Review Article

Pulmonary metastasectomy in pediatric patients: a narrative review

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Background and Objective: Metastatic pulmonary disease associated with primary solid tumors is associated with poor prognosis in the pediatric population. Indications for pulmonary metastasectomy in childhood is largely dependent on primary tumor histology; however, its role in the multimodal treatment of different tumors remains controversial. While surgical management traditionally involves open resection, utilization of video-assisted thoracoscopic surgery (VATS) has increased in recent years. Here, we review oncologic subtypes commonly treated by pulmonary metastasectomy and operative approaches for metasectomy as well as their associated outcomes.

Methods: A comprehensive review of the literature published from January, 1990 to February, 2023 was performed via independent searches of the publicly available databases the National Institute of Health National Library of Medicine PubMed and MEDLINE for indexed and published articles.

Key Content and Findings: More recent studies have been undertaken to describe the indications and outcomes of pulmonary metastasectomy in pediatric patients with specific tumor pathologies. VATS approach is associated with fewer complications and shorter length of stay (LOS) compared to open thoracotomy in children.

Conclusions: Significant advances have been made in evaluating the role of pulmonary metastasectomy for pediatric specific tumors as part of a multimodal treatment approach. Although the use of VATS for pulmonary metastasectomy has increased, open resection remains the standard approach for pediatric patients. While VATS is associated with short-term clinical benefits, further studies are needed to evaluate its long-term outcomes for pediatric malignancies.

Keywords: Pulmonary metastases; pulmonary metastasectomy; video-assisted thoracoscopic surgery (VATS); thoracotomy; solid tumor

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Introduction

Approximately 25% of pediatric solid tumors present with metastatic disease at initial diagnosis, and another 20% will develop metastases during or after treatment (1). The majority of these metastases occur at pulmonary sites (1). While the mainstay of treatment for patients with solid tumors and pulmonary metastases is systemic therapy, surgical resection of metastases can offer therapeutic benefit. In 1961, Richardson first described pulmonary metastasectomy associated with pediatric solid tumors, which resulted in improved overall survival (OS) (2,3). Since then, multiple studies have addressed management principles for pulmonary metastasectomy (1-3). Among these included data to support the importance of tumor histology as well as the concept that factors such as the number of metastases and disease-free interval are not inherent contraindications to tumor resection (2). Many early reports from 1960 to 2000 grouped numerous tumor types together and precluded independent analysis of outcomes associated with pulmonary metastasectomy (2). In recent decades, differences in outcomes between oncologic histologies have been described, and the role of metastasectomy in pediatric solid malignancies has been evaluated. In general, tumors that are refractory to adjuvant therapies are most appropriate for pulmonary metastasectomy (1,3).

Depending on individual tumor subtype, estimates for OS in children with metastatic disease range from 20% to 70% (4). Regarding operative strategy, open thoracotomy is considered the traditional approach for resection of pulmonary nodules (5). However, it remains controversial whether more recent approaches such as video-assisted thoracoscopic surgery (VATS) are a suitable alternative to open thoracotomy for pulmonary metastasectomy (6). Special consideration is given to open resection as it permits palpation of lesions that may be missed on imaging (4,6). Recent technological improvements in radiological diagnostic imaging of pulmonary metastases and thoracoscopic resection have partially addressed the previously stated limitation in VATS for metastasectomy (5,7). In this narrative review, we summarize the existing data for outcomes of metastasectomy performed for common pediatric solid tumors associated with pulmonary metastases, the most common surgical approach, and post-operative outcomes. Those tumor types without multiple studies of outcomes after pulmonary metastasectomy in the pediatric population (neuroblastoma, adrenocortical carcinoma, etc.) were not discussed. We present this article in accordance with the Narrative Review reporting checklist (available at https://vats.amegroups.com/article/view/10.21037/vats-23-24/rc).

Methods

A comprehensive review of the literature published from January 1, 1990 to February 28, 2023 was completed by searches of the public databases the National Institute of Health National Library of Medicine PubMed and MEDLINE for published and indexed articles (*Table 1*). Studies and editorials written in languages other than English without an accompanying available translation were excluded.

Discussion

Solid tumors associated with pulmonary metastases treated by metastasectomy

Osteosarcoma

The management of pulmonary metastases is highly dependent on the associated primary tumor histology (2,3). For certain histologies, including osteosarcoma, surgical metastasectomy is often indicated and shown to be associated with improved patient survival (3). Osteosarcoma is the most common pediatric bone tumor capable of metastasizing to the lungs. Although OS has recently improved, metastatic disease has been a major determinant of prognosis with survival less than 34% in those presenting with metastases compared to 40–70% among all osteosarcoma patients (2,8,9). Pastorino *et al.* provided early evidence that aggressive surgical resection of all osteosarcoma metastases resulted in enhanced survival rates close to 68% and 58% at 3 and 5 years in their patient cohort, respectively (10,11). Others have described survival benefits after pulmonary metastasectomy for osteosarcoma only for those with peripheral lesions compared to central lesions (12). Factors that have been shown to be further associated with augmented survival include fewer numbers of metastases, histologic response to chemotherapeutic regimens, and prolonged disease-free periods (13-19). Several series have demonstrated that multiple thoracotomies may also allow some potential for cure with only mild reduction and effects on pulmonary function long-term (20-22). If both primary and metastatic sites can be completely resected, the majority of studies recommend pulmonary metastasectomy as part of a multidisciplinary approach to care for the pediatric population with

