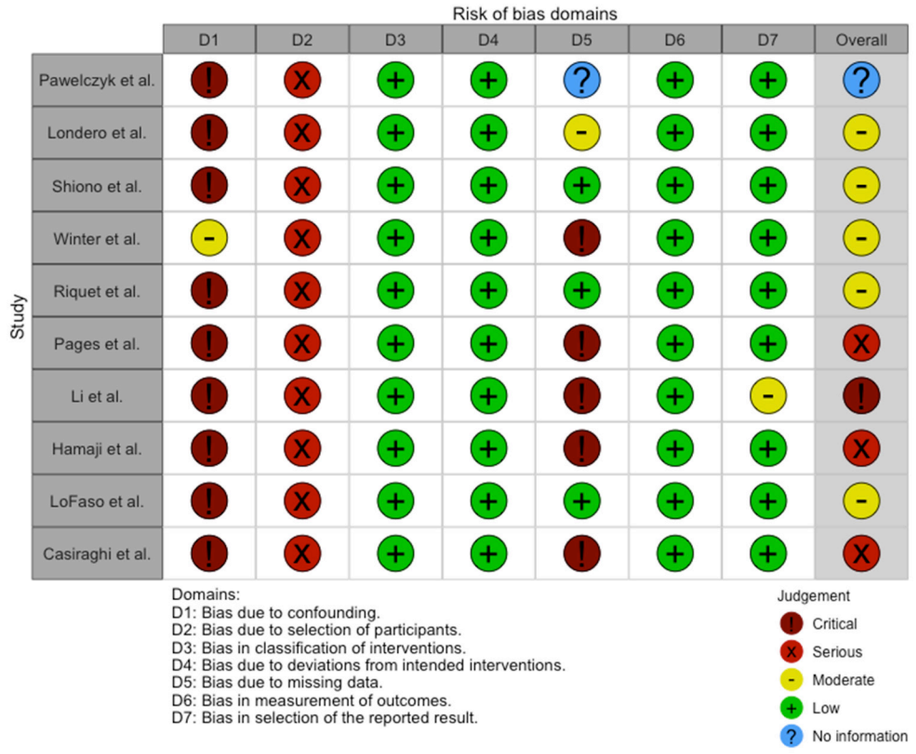

Figure S1 Traffic light plot of the risk of bias.

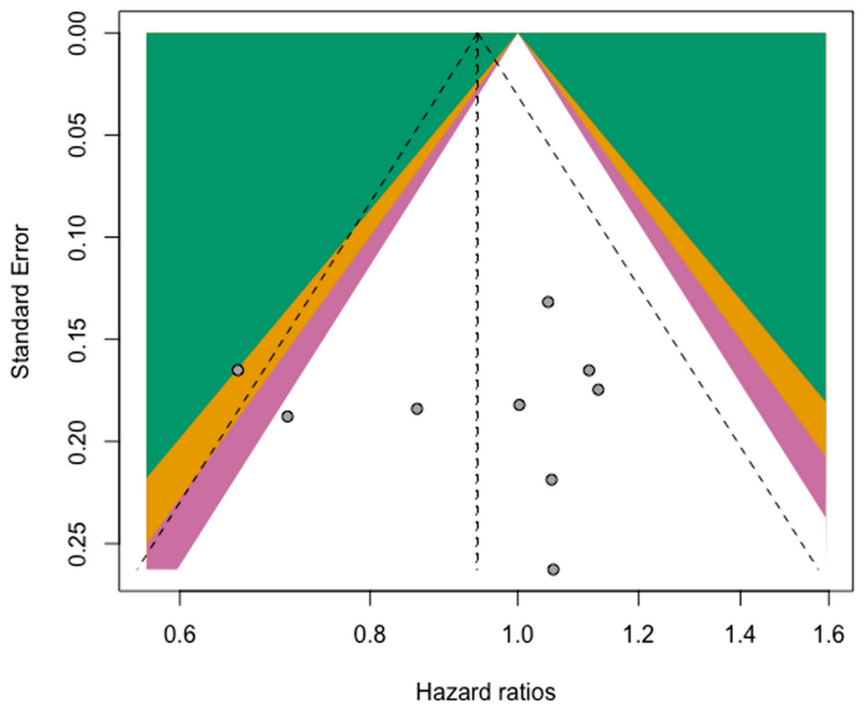

Figure S2 Funnel plot of the overall survival.

