Review Article

A narrative review of minimally invasive pulmonary metastasectomy for colorectal cancer

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Background and Objective: Pulmonary metastasectomy is a well-established intervention for the treatment of lung metastases from colorectal cancer (CRC). While minimally invasive approaches are used widely for this operation, the benefits and disadvantages of video-assisted thoracoscopic surgery (VATS) compared to open thoracotomy have not been thoroughly analyzed in the literature. Specifically, favorable prognostic factors and risk factors for pulmonary metastasectomy in the setting of VATS as well as benefits of repeat metastasectomy for recurrent lung metastasis using VATS compared to an open approach have yet to be explored. The aim of this study is to provide perspective on these specific topics, by reviewing the literature to compare advantages and outcomes of VATS *vs.* open thoracotomy.

Methods: A literature search was performed using the PubMed database up to March 2023 for studies reporting on minimally invasive pulmonary metastasectomy for the treatment of lung metastases in CRC. Articles that were published in languages other than English were excluded. Full texts of potentially eligible articles were reviewed, and eligible studies were selected for inclusion of their reported results in this manuscript.

Key Content and Findings: Several factors including number and size of pulmonary lesions, pre-operative serum carcinoembryonic antigen (CEA) level, length of disease-free interval (DFI), and mediastinal lymph node status were identified in the literature as being notable independent prognostic factors for post-metastasectomy outcomes, while prior extrapulmonary metastases (EPM) and anatomic resection were reported to be associated with high risk of metastatic recurrence of disease. For repeat metastasectomy for recurrent lung metastasis, VATS was shown to be equal or superior to open thoracotomy, due to decreased adhesion formation, decreased postoperative pain, shorter hospital length of stay, and improved compliance with adjuvant therapies.

Conclusions: Despite a likely negligible survival benefit, VATS can be considered a favorable method of surgical intervention for the treatment of lung metastases in colorectal carcinoma for its advantages in patient quality of life and in cases of potential re-operation.

Keywords: Metastasectomy; minimally invasive; colorectal cancer (CRC); video-assisted thoracoscopic surgery (VATS)

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Introduction

Background

About 50–60% of all patients with colorectal cancer (CRC) develop metastatic disease. The liver and lung are the most frequent metastatic sites of CRC, and pulmonary metastases are found in approximately 20% of all patients with CRC. Pulmonary metastases occur after previous liver metastases in 8–10% of CRC patients (1). Surgical treatment of pulmonary metastases from CRC has been well documented. However, the specific role of minimally invasive approaches like video-assisted thoracoscopic surgery (VATS) in the management of pulmonary metastasectomy for CRC is less well studied.

Rationale and knowledge gap: VATS has been shown to have distinct advantages compared to open thoracotomy for treatment of pulmonary metastases from CRC (2-4). Though there has been skepticism regarding the ability of minimally invasive approaches to detect small and deep nodules, several studies have shown no significant differences in the number of pulmonary recurrences when comparing minimally invasive approaches (VATS) to open thoracotomy. Of note, Chao *et al.* and Prenafeta Claramunt *et al.* use propensity score matching to avoid potential selection bias, since patients with less extensive disease typically undergo VATS, while those with central or multiple nodules undergo open surgery. Moreover, emerging advances in surgical techniques and medical devices allow for better localization of smaller pulmonary nodules, including preoperative CT-guided hook-wire localization, electromagnetic navigation bronchoscopy-guided dye marking or robot-assisted bronchoscopic dye marking, and microcoil implantation (2,5-7). This implies that the use of minimally invasive techniques for pulmonary metastasectomy does not compromise detection of pulmonary nodules, while also introducing widely-accepted benefits including decreased postoperative pain, shorter hospital length of stay, fewer adhesions at reoperation, and improved compliance with adjuvant therapies (2).

