Review Article

Impact of the extent of lung resection on postoperative outcomes of pulmonary metastasectomy for colorectal cancer metastases: an exploratory systematic review

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Background: Pulmonary metastasectomy (PM) with curative intent has become a widely accepted treatment for lung metastases from solid tumours in selected patients, with low perioperative morbidity and mortality. In particular, PM is strongly recommended in selected patients with secondary lesions from colorectal cancer (CRC), due to its excellent postoperative prognosis. Nevertheless, the impact of the extent of PM on recurrence and survival remains controversial. This review aimed at assessing differences in short- and long-term postoperative outcomes depending on the extent of lung resection for lung metastases.

Methods: A systematic literature review of studies comparing anatomical and non-anatomical resections of lung metastases was performed (Prospective Register of Systematic Reviews Registration: 254931). A literature search for articles published in English between the date of database inception and January 31, 2021 was performed in EMBASE (via Ovid), MEDLINE (via PubMed) and Cochrane CENTRAL. Retrospective studies, randomised and non-randomised controlled trials were included. The Cochrane Collaboration tool was used to determine the risk of bias for the primary outcome for included studies.

Results: Out of 432 papers, three retrospective non-randomised studies (1,342 patients) were selected for systematic reviewing. Although our search design did not exclude any primary tumour histology, all selected studies investigated surgical resection of lung metastases from CRC. Because of variations in the compared surgical approaches to pulmonary metastases, a meta-analysis proved unfeasible. There was a tendency to perform anatomical resections for larger metastases. Multivariate analyses revealed that anatomical resections were protective for recurrence-free survival (RFS), while the impact of such procedures on overall survival (OS) remained uncertain. A significantly higher incidence of resection-margin recurrences was observed in patients who underwent non-anatomical resections.

Discussion: Anatomical resections of lung metastases from CRC seem to be associated with improved RFS. However, well-constructed comparative clinical trials focusing on the extent of PM are needed.

Keywords: Lung metastases; pulmonary metastasectomy (PM); anatomical lung resection; non-anatomical lung resection

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Introduction

Metastasectomy: when, why and how?

Metastatic cancer has long been considered an incurable disease, only amenable to palliative and best supportive care. Curative approaches were thought to be ineffective, due to the diffusion of tumour cells from the primary site to distant organs, preventing an effective eradication of the malignancy. Further studies have demonstrated that the development of distant metastases results from an intricate interplay among tumour biology, size, stage, microenvironment, and other—partially unknown—factors (1,2).

The complexity of this process accounts for the extremely heterogeneous behaviour of secondary tumours with identical histotype, in terms of metastasis number and location, disease-free interval (DFI) and survival. This translates into a broad spectrum of clinical presentations with different prognostic significance and estimated life expectancy; consequently, these patients can hardly be regrouped under one category and the development of adequate management strategies appears difficult.

Presently, intention-to-treat therapies for metastatic malignancies are debated, and the role of ablative treatments remains dubious, despite the improved recurrence-free survival (RFS) and overall survival (OS) reported by several phase 2 randomised trials on oligometastatic cancer patients (3). However, phase 3 randomised trials designed to test these outcomes are still ongoing.

Pulmonary metastasectomy (PM): current challenges

The lungs are the second most common site of metastases after the liver, with an incidence ranging from 20% to 54% in patients deceased from an extra-thoracic malignancy (4,5).

PM has become a widely accepted treatment over the past decade (6) due to the development of novel screening tools, advances in surgical and anaesthetic techniques and improvements in anti-cancer therapies. PM with curative intent is now included in the multidisciplinary approach to metastatic malignancies (7). In fact, in selected patients with completely resectable lung metastases, local control of the primary tumour, clinically negative mediastinal lymph nodes (LNs) and no sign of disseminated extrapulmonary metastases, PM has proven to be safe and feasible, with low perioperative morbidity and mortality (8,9).

However, its oncological benefits have yet to be demonstrated by substantial evidence (10), and many aspects of this practice remain controversial. The extent of parenchymal resection, the maximum number of resectable nodules, the efficacy of non-surgical local therapies, and the role of intraoperative LN assessment have become a matter of intense debate.

Surgery should enable complete removal of all pulmonary metastases, ensuring adequate local control of the disease without impairing the respiratory function. Sublobar resections are generally preferred over lobectomies, based on the historically accepted principle of parenchymal-sparing and in anticipation of potential further PMs. This assumption, however, is not supported by evidence, as segmentectomies and lobectomies have shown comparable functional outcomes three months after surgery. PM leads to a significant loss in respiratory function (about 10%), which is relevant even in patients who underwent wedge resections only (11). On the other hand, major anatomical resections may be oncologically safer, as they ensure completeness of resection (R0). Pneumonectomy, however, is associated with higher morbidity and mortality and is rarely recommended to treat lung metastases (9,12).