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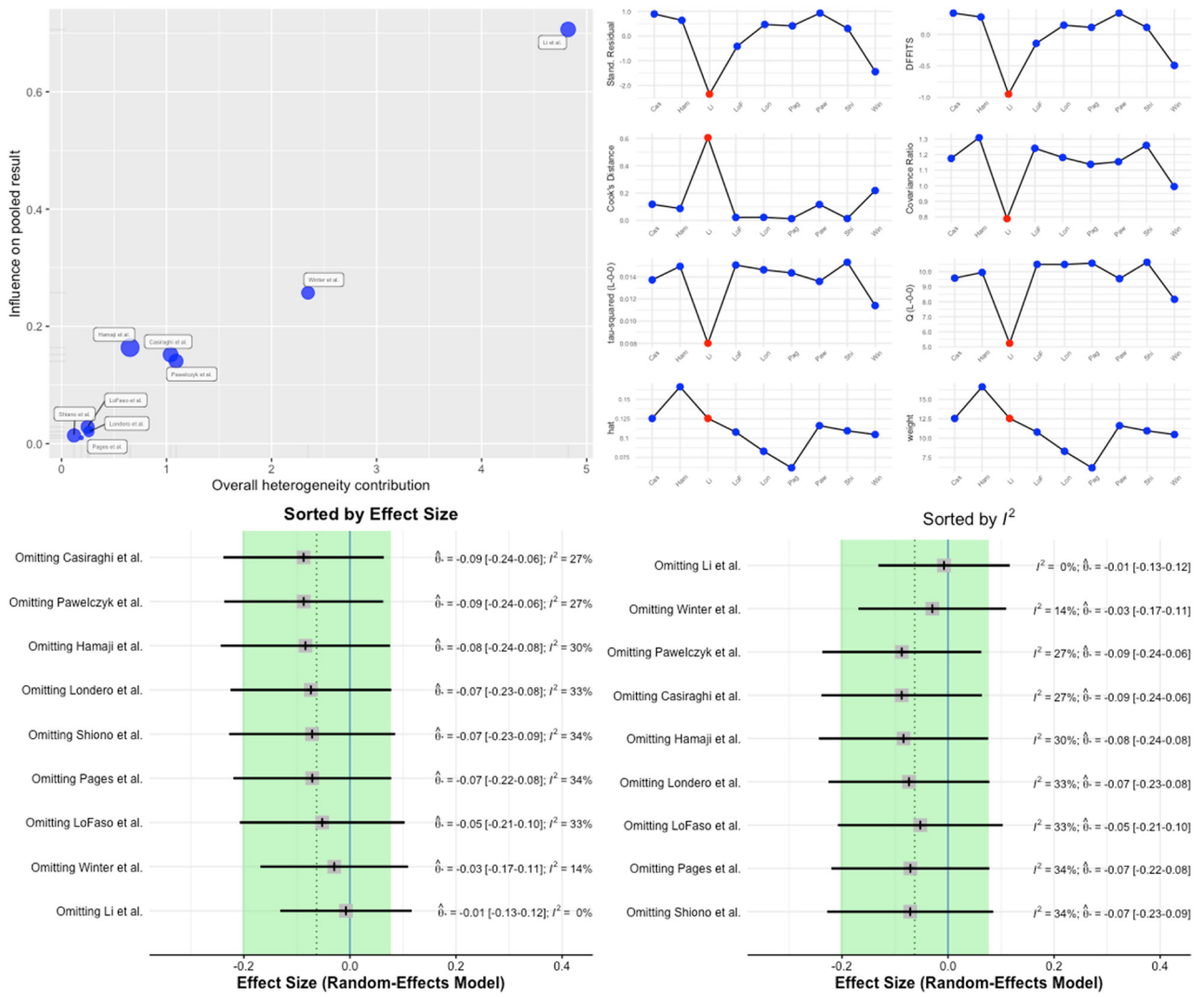

Figure S3 Results of the leave-one-out analysis. The study by Li *et al.* was identified as a potentially influencial outlier.

