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Pulmonary metastasectomy with lymphadenectomy for colorectal pulmonary metastases: A systematic review

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ABSTRACT

Background: Routine lymphadenectomy during metastasectomy for pulmonary metastases of colorectal cancer has been recommended by several recent expert consensus meetings. However, evidence supporting lymphadenectomy is limited. The aim of this study was to perform a systematic review of the literature on the impact of simultaneous lymph node metastases on patient survival during metastasectomy for colorectal pulmonary metastases (CRPM).

Methods: A systematic review was conducted according to the PRISMA guidelines of studies on lymphadenectomy during pulmonary metastasectomy for CRPM. Articles published between 2000 and 2020 were identified from Medline, Embase and the Cochrane Library without language restriction. Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess the risk of bias and applicability of included studies. Survival rates were assessed and compared for the presence and level of nodal involvement.

Results: Following review of 8054 studies by paper and abstract, 27 studies comprising 3619 patients were included in the analysis. All patients included in these studies underwent lymphadenectomy during pulmonary metastasectomy for CRPM. A total of 690 patients (19.1%) had simultaneous lymph node metastases. Five-year overall survival for patients with and without lymph node metastases was 18.2% and 51.3%, respectively ($p < .001$). Median survival for patients with lymph node metastases was 27.9 months compared to 58.9 months in patients without lymph node metastases ($p < .001$). Five-year overall survival for patients with N1 and N2 lymph node metastases was 40.7% and 10.9%, respectively ($p = .064$).

Conclusion: Simultaneous lymph node metastases of CRPM have a detrimental impact on survival and this is most apparent for mediastinal lymph node metastases. Therefore, lymphadenectomy during pulmonary metastasectomy for CRPM can be advised to obtain important prognostic value.

1. Definitions

The following definitions are used in this article:

- Lymphadenectomy: removal of lymph nodes, this can be either lymph node dissection with removal of the entire lymph nodes

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station, or lymph node sampling by taking one or more biopsies of a lymph node station.
- Routine lymphadenectomy: performance of a lymphadenectomy in all patients.
- Lymph node dissection: all lymph node tissue in the mentioned lymph node stations is removed.
- Lymph node sampling: one or more biopsies are taken from the mentioned lymph node stations.
- N1: in accordance with the Naruke lymph node map: ipsilateral hilar, interlobar, lobar, segmental and subsegmental lymph node stations.
- N2: in accordance with the Naruke lymph node map: ipsilateral mediastinal, paratracheal, retrotracheal, subcarinal, paraesophageal and pulmonary ligament lymph node stations, as well as subaortic and para-aortic lymph node stations for left sided pulmonary metastases.

2. Background

Metastasectomy for pulmonary metastases of colorectal cancer is an established local treatment for selected patients. Recently published results from the randomized controlled Pulmicc trial revealed that patients in the control group, receiving no local treatment for limited colorectal pulmonary metastases (CRPM), have better survival than previously assumed with a five-year survival of 29.6% (95% CI: 15.3–45.7%). Patients who were randomized to surgical metastasectomy had a five-year survival of 36.4% (95% CI: 21.3–53.0%) [1]. The trial was closed prematurely due to poor recruitment, however recently the investigators published the results of the prospective observational cohort [2]. A total of 169 patients receiving no pulmonary metastasectomy, had a five-year survival of 21.9% (95% CI: 16–29%). Without presenting the absolute five-year survival rate of patients that underwent pulmonary metastasectomy in this prospective cohort, the authors concluded that selection bias prevents a formal comparative analysis. The randomized SABR-COMET trial showed survival benefit after Stereotactic Ablative Radiotherapy (SABR) for limited pulmonary metastases with different primary sites of the original primary tumor, even with long-term follow-up [3]. However, the mix of primary sites in both study arms does not allow for an in-depth analysis of CRPM. The results of these randomized controlled trials (RCTs) suggest that pulmonary metastasectomy still has an important role in the treatment of selected patients with limited CRPM [4].