It has been demonstrated that PM has an excellent postoperative prognosis in selected patients with colorectal cancer (CRC)-related secondary lesions (5-year OS is 48–51.9%) (13,14). Surgical removal of lung metastases from CRC is strongly recommended (15), albeit not supported by solid guidelines or high-level evidence (16).

Aim of the study

Despite the vast interest attested by the numerous papers published on the topic, many aspects of PM remain unclear. Besides common practice, the impact of the extent of PM on morbidity and survival has not been addressed by comparative research and the question remains unanswered. Therefore, the purpose of this systematic review is to assess the differences in short- and long-term outcomes depending on the surgical extent of PM with curative intent. We present the following article in accordance with the PRISMA reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-239/rc).

Methods

This systematic review is being reported according to the PRISMA statement (17) and in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions (18). Details of the protocol for this systematic review were registered with the International Prospective Register of Systematic Reviews (PROSPERO Registration: 254931).

A systematic literature search for articles published in English between the date of database inception and January 31, 2021 was performed in EMBASE (via Ovid), MEDLINE (via PubMed) and Cochrane CENTRAL.

The following search string was constructed: ("pulmonary metastasis"(All Fields)) AND (("lobectomy"(All Fields)) OR ("wedge"(All Fields)) OR ("segmentectomy"(All Fields)) OR ("tumourectomy"(All Fields)) OR ("tumorectomy"(All Fields))).

Only papers comparing anatomical and non-anatomical resections (retrospective studies, randomised and non-randomised controlled trials) of lung metastases were included. Single-arm case series, case reports, letters, editorials, and expert opinions were not considered. Records identified through the designed search strategy were imported into a reference management software. In case of duplication, the most recent paper was selected.

Two reviewers (EP, LB) independently screened the titles and abstracts of all the imported articles. Full-text copies of potentially eligible reports were separately evaluated by the same reviewers (EP, LB). When multiple studies contained overlapping data, the most informative one was included. Any disagreements were resolved by consensus or arbitration by a third investigator (LJC).

Some of the excluded papers were retained for discussion. Data extracted for each article included: study characteristics, baseline patient characteristics, study period, inclusion criteria, main results and limitations.

The results of the selected studies were individually displayed in a table.

The Cochrane Collaboration tool was used to determine the risk of bias for the primary outcome for included studies (19). The risk of bias due to incomplete outcome data was evaluated at an outcome level, while the risks of bias due to sequence generation, allocation concealment, blinding, selective reporting or funding were evaluated at the study level. The risk of bias was individually estimated by two reviewers (EP, LB) and disagreements were settled by discussion and consensus.

Results

Results of the literature search

The literature search identified 432 articles, 24 (5.6%) of which were selected for in-depth full-text examination. Three retrospective comparative studies (0.7%) (20-22) reporting on 1,342 patients were finally withheld for the systematic review (*Figure 1*).

No randomised controlled trials were identified. A PRISMA checklist was added. A summary of the risk of bias for each included study is shown in *Figure 2*.

The main characteristics and outcomes of the included papers are presented in *Table 1*.

Because there were variations in the compared surgical approaches to pulmonary metastases [major *vs.* lesser resections (20), wedge resection *vs.* anatomical segmentectomy (21), lobectomy *vs.* sublobar resection (22)], a full meta-analysis was not feasible.

Analysis of the selected studies

The three selected studies investigated the extent of lung resection in patients with CRC: two (20,21) were multi-centre nationwide analyses, while one (22) reported a single-centre experience.

Hernández and colleagues (20) aimed at determining the role of major lung resections for PM in CRC patients. The authors retrospectively analysed a prospectively filled database of 543 patients operated at 32 Spanish hospitals over a 2-year period, with a minimum follow-up of 3 years. Twenty-one patients were excluded due to unspecified reasons resulting in a total of 522 patients (96.1%): 104 major resections (19.9%; 100 lobectomies and 4 pneumonectomies) and 418 lesser resections (80.1%; 394 wedge resections, 19 anatomical segmentectomies and 5 atypical resections). Eligibility criteria were: first PM with curative intent (macroscopic R0), pathological confirmation of CRC on at least one excised lesion. The two groups did not significantly differ in patient demographics, CRC stage, anatomical location (colon, rectum, or both), and induction and adjuvant treatments for the primary tumour. Also, the preoperative serum carcinoembryonic antigen (CEA) levels were comparable between the two groups