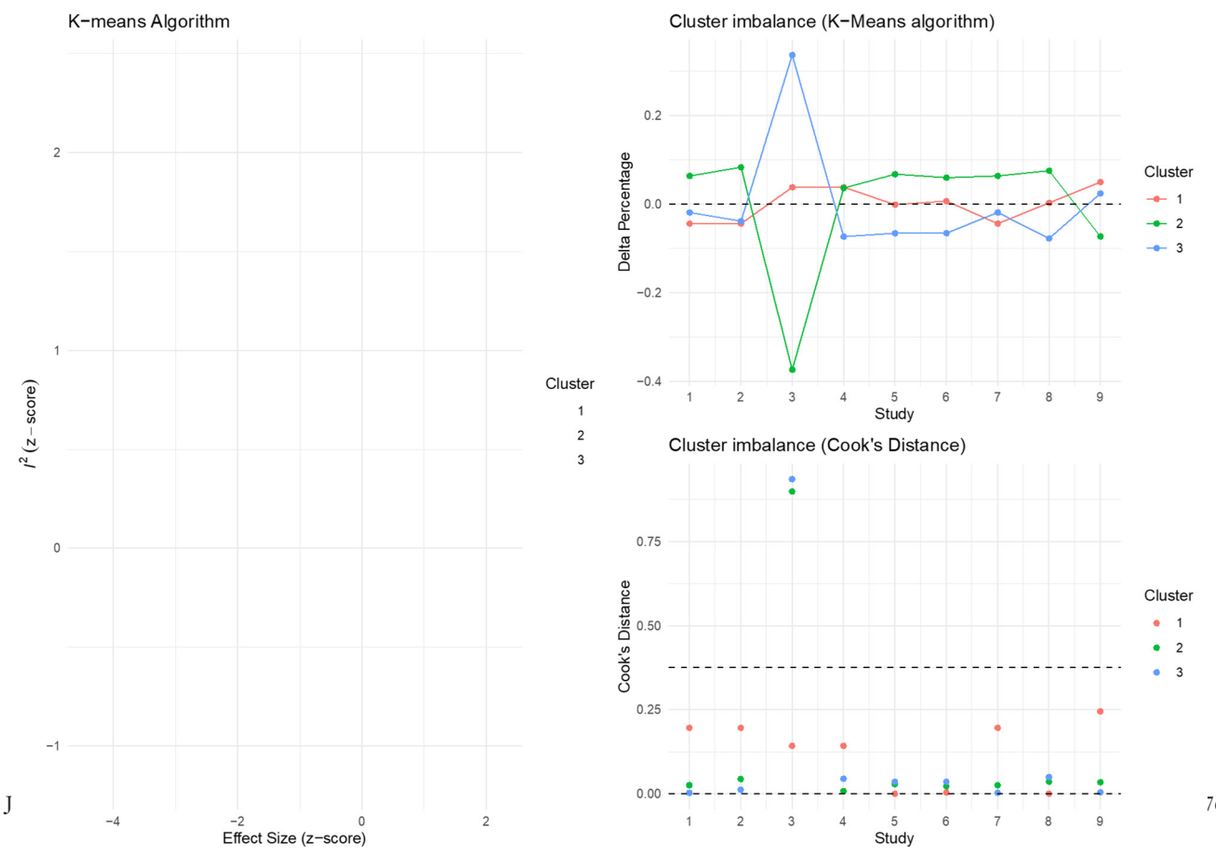

Figure S4 Graphic display of study heterogeneity (GOSH) plot. Clustering was performed using a K-means algorithm.