Several well-documented parameters are considered unfavourable prognostic factors, such as short disease-free interval, size and number of CRPM, elevated CEA, previous liver metastasis, positive surgical margins and positive thoracic lymph nodes [5]. Based on the results of a meta-analysis by Gonzalez et al. [6], the five-year survival rate for selected patients with CRPM is 44.4% (95% CI: 40.5–48.7%) after pulmonary metastasectomy. In this meta-analysis, mediastinal or hilar lymph node metastases were associated with an increased risk of death (HR 1.65, 95% CI: 1.38–2.02) and multiple lymph node metastases had the greatest impact on survival (HR 2.04, 95% CI: 1.72–2.41).

Controversy exists regarding the need for lymphadenectomy during pulmonary metastasectomy. In a survey of the Pulmonary Metastasectomy Working Group of the European Society of Thoracic Surgeons (ESTS) in 2007 55% of members indicated that they routinely performed mediastinal lymph node sampling and 13% carried out mediastinal lymph node dissection during pulmonary metastasectomy, whereas 32% performed no nodal sampling at all [7]. Analysis of the ESTS database revealed that the rate of lymphadenectomy by sampling or dissection was 58% and that video-assisted thoracic surgery was associated with significantly fewer lymph node assessments when comparing to open surgery [8]. Analysis of registry data has shown varying numbers for lymphadenectomies during pulmonary metastasectomy. In 1997, the International Registry of Lung Metastases [9] reported simultaneous lymphadenectomy in 4.6% of patients. The Spanish [10], Italian [11] and Japanese [12] registries reported lymphadenectomies in 28%, 65% and 89% of patients, respectively. More recently the Dutch registry [13] analysed more than 2000 patients with pulmonary metastasectomies, and found that 13.2% of patient with resected CRPM metastases underwent simultaneous lymphadenectomy.

The Chinese expert consensus on multidisciplinary therapy of colorectal cancer recommends lymph node sampling or dissection during pulmonary metastasectomy if lymph node metastases are suspected on preoperative imaging and states that routine lymph node dissection is not recommended [14]. The recently published National Institute for Health and Care Excellence (NICE) guidelines [15] on “treatment for metastatic colorectal cancer in the lung amenable to local treatment” did not provide any recommendations on the topic of lymph node evaluation. Several reviews have advocated that routine lymphadenectomy should be recommended during pulmonary metastasectomy to achieve accurate staging and guide additional chemotherapy [16–18]. However, recent meta-analysis showed that adjuvant chemotherapy did not improve overall survival in patients with CRPM and hilar or mediastinal lymph node metastases [19].

The present systematic review of the literature aimed to quantify the overall survival of patients with simultaneous lymph node metastases detected during pulmonary metastasectomy with lymphadenectomy for colorectal pulmonary metastases and analysed the impact of the anatomical location of the lymph node metastases.

3. Methods

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [20].

3.1. Eligible studies

Clinical (non)randomized trials or observational studies assessing the impact of lymph node metastases detected during metastasectomy for CRPM on overall survival were eligible for this systematic review. Patients were included if pulmonary metastasectomy with lymph node dissection or sampling for CRPM was performed. Inclusion for analysis required presentation of overall survival data of patients with and without lymph node metastases.

3.2. Search strategy and selection criteria

Searches were conducted on published literature restricted to series published between 2000 and 2020, so that the analysis reflected outcome of patients diagnosed and treated with modern surgical, oncological and radiological techniques. Studies were identified through electronic searches of the Medline, Embase and Cochrane databases without language restrictions. The search strategies consisted of a combination of search blocks, index terms and free text words related to pulmonary metastases, mediastinal lymph node dissection and colorectal cancer. Reference lists of included studies were scanned for additional relevant studies. Citation tracking was performed on review articles on the topic of pulmonary metastasectomy. The last search was performed on December 20th, 2020. The full search strategy and database

information were provided in the supplementary data, Appendix A. The systematic review was registered in PROSPERO on November 20th, 2020 (CRD42020168901).