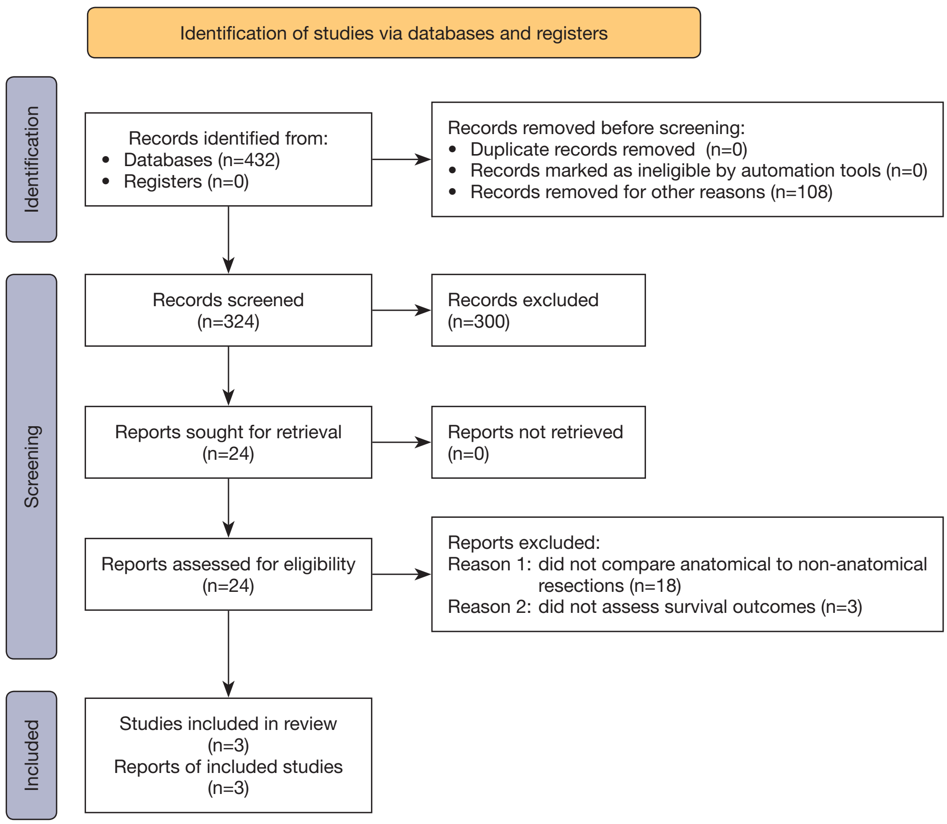

Figure 1 Flowchart of article selection process. From (17).

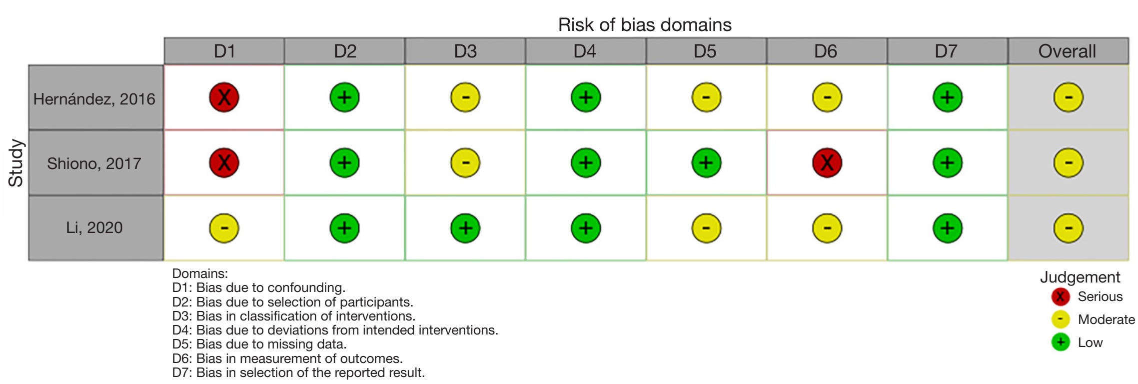

Figure 2 Risk of bias summary. Authors' judgements about each risk-of-bias item for each included study. Green, yellow, and red circles indicate low, moderate and serious risk of bias, respectively.

(P=0.4 and P=0.5 for CEA >5 and CEA >10, respectively). Previous liver metastases were significantly rarer in the major resection group (16.3% *vs.* 31.1% for lesser resection group, P=0.002), but there were no differences concerning previous hepatic metastasectomies (P=0.4). DFI was defined as the interval between the primary operation for CRC and the data of diagnosis of pulmonary metastasis and was significantly longer in the major resection group (P=0.03, P<0.001 and P<0.001 for DFI >12, 24 and 36 months respectively).

