

Minimally invasive thoracoscopic approach to pulmonary metastasectomy for esophageal cancer: a narrative review

Shuyin Liang[^], Ronald Kirshner, Neal Chuang

Rochester Regional Health, Rochester, NY, USA

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Correspondence to: Shuyin Liang, MD. Rochester Regional Health, 1415 Portland Ave Ste 240, Rochester, NY 14621-3022, USA.

Email: s.liang@mail.utoronto.ca.

Background and Objective: Metastatic esophageal cancer has poor prognosis. In the small group of patients with single or oligometastases to the lungs, the role and technique of pulmonary metastasectomy remains unclear. This review summarizes studies on minimally invasive approach to pulmonary metastasectomy for oligometastases to the lung, and compares the outcomes to alternative therapies. The challenges in operative technique and directions for the future are also discussed.

Methods: A literature search was conducted using PubMed and Cochrane databases until September 30, 2022. The following MeSH terms were applied: “(lung neoplasms-secondary) and (esophageal neoplasm) and (metastasectomy) or (stereotactic body radiotherapy) or (ablation techniques)”.

Key Content and Findings: Pulmonary metastasectomy for esophageal cancer is not commonly performed since most distant disease occurs in a disseminated fashion. Most of the past studies included patients with squamous cell carcinoma (SCC) histology and many used the traditional thoracotomy approach. With advances in minimally invasive approach, more institutions use video-assisted thoracoscopy. The 5-year overall survival ranges from 0% to 43.5%. Poor prognostic factors include short disease-free interval (DFI) less than 12 months and presence of extrapulmonary metastases.

Conclusions: This review summarizes the notable past studies on minimally invasive thoracoscopic management of pulmonary oligometastases from esophageal cancer, and highlights developing technologies that can help overcome challenges using minimally invasive approach.

Keywords: Esophageal cancer; pulmonary metastasectomy; video-assisted thoracoscopic surgery (VATS)

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Introduction

Background

Esophageal cancer is the tenth most common cancer in the world (1). Until recently, esophageal cancer had a poor prognosis for majority of the patients. The outcomes and prognoses of esophageal cancer have drastically improved

for all stages of disease over the last two decades, with the advent of neoadjuvant chemoradiation, surgical approaches, and targeted immunotherapy (2-6). The CheckMate 577 trial showed that after neoadjuvant chemoradiation therapy and surgical resection, the group who received nivolumab had a median disease-free survival of 22.4 months, compared to 11 months in the placebo group (4). Makowiec *et al.*

[^] ORCID: 0000-0003-2053-4600.

reviewed 304 patients with esophageal cancer at their institution over two decades, and they found that the median survival increased over time from 18 to 59.3 month from 1988 to 2011 (7). However, the recurrence rate after multimodal therapy with curative intent remains high. About 43.3–48% of patients recur despite maximal multimodal therapy, and 20% to 41.4% of them have distant recurrence (2,6). Lung is one of the most common sites of recurrence from esophageal cancer. Metastatic esophageal cancer has poor prognosis and most patients have multiple sites of metastases that preclude treatment with curative intent. However, there is a small group of patients that develop single metastasis or oligometastases. The determination as to what number or sites involved qualified as oligometastases vary in the literature. It is reasonable to consider limited number of metastases but also limited sites of metastases as oligometastatic disease (8).

Pulmonary metastasectomy is most commonly used to resect single metastasis or oligometastases in the setting of sarcoma and colorectal cancer, and its role in other cancer types remains unclear. Depypere *et al.* reviewed 766 patients with recurrent disease after multimodality treatment for esophageal cancer, where 471 patients underwent treatment for their recurrent disease. In the subgroup of 110 patients with solitary solid organ metastasis in a resectable organ, patients who underwent surgical resection had longer survival compared with those who underwent non-surgical treatments (54.8 *vs.* 11.6 months) (9). As for treatment of oligometastases after esophagectomy, Ghaly *et al.* did not find a survival advantage in patients who were treated with surgery with or without chemotherapy and radiation. The only significant independent predictor for survival after recurrence was the median time to recurrence (10). The traditional gold standard of pulmonary metastasectomy is performed through a thoracotomy. The rationale is to allow bimanual palpation and examination of the entire lung parenchyma. A thorough palpation is limited with a minimally invasive approach, as the access incision is usually not of adequate size to allow an entire hand to traverse. Past studies have shown video-assisted thoracoscopic surgery (VATS) approach is associated with a better overall survival than thoracotomy, as well as reduced hospital stay, lower cost, faster recovery and fewer complications (11-13).