However, the therapeutic effect and oncological benefit of pulmonary metastasectomy for colorectal carcinoma remains inconclusive, as surgery cannot be said to confer a definite survival benefit. The Society of Thoracic Surgeons (STS) published a statement in February 2019 including "metastatic disease survival is assumed to be zero", implying that survival beyond 5 years could be attributed to surgical intervention via metastasectomy. However, the publishing authors have since asserted that this statement is "a contention not supported by the literature", and the statement has been refuted (8-10). Milosevic *et al.* have shown in their randomized controlled trial that the survival for patients in the control arm, i.e., patients with pulmonary metastases from CRC who do not undergo metastasectomy, is better than previously assumed, and comparable to that of patients in the surgery arm. Despite the insufficient statistical power of this study, it challenges the beliefs that patients with pulmonary metastases from CRC who do not undergo surgery have low overall survival, and that metastasectomy confers additional survival benefit (11). Similarly, a study using the SEER database has also shown no significant differences in the overall survival of patients who undergo metastasectomy for pulmonary metastases from CRC *vs.* those who do not (12). Despite a probable lack of survival benefit, minimally invasive metastasectomy via VATS does confer several benefits for patient quality of life when compared with an open thoracotomy approach.

Objective

Several questions arise when considering minimally invasive approaches for pulmonary metastasectomy for CRC, including favorable prognostic factors, risk factors for pulmonary recurrence after minimally invasive intervention, and repeat metastasectomy for recurrent lung metastasis. These topics are less well studied for minimally invasive pulmonary metastasectomy via VATS, compared to the traditional open thoracotomy approach. In this review, we aim to explore the existing literature, to provide some perspective on these questions. We present this article in accordance with the Narrative Review reporting checklist (available at https://vats.amegroups.com/article/view/10.21037/vats-23-41/rc).

Methods

Search database

The search was performed using the PubMed database, from 1990 up to March 2023.

Search terms

Medical Subject Headings (MeSH) terms and keywords were used for the PubMed database search. The following keywords were used: minimally invasive pulmonary metastasectomy; minimally invasive lung metastasectomy;

Table 1 The search strategy summary

Items	Specification
Date of search	March 1, 2023
Databases and other sources searched	PubMed database
Search terms used	Keywords: minimally invasive pulmonary metastasectomy; minimally invasive lung metastasectomy; minimally invasive; pulmonary metastasectomy; lung metastasectomy; video-assisted thoracoscopic surgery; metastasis; colorectal cancer; lung; pulmonary
	MeSH terms: minimally invasive surgical procedures; thoracic surgery, video-assisted; thoracotomy; neoplasm metastasis; colorectal neoplasms; lung
Timeframe	From 1990 up to March 2023
Inclusion and exclusion criteria	Inclusion criteria: (I) cases of pulmonary metastasectomy were described; (II) surgical intervention was detailed; and (III) surgical outcomes were recorded
	Exclusion criteria: (I) conference abstract, review, case report, commentary, discussion and letter; (II) studies in which the surgical intervention was not described; (III) studies which were published in non-English; and (IV) studies whose full text could not be accessed online or by request to the authors
Selection process	Author M.S.K. conducted the literature review and selection process independently. The PubMed database was searched, and the reference lists of retrieved papers and recent reviews were reviewed and included if relevant. Following the search, the first screening was performed based on the title and abstract. Full texts of potentially eligible articles were subsequently reviewed. Studies were included if they met inclusion and exclusion criteria

MeSH, Medical Subject Headings.

minimally invasive; pulmonary metastasectomy; lung metastasectomy; video-assisted thoracoscopic surgery; metastasis; colorectal cancer; lung; pulmonary. The following MeSH terms were used: minimally invasive surgical procedures; thoracic surgery, video-assisted; thoracotomy; neoplasm metastasis; colorectal neoplasms; lung. Boolean AND/OR operators were used to combine MeSH terms and keywords. The reference lists of retrieved papers and recent reviews were reviewed and included if relevant. Following the search, titles and abstracts were screened. Full texts of potentially eligible articles were reviewed.

Inclusion/exclusion criteria

The search strategy is described in *Table 1* and Table S1. Following the search, the first screening was performed based on the title and abstract. Full texts of potentially eligible articles were subsequently reviewed. A study was included when it met all the following criteria: (I) cases of pulmonary metastasectomy were described; (II) surgical intervention was detailed; and (III) surgical outcomes were recorded. Studies were excluded based on the following criteria: (I) conference abstract, review, case report, commentary, discussion and letter; (II) those in which the surgical intervention was not described; (III) those which were published in non-English; and (IV) those that the full text of the studies could not be accessed online or by request to the authors.