Preoperative computed tomography (CT) scans disclosed nodules >30 mm more frequently among patients who

Table 1 Characteristics of the three studies meeting the inclusion criteria

	First author, year		
	Hernández, 2016 (20)	Shiono, 2017 (21)	Li, 2020 (22)
Type of study	Multicentre retrospective	Multicentre retrospective	Single-centre retrospective
Population	522 patients who underwent PM for CRC metastases—104 major resections (100 lobectomies + 4 pneumonectomies): mean age 64.7 years, M/F ratio 1.48, elevated serum CEA levels in 19.5% patients; 418 lesser resections (394 wedge resections + 19 segmentectomies + 5 atypical resections): mean age 64.4 years, M/F ratio 1.88, elevated CEA levels in 16.4% patients. No statistically significant differences in demographic characteristics and preoperative treatments prior to PM; incidence of previous liver metastases was lower for major resections (P=0.002); DFI was longer for major resections (P<0.05); lung metastasis size was significantly larger for major resections (P<0.001)	553 patients who underwent PM for CRC metastases—98 segmentectomies: median age 64 years, M/F ratio 0.96, elevated serum CEA levels in 30.5% patients; 455 wedge resections: median age 67 years, M/F ratio 1.41, elevated serum CEA levels in 32.9% patients. No statistically significant differences in demographic characteristics; lung metastasis size was significantly larger for segmentectomies (P<0.001)	267 patients who underwent PM for CRC metastases—93 lobectomies: 52.7% patients aged ≥60 years, M/F ratio 2.10; 174 sublobar resections (12 segmentectomies + 162 wedge resections): 42.5% patients aged ≥60 years, M/F ratio: 1.23. No statistically significant differences in demographic characteristics; lung metastasis size was significantly larger for lobectomies (P<0.001)
Study period	March 2008–March 2010	January 2004–December 2008	July 2011–July 2017
Median follow-up time	38.7 months (range, 0.7–60.3 months)	5.4 years (95% CI: 5.2–5.6 years)	32.5 months (range, 7.2–104.7 months)
Inclusion criteria	PM performed with radical and curative intention; no macroscopic disease at the end of PM; histological confirmation that at least 1 of the lesions excised was a CRC metastasis	1st PM for CRC metastases; PM performed with curative intent; pathologically complete resection (R0) resulting in disease-free status; pathological diagnosis of pulmonary CRC metastasis; no preoperative chemotherapy	PM performed with radical curative intent; single pulmonary metastasis; pathological diagnosis of CRC metastasis to the lung, confirmed by 2 pathologists
Results	Longer DSS after major resection (DSS median not reached *vs*. 52.2 months for lesser resection, 95% CI: 45.9–58.5 months, P=0.03); longer RFS after major resection (RFS median not reached *vs*. 23.9 months after lesser resection, 95% CI: 19.2–28.6 months, P<0.001); higher mean number of resected LN in major resection group (6.8 *vs*. 4.6 in lesser resection group, P<0.001); higher postoperative morbidity after major resections (25% *vs*. 13.4% after lesser resections, P=0.006); comparable postoperative mortality (1% after major resection *vs*. 0.2% after lesser resection, P=0.4)	Higher postoperative morbidity after segmentectomy (14.3% *vs*. 5.3% after wedge resection, P=0.001); recurrences more frequent after wedge resection (61.8% *vs*. 44.9% after segmentectomy, P=0.003); resection-margin recurrences more frequent after wedge resection (7.3% *vs*. 2.0% after segmentectomy, P=0.035); comparable 5-year OS (80.1% *vs*. 68.5%, HR 0.65, 95% CI: 0.38–1.05, P=0.08); longer 5-year RFS for segmentectomy (48.8% *vs*. 36.0% for wedge resection, HR 0.63, 95% CI: 0.44–0.87, P=0.005)	Longer 5-year RFS for lobectomy (44.9% *vs*. 29.8% for sublobar resection, log-rank P=0.03, HR 0.71, 95% CI: 0.52–0.89, P=0.026) in patients whose tumour diameter was ≥1.5 cm; comparable 5-year RFS in patients whose tumour diameter was <1.5 cm (33.3% *vs*. 41.2%, log-rank P=0.45); comparable 5-year OS in patients whose tumour diameter was ≥1.5 cm (61.2% *vs*. 70.0%, log-rank P=0.45); comparable 5-year OS in patients whose tumour diameter was <1.5 cm (100% *vs*. 80.6%, log-rank P=0.37); higher frequency of mediastinal LN dissection/sampling for lobectomy (89.2% *vs*. 13.2 for sublobar resection, P<0.001)
Limitations	Retrospective study; relevant difference in lung metastasis size, DFI and incidence of previous lung metastases between the two groups; no details about the extent of the surgical margins; surgical indications, procedures, approaches and diagnosis of recurrence were determined at the discretion of each institution; no specified diagnostic criteria for recurrence	Retrospective study; relevant difference in lung metastasis size between the two groups; no details about pathological findings and extent of the surgical margins; surgical indications, procedures, approaches and diagnosis of recurrence were determined at the discretion of each institution; no specified diagnostic criteria for recurrence	Retrospective study; single-centre study; short follow-up period; no cancer-specific survival analysis