Rationale and knowledge gap

There was a previous well-written review article by Schizas *et al.* (14) on pulmonary metastasectomy for oligometastases

from esophageal cancer in 2018. Ten studies prior to 2018 were included in Schizas *et al.*'s very thoroughly written review article, in which they made a table that clearly listed the number of patients, lesions, type of resection, and median survival from these studies. Two additional studies were published since that review, which will be included in this review. This review discusses several gaps in on this topic in the context of thoracoscopic approach to pulmonary metastasectomy for esophageal cancer, including patient selection based on prognostic factors from past studies, the choice of anatomic *vs.* non anatomic pulmonary resection, the necessity of mediastinal lymph node dissection, comparison with stereotactic body radiotherapy (SBRT) and thermal ablation, and technical challenges and solutions to thoracoscopic approach compared to traditional thoracotomy.

Objective

The purpose of this review is to summarize the studies on minimally invasive thoracoscopic approach to pulmonary metastasectomy for solitary metastasis and oligometastases to the lung. We will compare surgical outcome to alternative therapy, discuss the role and challenges of thoracoscopic approach and solutions, and propose directions for future studies. We present this article in accordance with the Narrative Review reporting checklist (available at <https://vats.amegroups.com/article/view/10.21037/vats-23-9/rc>).

Methods

The search strategy is shown in the [Table S1](#). A literature search was conducted using PubMed and Cochrane databases on September 30, 2022, including all studies from 1966 to September 30, 2022. The following MeSH terms were applied: “(lung neoplasms-secondary) and (esophageal neoplasm) and (metastasectomy) or (stereotactic body radiotherapy) or (ablation techniques)”. Case reports, case series and reviews were included. Studies that did not report on outcomes or were not written in the English language were excluded.

There were two additional studies that were performed since Schizas *et al.*'s review; they were by Komatsu *et al.* and Seesing *et al.* (15,16). The cohorts in both studies did not have any patients with extrapulmonary metastases. Despite the advances in surgical and medical treatment of advanced stage of esophageal cancer, no additional studies were found after 2019. Seesing *et al.*'s cohort on pulmonary resection

included patients with esophageal, gastroesophageal junction (GEJ) and gastric cardia patients, and did not include any tumors of the gastric body, antrum or pylorus.

Pulmonary metastasectomy

When comparing surgical with non-surgical treatments, both the benefits and risks need to be balanced on an individual basis. The benefits are compared in terms of accurate diagnosis and staging, local control, and survival outcomes. The risks are assessed with post-procedure complication types and severity, re-interventions for local control, and level of invasiveness. The technological advances in thoracoscopy and nodule targeting in recent years have made pulmonary resections better tolerated.

Pulmonary metastasectomy for esophageal cancer is not commonly performed since most distant disease occurs in a disseminated fashion. It is uncommon to find single metastasis or oligometastases in esophageal cancer that is limited to one organ system and that can be resected with curative intent (2,6). Kobayashi *et al.* showed the importance of poor prognostic factors (17). They found that the cumulative survival for the 12 patients in their series was 64.9% at 5 years, and those with one or more risk factors was 0%. Patient selection is therefore of utmost importance to maximize the benefits of a metastasectomy with curative intent. *Table 1* summarizes several studies that analyzed the prognostic factors for patients who underwent pulmonary metastasectomy (15,17-21). Factors that showed a near-significant level of trend were also included in *Table 1*, since most studies on this topic have small sample sizes. Nodal status of the esophageal cancer was found to be significant in some studies, though not consistently studied. Across studies, disease-free interval (DFI) and presence of extrapulmonary metastatic disease were found to be important prognostic factors for survival.

Most of the past studies on this topic took place in Japan, where the predominant histology is squamous cell carcinoma (SCC), and followed by relatively few adenocarcinoma (AC). Dresner *et al.* showed that distant dissemination occurred with higher frequency with AC than SCC (2). The majority of the patients in Seesing *et al.*'s study had AC (9 out of 15) (16). Their study was not included in *Table 1* as they did not analyze the prognostic factors. They reported a 5-year overall survival of 53%. They performed 11 wedge resections and 3 lobectomies with thoracotomy approach, with median length of stay of 7 days and four patients had complications of Clavien-Dindo grade 3.