Studies were evaluated independently for inclusion by two authors (MvD and JB) based on title and abstract and were finally evaluated independently based on full text. Titles and abstracts that reported on primary lung cancer, radiotherapy or other ablative therapies, other primary histology than colorectal cancer and case reports (or series <20 patients) were excluded. However, series with heterogeneous primary tumor histology were included in the title and abstract selection and included for the final analysis if separate data on colorectal cancer metastasis were extractable. Any disagreements between the two assessors were resolved by discussion or by consulting the senior author (DH).

Studies evaluating sentinel lymph node procedures (SNP) and studies in which patients were simultaneously treated for liver metastases or only underwent repeat resection of the pulmonary metastases were excluded. Studies without assessment of survival or studies that reported non-transparent data precluding calculation of survival rates for patients with lymph node metastases were excluded.

3.3. Data extraction

A data report form was developed to extract relevant information from each included study. Two authors (MvD and JB) independently extracted the data separately and resolved differences by discussion with the senior author (DH) until consensus was achieved. Data were extracted concerning study design, patient characteristics (age and sex), criteria for lymphadenectomy and sources of bias. The number of patients with and without lymph node metastases after lymphadenectomy were extracted. Data regarding the treatment of the pulmonary metastases were also registered (number of pulmonary metastases, type of resection, administration of adjuvant chemotherapy and the duration of follow-up). Finally, overall survival was registered as median survival or five-year survival for patients with and without lymph node metastases.

3.4. Critical appraisal

For adequate assessment of methodological quality, we consulted an epidemiologist (BT), who advised on the methodological part of this project. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool [21] was used to assess the risk of bias and applicability concerns of included studies. Two authors (MvD and JB) independently assessed the risk of bias for methodological quality of each included study and resolved differences by discussion with the senior author (DH) until consensus was achieved. Each study was judged based on selection bias, performance bias, detection bias, attrition bias, reporting bias and confounding. Methodological heterogeneity was investigated by the risk of bias assessment. As result of the GRADE approach the overall quality of evidence per outcome was determined high, moderate, low or very low.

3.5. Data analysis

Primary outcome measurement was overall survival in patients with or without malignant lymph node involvement. As overall survival was registered as either median survival or five-year survival, analysis of the entire population was not possible. Therefore, studies were subdivided based on the type of survival data presentation. We compared subgroups with or without nodal involvement. Subgroup analysis was done by dividing patients with metastases on the level of lymph node involvement (i.e. N0, N1 or N2). Secondary analysis was done by assessment of the effect of lymph node sampling or dissection on overall survival of patients with or without malignant lymph node involvement. The studies were subdivided based on the type of lymph node assessment by means of sampling or dissection.

Descriptive and inferential statistics were used for the analysis. All data were first tested for normality using a Kolmogorov-Smirnov test, a Q-Q plot and Levene's test. Descriptive statistics were used to outline the characteristics of the patients and studies. Continuous normally distributed variables were expressed as means and 95% confidence intervals (CI), non-normally distributed data by their median and range. To test groups, categorical variables were tested using the Pearson's Chi-square test or Fisher's exact test, when appropriate. Normally distributed continuous data were tested with the independent samples Student's t-test. In this systematic review it was also used to test the under or over-estimation of the presented study groups and their results. In case of non-normally distributed data, a Mann-Whitney *U* test was performed. To test the differences between three groups a one-way ANOVA test was used for normal distributed data and a Kruskal Wallis test for non-normally distributed data. The data were analysed using IBM SPSS statistics (Version 26.0) predictive analytics software and Review Manager (Version 5.3) for systematic reviews.