PM, pulmonary metastasectomy; CRC, colorectal cancer; M/F, male/female; CEA, carcinoembryonic antigen; CI, confidence interval; DSS, disease-specific survival; RFS, disease-free survival; LN, lymph node; DFI, disease-free interval.

underwent major resections (33.3% *vs*. 5.2% for lesser resections, P<0.001), but no differences in the number of patients with bilateral lung metastases were observed (P=0.2).

Survival analyses were performed on 456 patients; median OS, RFS and disease-specific survival (DSS) were 55, 28.3 and 55 months, respectively. The authors reported that RFS and DSS were both longer for patients who underwent major resections (P<0.001 and P=0.03, respectively); however, the Kaplan-Meier curve relating to DSS analysis showed longer survival for patients who received lesser resections. In the multivariate analysis, major resection was considered a protective factor for DSS and RFS (P=0.031 and P<0.001, respectively). There was no relevant difference between the two groups in the pattern of recurrence (P=0.78). Lesser resections were more frequently performed by video-assisted thoracic surgery (VATS) approach (20.8% *vs*. 5.8% for major resections, P<0.001).

Postoperative mortality did not significantly differ between the two groups (P=0.4), whereas a higher postoperative morbidity was related to major resections (25% *vs*. 13.4% for lesser resections, P=0.006).

The mean number of resected LNs was higher for the major resection group (6.8 *vs*. 4.6 for the lesser resection group, P<0.001). LN tumour involvement was a significant predictor of poor DSS (P=0.007); lymphadenectomy, however, was not routinely performed (72% cases did not undergo LN assessment) and was more frequently associated with major resections (P value not reported).

This study had some limitations, notably the heterogeneity of the selected population in terms of size, number and location of pulmonary metastases, the paucity of data regarding LN assessment, and the lack of established criteria to determine the extent of PM.

The study by Shiono *et al*. (21) compared the outcomes of wedge resections and segmentectomies performed at 46 Japanese institutions over a 5-year period. Inclusion criteria were: first PM for pathologically confirmed CRC metastases, performed with curative intent and pathological R0 radicality. Out of 898 eligible patients, those who underwent preoperative chemotherapy (N=113, 12.6%) and/or lobectomy (N=213, 23.7%) were excluded. Finally, 553 patients (61.9%) were selected. Ninety-eight (17.7%) underwent segmentectomy, while 455 (82.3%) received a wedge resection. There were no statistically significant differences in terms of patient characteristics between the two groups: the anatomical location (colon, rectum, or both), median DFI, and preoperative serum CEA levels were comparable (P=0.902, P=0.241, and P=0.654, respectively). Synchronous lung metastases were reported in 24 patients who underwent segmentectomy and 122 who underwent wedge resection (P=0.636).

The median number of resected CRC metastases per patient was 1 (range, 1–8) and did not significantly differ between the two groups (P=0.849), while the median tumour size was larger for segmentectomies (18 *vs*. 14 mm for wedge resections, P<0.001).

Postoperative complications were more frequently reported following segmentectomies (14.3% *vs*. 5.3% for wedge resections, P=0.001); the prolonged air leak rate in particular was significantly higher (5.1% *vs*. 1.8% for wedge resections, P=0.048). In contrast, tumour recurrences developed more often after wedge resections (61.8% *vs*. 44.9% for segmentectomies, P=0.003), especially resection-margin recurrences in patients with intrathoracic disease relapse after PM (7.3% *vs*. 2.0% for segmentectomies, P=0.035). LN assessment was carried out in 72 segmentectomies (73.5%) and 25 wedge resections (5.5%) (P value not available). 5-year OS and RFS were 80.1% and 48.8% for segmentectomies, and 68.5% and 36.0% for wedge resections, respectively. The P values for the OS and RFS comparison between the two groups were not mentioned in the paper. At multivariate analysis OS was not influenced by the surgical approach (P=0.08), while RFS was significantly longer in the segmentectomy group (P=0.005).