Choosing the right operation

The choice of pulmonary resection is mostly determined by tumor location and surgeon's experience and judgment. Wedge resections are the predominant type performed in most studies. However, segmentectomy and lobectomy are performed for non-peripherally located nodules. Some surgeons may choose to perform anatomic resection if there is significant suspicion that the cancer could be a new primary lung cancer. This diagnostic uncertainty is especially pronounced in the setting of SCC of the esophagus with a solitary lung nodule that is also SCC. Surgical pathology cannot always reliably decipher the origin of the SCC (22). For example, Sarsam *et al.* performed pulmonary metastasectomy from various primary tumors in 168 patients. Final surgical pathology revealed significant number of non-metastases, with 6 benign lesions and 5 primary lung cancer (23).

Few past studies report whether mediastinal or hilar lymph nodes were sampled at the time of pulmonary resections in the setting of pulmonary metastasectomy. Many surgeons do not routinely perform lymph node sampling or dissection during pulmonary metastasectomy, especially if the nodule is amenable to a wedge resection. Mediastinal and hilar lymph node dissection adds complexity and operative time to a straight-forward wedge resection. However, when a segmentectomy or lobectomy is performed, hilar lymph node dissection aids the resection by revealing anatomic structures, and it is performed without much added effort from the surgeon. The role of lymphadenectomy is not to increase survival, but to help predict prognosis. Ercan *et al.* analyzed 70 patients who underwent pulmonary metastasectomy for various cancer types, such as colon, renal cell, melanoma, endometrial, salivary gland, genitourinary cancers. Of all the patients, 28.6% were found to have lymph node metastases, with 9 patients having N1 metastases alone, 8 patients having N2 metastases alone, and 3 patients with metastases in both N1 and N2 stations. The 3-year survival was significantly lower among those with any lymph node metastases (38% compared to 69%), and they also found that survival was not improved when only N1 lymph nodes were involved (24). Specifically for esophageal cancer, Shiono *et al.*'s study included 10 patients with pulmonary metastases from esophageal cancer that underwent pulmonary metastasectomy and lymph node dissection, with one patient having lymph node metastasis (10%). In their total cohort of 617 patients, the 5-year survival

Table 1 Summary of studies on outcomes and prognostic factors for pulmonary metastasectomy for oligometastases from esophageal cancer

Study	No. of patients and histology	Breakdown of lung resection				Complications	5-year OS (%)	Trend or significant univariate poor prognostic factors	Trend or significant multivariate poor prognostic factors
		Wedge	Seg.	Lobectomy	VATS/open				
Shiono <i>et al.</i> 2008 (18)	49 (48 SCC, 1 AC)	23	8	16	Approach not reported	None	29.6	DFI <12 months (P=0.048)	DFI <12 months (P=0.04)
Ichikawa <i>et al.</i> 2011 (19)	23 (21 SCC, 1 AC, 1 carcinosarcoma)	17	3	3	23/0	1 pneumonia, 1 empyema	43.5	Extrapulmonary metastases (P=0.04)	Extrapulmonary metastases (P=0.054)
Kobayashi <i>et al.</i> 2014 (17)	23 (22 SCC, 1 carcinosarcoma)	26	2	2	30/0	1 pneumonia, 1 stroke	34.1	Differentiation of SCC (P=0.01), extrapulmonary metastases (P=0.012), DFI <12 months (P=0.02)	Not performed
Kozu <i>et al.</i> 2015 (20)	15 (all SCC)	11	2	2	8/7	3 prolonged air leak, 1 aspiration pneumonia, 1 surgical site infection	0	Tumor diameter >20 mm (P=0.087)	Not performed
Kanamori <i>et al.</i> 2017 (21)	33 (32 SCC, 1 basaloid carcinoma)	20	6	7	12/21	4 pneumothorax, 1 pneumonia	43	Nodal status of esophageal cancer (P=0.005), DFI <16 months (P=0.01), curability of resection (P=0.059)	Nodal status of esophageal cancer (P=0.074), DFI <16 months (P=0.062)
Komatsu <i>et al.</i> 2019 (15)	16 (13 SCC, 2 AC, 1 basaloid carcinoma)	11	3	2	Approach not reported	1 prolonged air leak	40.2	No patients had extrapulmonary metastases, no chemotherapy after esophagectomy (P=0.0166), chemotherapy before pulmonary metastasectomy (P=0.0240)	No patients had extrapulmonary metastases, no chemotherapy after esophagectomy (P=0.0173), chemotherapy before pulmonary metastasectomy (P=0.0186)