https://dx.doi.org/10.21037/jtd-23-769

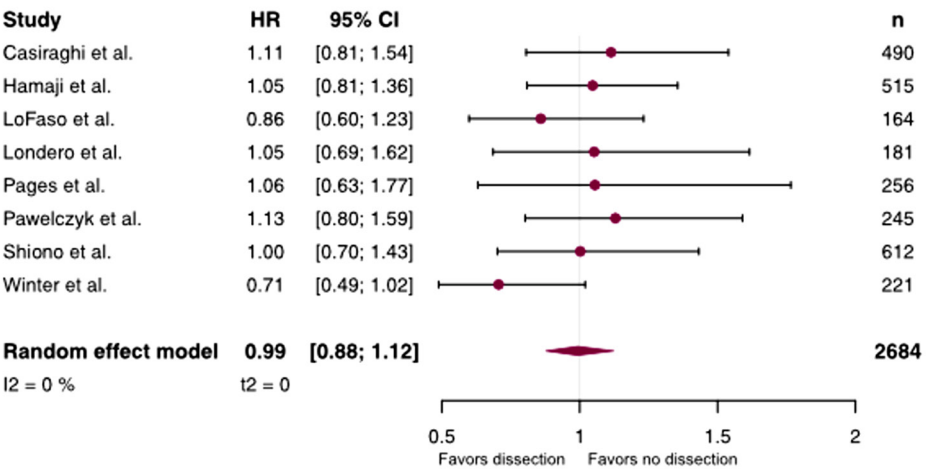

Figure S5 Forest plot of the overall survival after lymph node dissection excluding the study by Li *et al.*

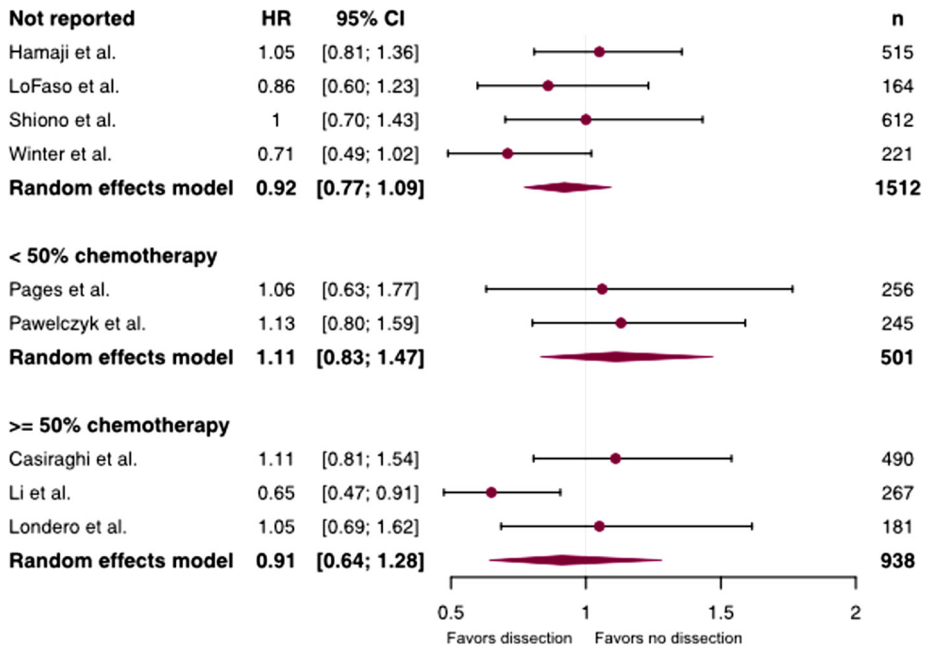

Figure S6 Forest plot of the overall survival after lymph node dissection by chemotherapy regiment.