The main limitations to this study were: the numerical difference between the two study cohorts, and the lack of standardised criteria of choice for surgical approach and follow-up. Moreover, the authors report that propensity-score matching could not be performed to minimise the potential differences in patient characteristics between the two groups due to the lack of essential data (mainly tumour location and respiratory function).

Li and colleagues (22) evaluated 267 patients who underwent PM at their institution during a 6-year period. Eligibility criteria were: PM with curative intent (macroscopic R0), single pulmonary nodule, histological diagnosis of CRC metastasis confirmed by 2 pathologists. The study population was divided into two groups according to the extent of PM: 93 patients (34.8%) underwent lobectomy and 174 (65.2%) received a sublobar resection (162 wedge resections and 12 anatomical segmentectomies). No remarkable differences between the two groups in terms of baseline characteristics were reported, although no data on the primary tumour were provided. DFI was comparable between the two groups (P=0.38).

Lobectomy was more frequently performed in patients with tumour diameter ≥15 mm (90.3% *vs.* 55.2% for sublobar resection, P<0.001). A VATS approach was more frequently used for sublobar resections (79.3% *vs.* 23.7% for lobectomies, P<0.001).

A subgroup survival analysis depending on tumour size was carried out. In patients with tumour size <15 mm, no differences in 5-year RFS and OS between the two groups were disclosed (P=0.75 and P=0.37, respectively); in patients whose tumour diameter was ≥15 mm lobectomies showed significantly longer 5-year RFS (44.9% *vs.* 29.8% for sublobar resections, P=0.03) and comparable 5-year OS (61.2% *vs.* 70.0% for sublobar resections, P=0.45).

LN assessment was more frequently performed in patients who underwent a lobectomy (89.2% *vs.* 13.2% for sublobar resection, P<0.001). Comparable survival outcomes were reported for PM with or without lymphadenectomy (P value not available); however, patients whose tumour size was ≥15 mm and who received a LN dissection showed improved 5-year RFS.

There were several limitations in this research, including its retrospective, single-centre nature, short follow-up period, and lack of cancer-specific survival data.

Overview of study outcomes

The present systematic review included three studies (20-22) aimed at assessing survival outcomes in patients who underwent PM for CRC depending on the extent of lung resection (*Table 1*).

There were no relevant differences in demographic characteristics between patient groups (20-22), although the size of the lung metastases was larger for anatomical resections [major resection group (20), segmentectomy group (21) and lobectomy group (22)]. Overall, median follow-up time was longer than 2.5 years (20-22). PM performed with curative and radical intent, and pathological confirmation of CRC metastasis were common eligibility criteria (20-22); however, Shiono and colleagues (21) excluded patients who had undergone previous PM and/or neoadjuvant chemotherapy, while Li *et al.* (22) only included patients with a single lung metastasis.

All the selected studies reported a significantly longer RFS after anatomical resections: P<0.001 (major resections: lobectomies and pneumonectomies) (20), P=0.005 (segmentectomies) (21), and P=0.03 (lobectomies for metastases with size ≥15 mm) (22).

Hernández and colleagues (20) disclosed a longer DSS following major resections (lobectomies and pneumonectomies); oppositely, 5-year OS was comparable between segmentectomies and wedge resections (21), and lobectomies and sublobar resections (22).

Discussion

The present systematic review aimed at summarising, in the available literature, studies comparing the impact of different types of lung resection for PM on survival. Of over 400 papers, only three non-randomised studies on PM for CRC metastases were included, and no prospective trials were identified by our search, testifying to the extreme paucity of research conducted on this topic. Although we could not perform a meta-analysis, we observed a tendency to perform anatomical resections for larger metastases; moreover, anatomical resections seem to be associated with longer RFS.

The concept of *oligometastatic state* was introduced in 1995, with the aim of identifying subsets of patients with metastatic cancer that may benefit from curative approaches (1). The term ‘oligometastatic’ implies a limited tumour burden (number and sites of extension) and configures an intermediate degree of progression between localised and widespread disease (3).

The clinical implication of the oligometastatic hypothesis is that, in carefully selected patients whose primary tumour is controlled, metastasis-directed treatments can achieve long-term survival or even cure (23-25).

Since its first report almost a century ago (26), PM has become a widespread routine procedure.