4. Results

4.1. Description of studies and patient characteristics

A total of 8054 unique studies were identified, of which 27[22–48] retrospective observational cohort studies were included for survival analyses (Fig. 1. Flow chart). The included studies contained 5258 patients that underwent pulmonary metastasectomy, of which 3619 patients (68.8%) underwent pulmonary metastasectomy combined with lymphadenectomy (either lymph node sampling or dissection) and were included for survival analyses. In 10 studies all patients underwent routine simultaneous lymphadenectomy. Four other studies described the indication for lymphadenectomy (only for lobectomy [41,43] large or central pulmonary metastasis [32,39]). The remaining thirteen studies did not describe the indication for lymphadenectomy. The mean age of included patients was 61 years (range 23–87) and 57% was male (range 32–68). In total 61.3% of patients were treated for a solitary pulmonary metastasis, 73.6% of patients were treated by means of a sublobar resection and 34.8% of patients received adjuvant chemotherapy following pulmonary metastasectomy. Other clinical characteristics of the included studies are presented in Table 1.

4.2. Nodal involvement after lymphadenectomy

Lymphadenectomy during surgery detected simultaneous lymph node metastases in 19.1%. The percentage of patients per study with lymph node metastases following lymph node dissection was 22.7% (95% CI: 16.1–29.3%) compared to 15.5% (95% CI: 12.3–18.7%) following lymph node sampling ($p = .025$). In total, 13 studies [22–25,28,30,34,36,37,42–45] were included in analysis of the survival rate of patients with N1 lymph node metastases and 11.5% (95% CI: 7.2–15.8%) of patients had N1 lymph node metastases without mediastinal lymph node involvement. A total of 12 studies [22–25,28,30,33,34,36,37,42,45] were included in analysis of the survival rate of patients with N2 lymph node metastases and 10.8% (95% CI: 8.3–13.3%) of patients had N2 lymph node metastases independent of N1 lymph node involvement.

Patients with suspicious mediastinal lymph nodes on preoperative imaging were excluded in 12 studies, three studies included several patients with suspicious lymph nodes on preoperative

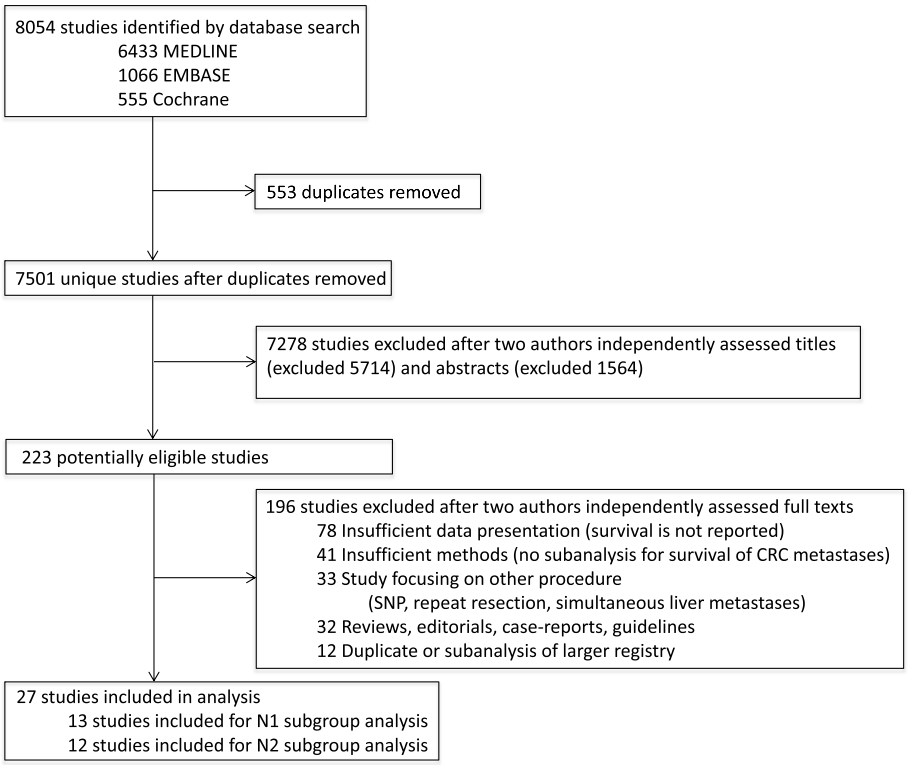

Fig. 1. Flow chart of study selection.

imaging and another 12 studies did not analyse preoperative imaging of mediastinal lymph nodes.