The literature search yielded 590 articles, and 19 additional articles were included after reviewing references lists. After screening titles and abstracts, 76 articles remained for full-text review. After review, 27 articles were suitable for qualitative synthesis.

Key findings

Favorable prognostic factors for minimally invasive pulmonary metastasectomy

Factors most commonly associated with prolonged survival after surgery for pulmonary metastases from CRC have been identified in several prior studies, including long disease-free interval (DFI), normal preoperative carcinoembryonic antigen (CEA) level, lower number of pulmonary metastases, size of metastases <3 cm, and absence of thoracic lymph node invasion (13). Other groups have reported various other factors impacting prognosis,

including history of resected liver metastases, tumor resection margins, and location of the primary colorectal carcinoma (3,14,15).

Zabaleta *et al.* report poorer overall median survival for patients with previous liver metastases undergoing pulmonary metastasectomy for CRC, compared to those without prior liver metastases. They also identified positive resection margins, CEA level, number and size of lung metastases, and spread of tumor to pulmonary lymph nodes, as being independent prognostic factors significantly affecting survival. VATS did not have any impact on survival in this study (14). Davini *et al.* report that a lung resection margin of ≥2 cm correlates with the best prognosis, and that narrow resection margin is an independent prognostic factor of worse survival even though the surgical approach and type of lung resection do not have any significant impact on survival outcomes (3). Even with this evidence, there is no literature demonstrating that thoracotomy can provide wider surgical margins compared to VATS. Furthermore, surgical margins may depend more on the type of resection (wedge resection *vs.* segmentectomy or lobectomy) rather than the surgical approach (thoracotomy *vs.* VATS). Cho *et al.* suggest that the location of the primary colorectal carcinoma affects prognosis of pulmonary metastasectomy. Specifically, patients with pulmonary metastases from colon cancer as the primary tumor site have better disease-free survival (DFS) than patients with rectal cancer as the primary tumor site: 5-year DFS for colon cancer patients was 67.2% compared with 60.1% for rectal cancer patients (P=0.004) (15). The number of pulmonary metastases has also been reported to affect prognosis of pulmonary metastasectomy (14,16). Cho *et al.* report on 5-year survival rate for patients with different numbers of metastases: survival rates were 70.0%, 56.2%, and 33.7% for patients with 1, 2–3, and 4+ metastases, respectively (group I *vs.* II, P<0.001; group II *vs.* III, P=0.012). The authors suggest that surgical treatment can benefit patients with three or fewer pulmonary metastases; however, for patients with four or more lung metastases, a surgical approach may not be feasible or beneficial, and special consideration is required (16). However, it is worth noting that the proportion of cases treated with VATS *vs.* open thoracotomy in these three groups decreased as the number of metastases increased: group I had 60.3% VATS *vs.* 39.7% open thoracotomy, group II had 41.5% VATS *vs.* 58.5% open thoracotomy, and group III had 21.4% VATS *vs.* 78.6% open thoracotomy. When patients have more metastases, they tend to undergo an open approach, likely due to the anticipated complexity of the surgery. However, even with the open approach, the overall survival is much worse. The prognostic factors discussed thus far have been reported in studies comparing open thoracotomy versus minimally invasive approach for lung metastasectomy for CRC, rather than analyzing minimally invasive approaches specifically.