https://dx.doi.org/10.21037/jtd-23-769

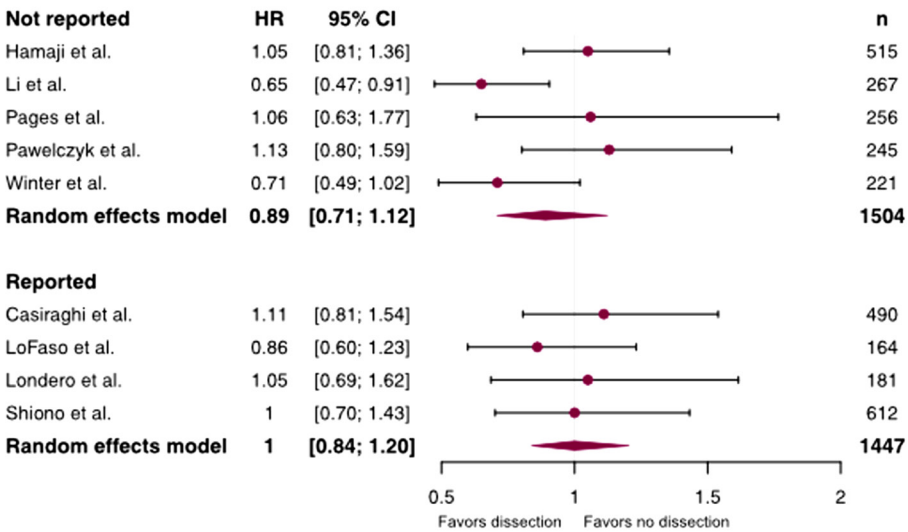

Figure S7 Forest plot of the overall survival after lymph node dissection by reported resection status.

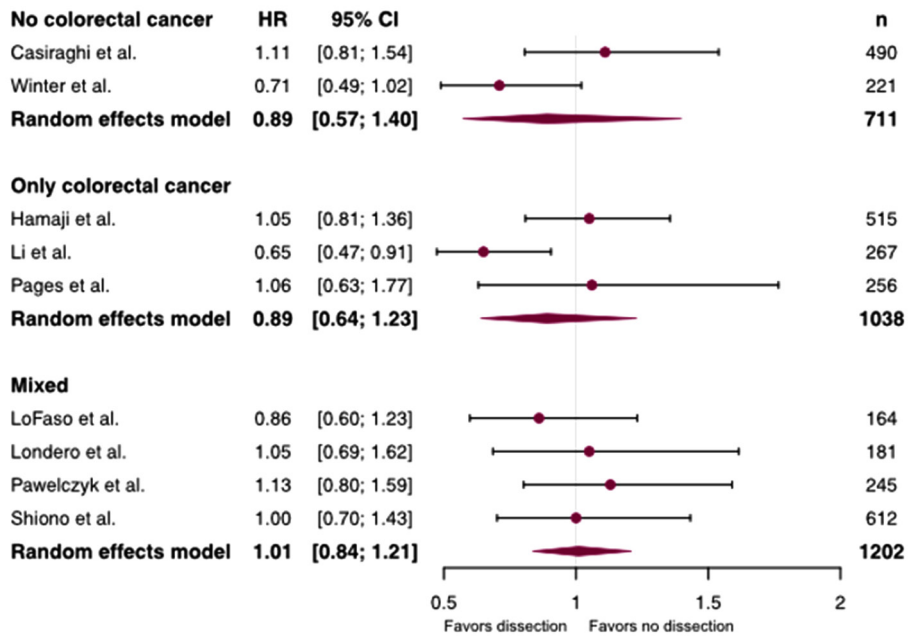

Figure S8 Forest plot of the overall survival after lymph node dissection by inclusion of colorectal cancer patients.