4.3. Five-year overall survival rate following pulmonary metastasectomy with lymphadenectomy

A total of 22 studies [23–25,27,29–34,36–43,45–48] were included in the analysis of five-year overall survival rate (Table 1). Five-year overall survival for patients with (n = 488) and without (n = 2546) lymph node metastases were 18.2% (95% CI: 13.1–23.4%) and 51.3% (95% CI: 46.0–56.6), respectively (p < .001). In the group of patients with lymph node metastases five-year overall survival for patient with N1 lymph node metastases (n = 81) was 40.7% (range: 24.0–78.5) compared to 10.9% (range: 0.0–30.5%) in patients with N2 lymph node metastases (n = 71) (p = .064) (Table 2).

Five-year overall survival of patients without lymph node involvement following lymph node dissection (n = 926) was 47.3% (95% CI: 37.2–57.5%) compared to 53.2% (95% CI: 46.4–60.0%) in patients after lymph node sampling (n = 1620) (p = .286). Five-year overall survival for patients with lymph node involvement following lymph node dissection (n = 198) and sampling (n = 290) was 17.9% (95% CI: 7.3–28.4%) and 18.5% (95% CI: 11.8–25.1%), respectively (p = .908).

4.4. Median survival following pulmonary metastasectomy with lymphadenectomy

A total of 12 studies [22,23,25–28,30,34–36,39,44] were included in the analysis of median survival (Table 1). Median survival for patients with (n = 422) and without (n = 1767) lymph node metastases was 27.9 months (range: 7.5–44.0 months) and 58.9 months (range: 39.0–94.0 months), respectively (p < .001). In the group of patients with lymph node metastases median survival for patient with N1 lymph node metastases (n = 136) was 26.0 months (range: 21.5–32.5 months) compared to 23.2 months (range: 15.3–34.0 months) in patients with N2 lymph node metastases (n = 143) (p = .886) (Table 2).

4.5. Subgroup analysis based on risk of bias

Because of the lack of dispersion on the documented survival data in the included studies, it was not possible to perform a meta-analysis. Therefore, a separate analysis of the survival rate for the different studies based on the GRADE score was performed (Table 3). A total of four studies received a moderate GRADE score, 16 studies received a low GRADE score and seven studies a very low GRADE score. Five-year overall survival rate for patients without lymph node metastases in the moderate, low and very low GRADE score studies were 48.8% (95% CI: 35.6–62.0%), 50.7% (95% CI: 41.7–59.7%) and 54.0% (95% CI: 42.2–65.8%), respectively (p = .781). Five-year overall survival rate for patients with lymph node metastases in the moderate, low and very low GRADE score studies were 10.6% (95% CI: 5.1–26.2%), 17.5% (95% CI: 11.6–23.4%) and 23.2% (95% CI: 7.7–38.5%), respectively (p = .233).

5. Discussion

In this systematic review of the literature comprising 3619 patients, the five-year overall survival rate for all patients with lymph node metastases detected during metastasectomy for colorectal pulmonary metastases was 18.2% (95% CI: 13.1–23.4%) compared to 51.3% (95% CI: 46.0–56.6) for patients without simultaneous lymph node metastases (p < .001). The five-year overall survival rate of patients with lymph node metastases located in the mediastinum (N2 nodes) was 10.9% (95% CI: 0.0–29.7%). Studies that presented outcome on lymph node dissection had significantly more patients

Table 1
Characteristics and outcome of included studies.