Three studies have reported on prognostic factors specifically for lung metastasectomy for CRC via VATS. Maeda *et al.* report that independent significant unfavorable prognostic factors for DFS are high preoperative serum CEA level and a greater number of pulmonary metastases, which aligns with findings reported by other studies (13). Per the authors' subgroup analyses that combined these two risk factors, the 5-year DFS rates were 58%, 25%, and 12% for patients with zero, one, or two risk factors, respectively. These factors can be used to stratify patients into higher- and lower-risk subgroups, which may help with selecting patients who would benefit the most from VATS compared to open thoracotomy (13). Sun *et al.* identified history of metastasis to other sites, mediastinal lymph node status, and preoperative CEA level as independent prognostic factors (17). They report that number of risk factors significantly influenced patient survival, similar to findings reported by Maeda *et al.* (13). Their subgroup analysis that combined the three independent prognostic factors revealed 5-year overall survival rates of 91.0%, 70.0%, 30.3%, and 0.0% for patients with zero, one, two, and three risk factors, respectively. Of note, the authors also report that other factors, such as sex, T-stage of the primary tumor, status of lymph nodes near the primary tumor, and DFI were not significantly associated with prognosis (17). Similarly, Yun *et al.* report that independent factors predicting poor prognosis are older age (≥70 years) and prior extrathoracic metastasis. In line with other studies, their subgroup analysis suggests a correlation between increased number of risk factors and poorer overall survival (18).

Risk factors for recurrence after pulmonary metastasectomy

Several risk factors have been reported to correlate with recurrence after pulmonary metastasectomy in the literature. Onaitis *et al.* report that age younger than 65 years, female sex, DFI <1 year, and number of metastases predict recurrence. The most significant predictor of recurrence reported in this study was number of metastases: patients who had three or more pulmonary metastases were twice as likely to experience a recurrence, which the authors postulate reflects the underlying biology of the

disease. They suggest that for patients who have both three or more pulmonary metastases and <1 year DFI, surgical approaches may not provide optimal benefit; medical management should therefore be the preferred approach in those cases. The authors note that in their study, the patients older than 65 years seemed to show a survival advantage: they hypothesize that selection bias may account for this effect, since younger patients are more frequently offered aggressive treatment despite the anticipated unfavorable outcomes than their elder counterparts for a given disease burden (19). Findings from Sakamaki *et al.* indicate that colorectal carcinoma patients with pulmonary metastases whose DFI is <1 year after lung resection, or those with prior extrapulmonary metastases (EPM), more frequently experience multi-site recurrence after pulmonary metastasectomy. They report that for patients with lung recurrence after pulmonary metastasectomy, those patients with no history of EPM were more likely to be eligible for repeat lung metastasectomy compared to patients with a history of EPM. This is because of differences in recurrence patterns: patients with no history of EPM more frequently had disease limited to the lungs, a similar reflection of the underlying biology of the disease (20).

Anatomic resection has also been shown to improve DFS and reduce the risk of tumor recurrence, as reported by Liu *et al.* and Prisciandaro *et al.* Of note, anatomic resections by Prisciandaro *et al.* were performed via open thoracotomy; VATS was not used. Both groups report finding that anatomic resection (lobectomy and segmentectomy) is associated with longer recurrence-free survival following pulmonary metastasectomy, as opposed to non-anatomic resection (wedge resection) (4,21). Renaud *et al.* similarly report that anatomic resection improves time to pulmonary recurrence after lung metastasectomy as well as overall survival in CRC patients, specifically those with *KRAS* mutations (22). Notably, Renaud *et al.* performed VATS whenever possible, however the breakdown of cases using VATS *vs.* open thoracotomy approach was not reported. Whether the advantages of VATS persist in anatomical resections done via VATS, as opposed to open thoracotomy, remains to be fully elucidated.

Repeat pulmonary metastasectomy for recurrent lung metastasis

Repeat metastasectomy for recurrent lung metastasis has been shown to be beneficial in the literature. Several authors suggest that in patients with pulmonary tumor recurrence, if the primary cancer as well as lung and extrathoracic metastases are isolated and resectable, patients can be treated with repeat metastasectomy, and repeat lung metastasectomy shows comparable survival to single lung metastasectomy (23-25).

Davini *et al.* report no statistically significant difference in overall survival between patients treated by repeat metastasectomy compared to those who were treated by other therapies for their recurrent lung metastases. However, 5-year survival rate was significantly different in the two groups of patients (57% *vs.* 37%). Therefore, the authors suggest that in patients with controlled CRC metastatic disease, there is benefit to repeating pulmonary metastasectomy (3,23,24). Fukada *et al.* report similar outcomes of second pulmonary metastasectomy compared to initial metastasectomy. Patients in this study had 1- and 3-year survival rates of 90.7% and 84.6%, respectively, after the second pulmonary metastasectomy. This was comparable to outcomes after initial metastasectomy (97.4% and 84.9%, respectively). Of note, patient groups were not significantly different in clinical characteristics of the primary or metastatic tumors, or in surgical outcomes, including length of hospital stay and postoperative complications (26).