Seg., segmentectomy; VATS, video-assisted thoroscopic surgery; OS, overall survival; SCC, squamous cell carcinoma; AC, adenocarcinoma; DFI, disease-free interval.

was significantly higher in patients without lymph node metastases (53.8%), compared to those with hilar (39.4%) and mediastinal (30.8%) metastases (25). It is unclear if lymph node dissection could decrease local recurrence by removing as much nidus of disease as possible. In the setting of metastasectomy, where the disease is spread by hematogenous route, removing local nidus of lymph node disease is unlikely to change survival. However, it could affect decisions on adjuvant therapy.

Comparison to alternative therapies

Primary tumors and metastases to the lung can be treated with SBRT and thermal ablative therapy, such as radiofrequency ablation (RFA) and microwave ablation. SBRT is more commonly used. Local control in the lung and liver is about 66% to 80% in 3 years (26,27). The size

of lesion is a major factor in lesion local control, with lesions smaller than 3 cm having 100% control at 2 years, compared to 77% if larger than 3 cm (28). A nationwide survey in Japan focused on pulmonary oligometastases treated by SBRT included 114 cases from esophageal cases out of total of 1,378. The median survival time was 27.1 months for the esophageal group (29). Yamamoto *et al.* specifically studied SBRT for pulmonary oligometastases from esophageal cancer in 114 patients, and showed a 5-year overall survival rate of 37.5% with median survival of 27.1 months. The lesion local control rate was 81.4% at 3 and 5 years. Adverse events among 90 of the 114 patients included radiation pneumonitis in 6 patients, radiation dermatitis and gastrointestinal complications. Multivariate analysis showed Eastern Cooperative Oncology Group (ECOG) performance score was an independent predictor of overall survival. DFI, chemotherapy, and history of local therapy for metastasis

were predictors of freedom from further metastasis but not overall survival (30). One important thing to note is that pre-treatment tissue diagnosis may not always be obtained, and surgical metastasectomy studies have shown pathologic discordance with clinical suspicion (23).

The literature on thermal ablative therapy for pulmonary oligometastases from esophageal cancer is scarce. Matsui *et al.*'s study included 26 patients who underwent RFA, and showed 3-year overall survival of 38.4%, and local tumor progression in 25.8% of the 31 tumors treated. The complication profile from this study included pneumothorax after 37% of the sessions, pulmonary fistula, reactive pneumonitis, pleural effusion, hemothorax (31).

Comparing studies specifically on treatment of pulmonary oligometastases from esophageal cancer, surgical metastasectomy and SBRT have similar percent 5-year overall survival in the 30s to 40s range. Surgical metastasectomy with R0 resection and lymph node sampling has the added advantage of diagnostic certainty, reliable local control and prognostication for future therapies. The advantage of SBRT is that it is an outpatient, non-invasive treatment. Patients with long DFI, no extrapulmonary metastases, good functional status can have a good survival outcome with either surgical resection or SBRT. However, those with poor prognostic factors may be better served with SBRT.

Challenges of pulmonary metastasectomy

There are several challenges in pulmonary metastasectomy for esophageal cancer. When the primary esophageal cancer was treated with esophagectomy with curative intent, the pleural cavity could contain significant amount of adhesions depending on operative approach and history of anastomotic leak. Extensive adhesions could obscure operative field and prolong operative time and increase rate of conversion from thoracoscopic approach to thoracotomy. The next challenge is the location of the metastases. Lesions located on or near the visceral surface can often be visible or palpable with thoracoscopic approach. However, when the lesion of interest is small and deep, palpation from thoracoscopic approach can become difficult. There are several strategies in dealing with this. One can locate the access incision or specimen extraction incision close to the visceral surface overlying the lesion, and direct digital palpation can be more sensitive than using an instrument to rub over the surface of the lung alone. However, there remains the question of whether bimanual palpation is critical. Some