	Number of patients	Patients with lymphadenectomy (%)	Prevalence of metastatic lymph nodes (%)	Solitary pulmonary metastasis (%)	Sublobar resection (%)	Adjuvant chemotherapy (%)	Follow-up (months)	Five-year survival N0 (%)	Five-year survival N+ (%)
Renaud et al., 2014	320	100	44	49.4	N/S	N/S	33.0	N/S	N/S
Bolukbas et al., 2014	165	100	22	49.1	73.3	N/S	36.0	59.0	23.0
Nanji et al., 2018	265	63	20	61.0	56.9	26.9	43.1	49.0	19.0
Hamaji et al., 2012	319	62	13	56.0	82.9	2.3	28.0	27.5	20.7
Meimarakis et al., 2014	89	52	22	74.3	79.9	N/S	35.2	N/S	N/S
Riquet et al., 2010	82	70	16	64.1	N/S	23.9	46.0	47.6	38.5
Pfannschmidt et al., 2006	114	100	32	N/S	N/S	N/S	N/S	N/S	N/S
Hwang et al., 2010	101	91	17	61.6	N/S	67.2	46.0	53.3	19.6
Pfannschmidt et al., 2003	167	100	19	50.3	65.5	N/S	59.0	38.7	0.0
Hofmann et al., 2019	77	88	12	N/S	78.7	N/S	N/S	56.5	22.0
Ogata et al., 2005	30	40	33	N/S	N/S	N/S	47.0	N/S	0.0
Sun et al., 2017	88	57	18	81.2	70.1	61.7	37.0	72.6	30.5
Welter et al., 2007	169	100	17	47.9	75.3	N/S	N/S	42.0	19.2
Javed et al., 2014	66	100	6	63.6	70.1	34.8	N/S	N/S	N/S
Iida et al., 2013	681	56	15	58.6	N/S	19.7	40.3	59.4	37.3
Jarabo et al., 2011	71	90	14	39.2	86.7	N/S	35.0	64.0	16.7
Inoue et al., 2004	89	100	24	74.2	N/S	N/S	85.9	50.8	19.3
Koga et al., 2006	28	48	18	N/S	N/S	41.4	24.0	30.0	0.0
Kanzaki et al., 2011	141	91	11	64.1	N/S	N/S	N/S	59.4	28.1
Watanabe et al., 2009	39	35	13	N/S	N/S	N/S	N/S	72.0	0.0
Inoue et al., 2000	25	100	28	64.0	N/S	N/S	108.0	49.5	14.3
Lin et al., 2009	63	100	10	65.1	58.7	N/S	37.3	45.1	30.0
Kim et al., 2010	27	100	7	44.4	100	85.2	39.5	N/S	N/S
Hirosawa et al., 2012	82	30	21	N/S	93.6	N/S	N/S	57.9	28.3
Zampino et al., 2014	139	70	12	47.7	73.9	21.6	48.0	49.0	13.0
Saito et al., 2002	138	86	14	63.0	64.0	38.2	N/S	48.5	6.2
Iizasa et al., 2006	44	59	18	N/S	45.3	N/S	N/S	45.1	15.6
Median (IQR) or Mean (95% CI)	89 (63–141)	88% (57–100%)	17% (13–21%)	61% (49–64%)	74% (64–81%)	35% (22–57%)	40 (35–47)	51.3% (95% CI 46–57%)	18.2% (95% CI 13–23%)
Number of studies	N = 27	N = 27	N = 27	N = 20	N = 16	N = 11	N = 18	N = 21	N = 22

Table 2
Overall survival following pulmonary metastasectomy with lymphadenectomy.

	Five-year overall survival	Number of studies	Median survival (months)	Number of studies
Node negative	51.3% (95% CI: 46.0–56.6%)	N = 20	58.9 m (range: 39.0–94.0 m)	N = 12
N1 lymph node metastases	40.7% (range: 24.0–78.5%) [a]p = .18	N = 4	26.0 m (range: 21.5–32.5 m) [a]p = .001	N = 5
N2 lymph node metastases	10.9% (95% CI: 0.0–30.5%) [a]p < .001 **p = .064	N = 5	23.2 m (range: 15.3–34.0 m) [a]p = .001 **p = .886	N = 4

[a] Compared to node negative group. ** compared to N1 lymph node metastases.

with lymph node involvement, and therefore a higher rate of nodal upstaging, compared to studies that presented outcome on lymph node sampling. Although lymph node dissection had no significantly different impact on overall survival compared to lymph node sampling.