These findings hold true for minimally invasive approaches to pulmonary metastasectomy in the literature. In fact, authors report that VATS may be preferable to traditional open thoracotomy for repeat lung metastasectomy for CRC. Prenafeta Claramunt *et al.* report that due to decreased development of postoperative adhesions after the VATS approach compared to open thoracotomy, VATS is a more suitable and preferred approach for treating pulmonary metastases that may require repeated resections for recurrent disease (5,27,28). Although some surgeons are critical of the VATS approach since it has the potential to overlook smaller and deeper metastatic lesions due to inability to palpate lesions intraoperatively, intrathoracic recurrence rates after pulmonary metastasectomy have been reported to be similar between open thoracotomy and VATS approaches (5,29-33). Prenafeta Claramunt *et al.* also report that, although there is limited literature specifically examining and supporting the use of VATS, it is currently common clinical practice to use VATS for lung metastasectomy for all cancer types (5). Additionally, as mentioned previously, newer advances in surgical techniques and medical devices allow for improved localization of small pulmonary nodules, including preoperative computed tomography (CT)-guided hook-wire localization, electromagnetic navigation bronchoscopy-guided dye marking or robot-assisted bronchoscopic dye

marking, and microcoil implantation (2,5-7,28).

Limitations of this study

Limitations of this study include selection bias, within individual studies as well as on a broader scale. Some studies included in this review include a mix of VATS and thoracotomy approaches. This is because although VATS has become the standard approach for metastasectomy, open thoracotomies are still required for complicated cases, including cases with multiple metastases or lymph node involvement: this is a notable source of selection bias. Additionally, the nature of this review is retrospective and therefore exploratory in nature, as well as non-random. Finally, there is heterogeneity in the reporting of methods and data analysis across studies.

Conclusions

Pulmonary metastasectomy for the treatment of CRC metastases via minimally invasive approaches like VATS has been well-established for its advantages as an operative treatment. Several factors including number and size of pulmonary lesions, serum CEA level, length of pre-operative DFI, and lymph node involvement are notable independent prognostic factors for post-metastasectomy outcomes, while prior EPM and anatomic resection have been reported to be associated with high risk of metastatic recurrence of disease. Finally, repeat metastasectomy for recurrent lung metastasis has been shown to have similar outcomes as initial pulmonary metastasectomy, and the VATS approach is equivalent or better for this purpose than open thoracotomy, with decreased adhesion formation after initial surgery being an especially attractive advantage of this approach. Of note, the survival benefit of surgical intervention via pulmonary metastasectomy for CRC metastases (via any approach) has been shown to be likely negligible. However, as discussed in this study, there are factors affecting survival outcomes when surgical intervention is opted for; as well, there are marked benefits of minimally invasive pulmonary metastasectomy compared to open thoracotomy for the treatment of pulmonary metastases from CRC.

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://vats.amegroups.com/article/view/10.21037/vats-23-41/coif). The series "The Role of Minimally Invasive Approaches in the Pulmonary Oligometastases" was commissioned by the editorial office without any funding or sponsorship. T.H. served as the unpaid Guest Editor of the series. The authors have no other 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

Table S1 Detailed search strategy for PubMed database search

Database	Search
PubMed	("Minimally Invasive Surgical Procedures"[Mesh] OR "Thoracic Surgery, Video-Assisted"[Mesh] OR "Thoracotomy"[Mesh] OR minimally invasive pulmonary metastasectomy OR minimally invasive lung metastasectomy OR minimally invasive OR pulmonary metastasectomy OR lung metastasectomy OR video-assisted thoracoscopic surgery) AND ("Neoplasm Metastasis"[Mesh] OR metastasis) AND ("Colorectal Neoplasms"[Mesh] OR colorectal cancer) AND ("Lung"[Mesh] OR lung OR pulmonary)

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