https://dx.doi.org/10.21037/jtd-23-769

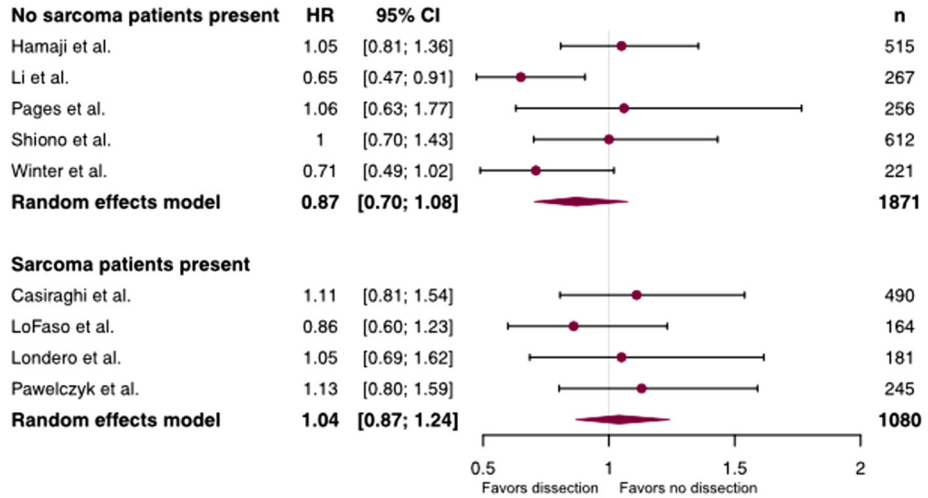

Figure S9 Forest plot of the overall survival after lymph node dissection by inclusion of sarcoma patients.

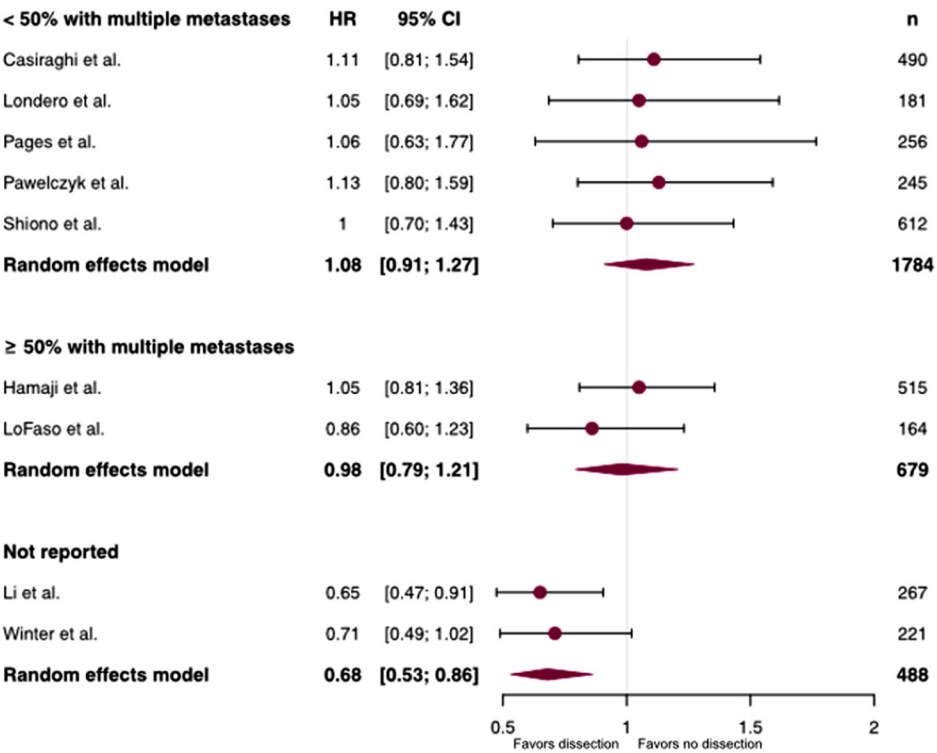

Figure S10 Forest plot of the overall survival after lymph node dissection by percentage of patients with multiple metastases in the study.

https://dx.doi.org/10.21037/jtd-23-769