Of all patients who underwent lymphadenectomy, either by means of lymph node sampling or dissection, 19.1% had lymph node involvement. However, many patients with lymph node metastases in this systematic review have unsuspected lymph node involvement based on the selection criteria of the individual studies. It is likely that patients with suspect or proven mediastinal lymph node metastases in the preoperative workup have a worse outcome. The results of this study objectify the poor oncological outcome of patients with CRPM and simultaneous lymph node metastases.

Different survival rates were found when analysing the anatomical location of the involved lymph node stations (Table 2). Mediastinal lymph node metastases were associated with a five-year overall survival rate of 10.9% and a median survival rate of 23.2 months. The next step will be to better identify patients with mediastinal lymph node metastases, to better select patients that are suited for pulmonary metastasectomy. Several studies reported on preoperative invasive staging of the mediastinum in patients

Table 3
GRADE assessment of included studies.

	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Confounding	GRADE Score
Lymph node dissection							
Renaud et al. 2014	☹	☺	☺	☹	☺	?	LOW
Bolukbas et al. 2014	☹	☺	☺	☺	☺	?	MODERATE
Nanji et al. 2018	☹	☹	☺	☺	☺	?	LOW
Hamaji et al. 2012	☹	☹	☺	☺	☺	?	LOW
Meimarakis et al. 2014	☹	☹	☺	☹	☺	☹	VERY LOW
Riquet et al. 2010	☹	☹	☹	☺	☺	☹	VERY LOW
Pfannschmidt et al. 2006	☹	☺	☺	☹	☺	?	LOW
Hwang et al. 2010	☹	☹	☺	☺	☺	?	LOW
Pfannschmidt et al. 2003	☹	☺	☺	☺	☺	☺	MODERATE
Hofmann et al. 2019	☹	☺	☺	☹	☺	?	LOW
Ogata et al. 2005	☹	☹	☺	☺	☺	?	LOW
Lymph node sampling							
Sun et al. 2017	☹	☹	☺	☺	☺	?	LOW
Welter et al. 2007	☹	☹	☺	☹	☺	☹	VERY LOW
Javed et al. 2014	☹	☺	☺	☹	☺	?	LOW
Iida et al. 2013	☹	☹	☺	☺	☺	☹	VERY LOW
Jarabo et al. 2011	☹	☹	☺	☺	☺	?	LOW
Inoue et al. 2004	☹	☹	☺	☺	☺	?	LOW
Koga et al. 2006	☹	☹	☺	☺	☺	?	LOW
Kanzaki et al. 2011	☹	☹	☺	☺	☺	?	LOW
Watanabe et al. 2009	☹	☹	☺	☹	☺	☹	VERY LOW
Inoue et al. 2000	☹	☺	☺	☹	☺	?	LOW
Lin et al. 2009	☹	☹	☺	☺	☺	?	LOW
Kim et al. 2010	☹	☹	☺	☺	☺	?	LOW
Hirosawa et al. 2012	☹	☹	☺	☹	☺	?	VERY LOW
Zampino et al. 2014	☹	☺	☺	☺	☺	☺	MODERATE
Saito et al. 2002	☹	☺	☺	☺	☺	☺	MODERATE
Iizasa et al. 2006	☹	☹	☹	☹	☺	?	VERY LOW

☺ Low risk of bias / no applicability concerns, ☹ High risk of bias / high applicability concerns, ? Unclear risk of bias / unclear applicability concerns

with CRPM by means of mediastinoscopy [49] or endosonography [50–54]. So far, the implementation of invasive staging of the mediastinum in these patients has been limited. This is mostly due to the lack of consensus whether lymph node metastases should be a contraindication for local radical therapy. Recently, Guerra et al. [55] analysed the value of Fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) in 521 patients with CRPM. Demonstrating a low sensitivity of both CT and PET in detecting lymph node metastases (11% and 34% respectively), concluding that PET-CT is not able to correctly define lymph node metastases and therefore not suited to define an optimal treatment strategy.