studies show that bimanual palpation through thoracotomy found more nodules than VATS (32,33). One of the factors for this discrepancy is using computed tomography image with slice thickness of 3–5 mm (34). In the current era where the technology of slice thickness 0.5–1 mm is widely used, fewer such nodules may be missed (23). Positron emission tomography (PET) scan is also valuable in detecting nodules that are more than 1 cm. It is reasonable to question whether the risks of resecting every tiny metastasis of a few millimeters size through a thoracotomy outweigh the benefits. In addition, with decreased morbidity from thoracoscopic approach, repeat metastasectomy does not carry the same morbidity as a re-do thoracotomy; SBRT always remains an alternative to surgical resection for undetected nodules that later grow to a significant size.

In recent years, there has been rapid development in technology used for pre-operative nodule localization. Deep nodules can be tagged with a hook wire or coil (17). Navigational bronchoscopy with or without the robotic platform can be used to label the vicinity of the lesion with dye such as methylene blue, indocyanine green, or contrast. Moreover, 3D models can be constructed to facilitate pre-operative planning (23).

Conclusions

This review highlighted the notable past studies on minimally invasive thoracoscopic management of pulmonary oligometastases from esophageal cancer. The main finding is that there are very few studies on the specific topic of pulmonary metastasectomy for esophageal cancer, and the prognosis heavily depends on patient selection. Based on these limited studies of small sample sizes, some general guidance can be applied when weighing the benefits versus risks of pulmonary metastasectomy. Across studies, short DFI and presence of extrapulmonary metastatic disease were found to be negative prognostic factors for survival. Therefore, in the presence of these negative prognostic factors, surgery may not be warranted. There is little direct comparison between thoracotomy *vs.* thoracoscopic approach based on these studies. The approach can be individualized based on tumor location, ease of tumor marking technology, and patient factors.

There remain several gaps in this field that future studies can target. Firstly, the current literature is predominantly from the Japanese population with SCC type of esophageal cancer. In contrast, AC is not as well studied. Secondly, there is a paucity of studies since 2019, despite the fact

that patients are now living longer because of advent of adjuvant therapy. We are entering an exciting era where the median survival of patients with esophageal is rapidly improving. It is possible that with better immunotherapy, the distant recurrence patterns could change favorably, with more patients having oligometastases that are amenable to treatment with curative intent. Thirdly, new studies are needed to assess the role of new technology. The “Achilles heel” of using thoracoscopic approach has been the inability for bimanual palpation for hidden metastases. However, advances in imaging and nodule marking technology have provided thoracoscopic approach with accurate pre-operative planning and intraoperative localization. Current technology of computed tomography and PET are very good at pre-operative detection of pulmonary metastases. The use of manual palpation in thoracotomy is unlikely to uncover metastases completely unseen on modern imaging modalities. Moreover, as intraoperative nodule marking techniques using various navigational bronchoscopy platforms mature, the thoracoscopic approach can locate and resect nodules that are not palpable from the surface. The same technology that allows endobronchial navigation to mark tumors can be developed to deliver ablation or brachytherapy. Future studies will need to evaluate and compare emerging and hybrid techniques. Lastly, we are hopeful that the widespread use of adjuvant immunotherapy may positively affect the cure rate and recurrence pattern in patients with esophageal cancer.

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Footnote

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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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Table S1 Search strategy

Items	Specification
Date of search	September 30, 2022
Databases searched	PubMed, Cochrane
Time frame	1966 to September 30, 2022
Inclusion and exclusion criteria	Inclusion: case reports, case series, clinical trials, and reviews in the English language were included Exclusion: studies that did not report on outcomes
Search terms used	((“Lung Neoplasms/secondary”[Mesh]) AND “Esophageal Neoplasms”[Mesh]) AND “Metastasectomy”[Mesh] ((“Lung Neoplasms/secondary”[Mesh]) AND “Esophageal Neoplasms”[Mesh]) AND “Radiosurgery”[Mesh] ((“Lung Neoplasms/secondary”[Mesh]) AND “Esophageal Neoplasms”[Mesh]) AND “Ablation Techniques”[Mesh]