Remarkably, the main selection criteria outlined by Thomford *et al.* (27) in 1965 (low surgical risk, controlled primary malignancy, no sign of extrapulmonary metastatic disease) are still valid and have been followed by many thoracic surgeons (6,9,28,29). Although the therapeutic spectrum of PM has widened, limited progress has been made towards the standardisation of this practice. Several expert consensus statements, surveys and societal reports have attempted to provide recommendations for PM (9,12,15,30), but still, many issues remain unaddressed.

The extent of lung resection for PM with curative intent has rarely been investigated by comparative studies. Sublobar pulmonary resections are the most frequently used technique (9), while lobectomies are occasionally indicated, and pneumonectomies are generally discouraged.

Lung metastases are not uncommon in patients with

CRC, being detected in up to 15% of all CRC cases (31). The 5-year survival rate of untreated metastatic CRC is remarkably poor (32), however, in a subset of patients with resectable disease, radical PM with curative intent can lead to long-term survival (31,33).

The results of a long-awaited randomised trial assessing the effectiveness of PM and for CRC metastases have recently been published (34), much to the disappointment of the scientific community (35,36): the study was interrupted due to poor recruitment, and the desired statistical endpoints were not reached (37). Out of 512 patients with signed informed consent, only 93 participants (18%) were randomised. The authors demonstrated that there was no statistically significant difference in median survival between the two groups (3.5 years for PM *vs.* 3.8 for controls), thus challenging the legitimacy of PM and prompting physicians to call for better scientific evidence (38). The PulMiCC trial further fuelled the controversy about PM, as some experts argued that its findings are too weak to undermine the foundations of an established surgical practice with low reported morbidity (~2.5%) (39), such as PM (40). A larger randomised trial is undeniably needed to assess the actual benefits of PM, investigating the indications, timing and modalities of surgery for all tumour histologies. Propensity-score matching would enable stratifying patients by number and size of metastases, clinical hilar-mediastinal nodal status, DFI, respiratory function and, of course, histology, allowing unbiased comparisons of anatomical *vs.* non-anatomical resections, LN resection *vs.* no lymphadenectomy, neoadjuvant treatments *vs.* upfront surgery.

In our systematic review, although our search design did not set any primary histology limitations, all the selected studies focused on surgical resection of lung metastases from CRC, analysing a total population of 1,342 patients (>250 per study). A meta-analysis could not be performed due to intrinsic differences between the studies, namely the type of lung resection, pre- and postoperative treatments, and the reporting of baseline and outcome measures. Nonetheless, several relevant observations were made.

First, the extent of lung resection seems to be influenced by the size of the metastasis. In fact, segmentectomies were performed more frequently than wedge resections for lung metastases larger than 15 mm (21) and major anatomical resections were carried out more often than minor resections for nodules larger than 30 mm (20). In the study by Li *et al.* (22), lobectomies were the procedure of choice for metastases larger than 15 mm and were associated with a longer RFS, while no survival differences were observed in patients whose tumour was smaller than 15 mm. It must be noted, however, that none of the aforementioned studies take the parenchymal location of the metastases into account: it is more likely that minor resections are performed for peripheral metastases, while central parenchymal or hilar tumours often require major anatomical resections.

Secondly, multivariate analyses revealed that anatomical resections were protective factors for RFS in two studies (20,21), while the impact of such procedures on OS (or DSS) remains uncertain. Perhaps these results should be interpreted in the light of the data concerning intraoperative hilar-mediastinal LN dissection, which was more frequently performed in the anatomical resection groups (20-22).

Furthermore, RFS might be affected by the distance of the metastasis from the resection margins; in fact, a significantly higher incidence of resection-margin recurrences was observed in patients who underwent non-anatomical (wedge) resections (21).

On the other hand, there are issues concerning the baseline features of the study populations, notably the primary tumour characteristics, that need to be addressed before drawing valid conclusions from these papers. For instance, Li *et al.* (22) did not provide any information about the diagnosis, staging and treatment of CRC, except for the DFI. In the study by Hernández and colleagues (20), the major resection group had longer DFI and lower incidence of previous liver metastases. Consequently, one could legitimately hypothesise that patients in the major resection group displayed a more favourable tumour biology (slow growth, low metastatic capacity) and that this, rather than the extent of parenchymal resection they received, may account for their longer survival.

Therefore, the reported findings prevent us from recommending anatomical lung resections for CRC metastases. However, they are consistent with data reported in other studies: in their meta-analysis on PMs in CRC patients, Zabaleta and colleagues (13) disclosed a shorter survival for wedge resections when compared to lobectomies [hazard ratio (HR) 0.7, 95% confidence interval (CI) 0.63–0.96].