Multiple comparisons can be made with local treatment for colorectal liver metastases (CRLM). The impact of regional lymph node metastases is one of the worst prognostic factors for CRLM. The overall prevalence of lymph node metastases is approximately 16% for liver metastases of colorectal cancer [56]. Five-year overall survival rates for patients with CRLM treated by partial hepatectomy and simultaneous lymphadenectomy presented quite similar outcome compared with the survival rates in this systematic review. Five-year survival for patients with colorectal liver metastases and regional lymph node metastases is 18% and patients with liver metastases without regional lymph node metastases have a five-year survival of 53%. Moreover, the location of these lymph node metastases strongly affects survival, with observed five-year survival of 25% for pedicular and 0% for coeliac lymph nodes [57].

The main limitations of this systematic review were the lack of detailed data description from individual studies and the lack of dispersion on the obtained survival data. Two of the 22 studies that documented five-year overall survival and six of the 12 studies that reported median survival presented dispersion on their survival rates. This precluded performing a meta-analysis based on the available data and from measuring the level of heterogeneity. The mean survival rates per study were used as individual data entry points for the comparison of survival within and between the different groups. Using the GRADE tool for risk of bias, none of the included articles obtained a high GRADE score. However, no difference in survival rate was found based on the level of the GRADE score for patients with and without lymph node metastases.

The results from this systematic review do not allow to determine the potential therapeutic effect of lymphadenectomy in pulmonary metastasectomy. Attempts have been made to objectify the role of lymphadenectomy on survival [58], however selection bias precludes generalizability. Currently, a Danish randomized controlled trial (NCT03113318 [59]) will assess the impact on survival of routine mediastinal lymphadenectomy with pulmonary metastasectomy for CRPM. This trial will hopefully reveal whether lymphadenectomy during metastasectomy for CRPM is associated with survival benefit. Until we have the results of this RCT, we can only conclude that lymphadenectomy during pulmonary metastasectomy for colorectal pulmonary metastases has prognostic value.

Especially mediastinal (N2) lymph node metastases contribute to impaired patient survival and are therefore not suited for

surgical treatment. Mediastinal lymph node metastases should preferably be identified preoperatively. Because of the impaired accuracy of PET-CT in detecting thoracic lymph node metastases from colorectal cancer, there might be a role for preoperative endosonographic staging of the mediastinum in selected patients or when extensive surgery is considered as radical treatment.

6. Conclusion

Simultaneous lymph node metastases during metastasectomy for colorectal pulmonary metastases have a detrimental impact on survival and this is most apparent for mediastinal lymph node metastases. Therefore, lymphadenectomy during pulmonary metastasectomy for colorectal pulmonary metastases can be advised to obtain important prognostic value. However, these data do not allow to determine a survival benefit due to the performance of simultaneous lymphadenectomy during pulmonary metastasectomy for colorectal pulmonary metastases.

CRediT authorship contribution statement

Martijn van Dorp: Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review. **Jelle Egbert Bousema:** Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Manuscript preparation, Manuscript editing, Manuscript review. **Bart Torensma:** Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript review. **Christian Dickhoff:** Study concepts, Data analysis and interpretation, Manuscript editing, Manuscript review. **Frank Jozef Christiaan van den Broek:** Study concepts, Data analysis and interpretation, Manuscript editing, Manuscript review. **Wilhelmina Hendrika Schreurs:** Study concepts, Study design, Data analysis and interpretation, Manuscript editing, Manuscript review. **Michel Gonzalez:** Study concepts, Study design, Data analysis and interpretation, Manuscript editing, Manuscript review. **Geert Kazemier:** Study design, Data analysis and interpretation, Manuscript review. **David Jonathan Heineman:** Study concepts, Study design, Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation, Manuscript editing, Manuscript review.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.09.020.

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Disclosure

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