Notably, Renaud *et al.* (41) revealed significantly improved OS and lung-specific RFS in patients harbouring *KRAS* mutations who underwent anatomical resections (segmentectomies), while no relevant survival differences between anatomical and non-anatomical resections were disclosed in the wild-type population; besides, the resection-margin recurrence rate was higher for patients who underwent non-anatomical resections in the *KRAS*-mutated group (P=0.001).

Indeed, the risk of resection-margin recurrence seems to be a significant concern for non-anatomical (wedge) resections for PM: Shiono *et al*. (42) demonstrated that short resection margins were significant risk factors for recurrence (P=0.036) and that an adequate distance from the margin should be 10 mm. Similarly, Davini *et al*. (43) showed that narrow resection margins were independent prognostic factors of worse survival (P=0.006) after PM for CRC metastases.

Local (resection-margin) recurrence assumes greater importance when major anatomical resections cannot be performed, due to reduced respiratory function. Parenchyma-sparing procedures [sublobar resections and/or thermal ablation (44)] are a valid option for respiratory-impaired patients as long as they ensure radicality, hence the relevance of predicting resection-margin recurrence as a primary outcome, alongside OS and RFS.

In particular, compared to conventional stapler PMs, laser-assisted resections (neodymium-doped yttrium aluminium garnet, Nd:YAG) seem to achieve equivalent survival, with the advantages of a lesser parenchymal sacrifice and a lower complication rate (45). Nd:YAG laser surgery allows to treat a larger number of metastases (46), also centrally located (47), with comparable (46) or even better (47) perioperative outcomes than standard PM. It must be noted, however, that the histological analysis of the resection margins following Nd:YAG laser-assisted PM is often unfeasible, due to the thermal damage to the lung parenchyma in the coagulation site, resulting in tissue necrosis. Resection-margin recurrences are, therefore, difficult to assess on the pathological specimens and necessitate clinical and radiological postoperative confirmation. To this extent, however, postoperative chest CT scans are often inconclusive, as the inflammatory reaction of the parenchyma surrounding the area of previous Nd:YAG laser resection may mimic a local disease relapse. Only after the remission of the inflammatory infiltrates (generally requiring several months) resection-margin recurrences can be safely excluded (47).

Several single-centre experience reports on PM for various primary tumour histologies evaluated the extent of lung resection as an independent prognostic factor for survival; in the studies by Corona-Cruz *et al*. (48) and Lo Faso *et al*. (49) multivariate analyses did not disclose any statistically significant difference between anatomical and non-anatomical resections.

The role of hilar-mediastinal LN dissection is controversial, as it is not routinely performed during PM. The nodal status has been shown to have prognostic impact in patients who underwent PM (50-52) for CRC metastases (53,54). In a retrospective study of 160 patients who underwent PM for CRC, the multivariate analysis disclosed that the number of lung metastases and colon cancer (as opposed to rectal cancer) were significant predictive factors of thoracic nodal tumour involvement (55). However, only one of the selected papers of our review evaluated the survival benefit of lymphadenectomy, revealing that it did not improve either RFS or OS (22). Current research approaches are moving towards the understanding of the tissue microenvironment and the implications it may entail for PM (56,57). Welter and colleagues (58) suggested that the growth patterns of lung metastases should be taken into account when pondering the extent of PM. For instance, they recommended large circular resection margins for CRC metastases (due to the high rate of interstitial spread and aerogenous spread of floating cancer cell clusters) and broad lateral margins and non-anatomical resections for sarcoma secondary lesions (given their tendency towards pleural infiltration).

Study limitations

The present systematic review has some limitations, namely the small number of included studies and the heterogeneity in describing baseline characteristics and outcome measures, which prevented us from performing a meta-analysis. Furthermore, confounding bias may occur due to unreported baseline data (postoperative predicted respiratory function, central/hilar/peripheral location of the lung metastases) that might have influenced the choice of the extent of resection.

Conclusions

Regardless of the vast interest attested by the numerous papers published on the topic, many aspects of PM remain unclear. There is an undeniable knowledge gap that needs to be addressed by well-constructed comparative studies. To the best of our knowledge, this was the first systematic review to assess the impact of the extent of lung resection for PM. Although a meta-analysis proved unfeasible, the included studies suggested that anatomical resections of lung metastases from CRC are associated with improved RFS, while they do not significantly affect OS.

Despite the aforementioned limitations, the main strength of our work lies in its methodology in compliance with stringent, reliable, and reproducible criteria.

In common practice, many variables, namely the location, size and number of metastases, as well as predicted postoperative respiratory function, play a role in surgical decision-making. Therefore, defining an adequate treatment strategy remains challenging.

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