Table 1 The search strategy summary

Items	Specification
Date of search	February 28, 2023
Databases and other sources searched	National Institute of Health National Library of Medicine PubMed and MEDLINE
Search terms used	All combinations of the following terms: "pulmonary metastasectomy", "pediatric metastasectomy", "metastasectomy", "children", "pediatric", "solid tumor metastases", "pulmonary metastases", "thoracoscopic metastasectomy", "open metastasectomy"
Timeframe	January 1, 1990 to February 28, 2023
Inclusion and exclusion criteria	Inclusion: reports and literature reviews of patients <18 years old undergoing pulmonary metastasectomy
	Exclusion: patients 18 years old or older, studies written in languages other than English without an accompanying translation
Selection process	All authors

osteosarcoma (4,9,15,23,24).

Ewing sarcoma

Ewing sarcoma is the second most common bone tumor in children with decreased survival for those with metastases (25). Given this malignancy's sensitivity to chemotherapy and radiation, it remains controversial whether there is any effect on OS for patients treated with systemic therapy regardless of surgical resection (1,2,25). Some suggest a possible benefit for Ewing sarcoma patients who undergo pulmonary metastasectomy with one series demonstrating 5-year survival estimates in these patients approaching 80% compared to 0% among those not receiving surgical resection (25). A more recent study by Raciborska *et al.* of 38 patients with Ewing sarcoma of whom 23 received pulmonary metastasectomy following chemotherapy found improvements in event-free survival (EFS) with no clear benefit on OS (26). The authors concluded that resection of isolated metastases may play a role in therapy depending on histologic response to treatment. Overall, future studies are still needed to better delineate the advantages and selection criteria for individual patients with metastases secondary to Ewing sarcoma who are most likely to benefit from surgical intervention.

Hepatoblastoma

Pulmonary metastases present in approximately 20–44% of patients with hepatoblastoma and metastases are associated with a significantly lower survival rate compared to those without (1,27). Although some patients may demonstrate a complete response to systemic therapy, several series have ascribed benefits in EFS and OS for patients undergoing resection of metastatic hepatoblastoma sites. Early studies found benefits associated with metastatic resection in disease-free survival (DFS) in patients with recurrence if the recurrent sites occurred in isolation in the lung (28). Meyers *et al.* (29) recommended cautious utilization of thoracotomy for patients with both initial pulmonary metastases refractory to neoadjuvant chemotherapy as well as those with metastatic relapse. However, there was significant heterogeneity in timing and surgical approach within their patient population.

Pulmonary metastasectomy has been described as successful in achieving a disease-free state after resection of primary hepatoblastoma lesions. Shi *et al.* provided further evidence through a retrospective review of 10 patients with pulmonary metastatic recurrence to support the efficacy of surgical resection in hepatoblastoma patients with metastatic relapse (30). A recent retrospective comparative study by Fleming *et al.* (31) comprising 16 years and 50 patients with hepatoblastoma stratified patients by those who were high-risk versus not high-risk. They demonstrated that aggressive pursuit of no evidence of disease (NED) utilizing repeated pulmonary metastasectomy and complex local control strategies was associated with improved OS and EFS at 10 years (31). While future prospective studies and more standardized practices are needed, these series taken together support the utility of pulmonary metastasectomy for these patients.

Synovial sarcoma and other non-rhabdomyosarcoma soft tissue sarcomas (NRSTSs)

Synovial sarcoma is included in the family of NRSTS. Metastatic disease is present in up to 40% of patients

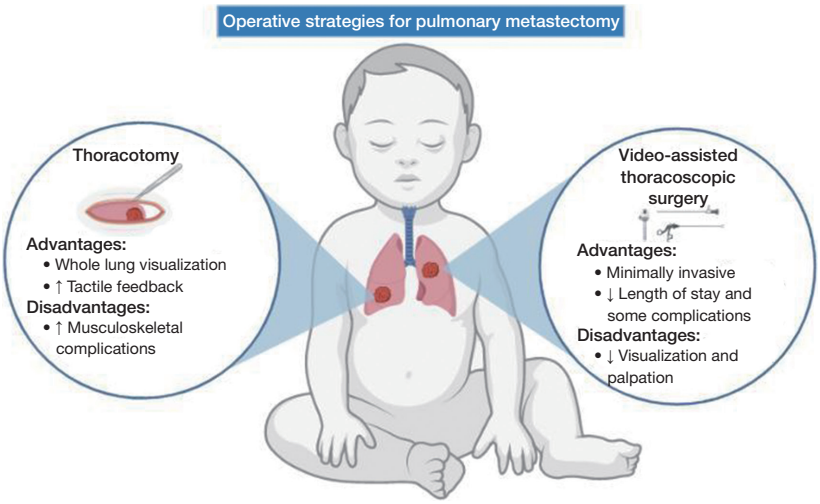

Figure 1 Comparative operative approaches for pulmonary metastasectomy in children (the figure was created in Biorender.com).

with the majority (approximately 80%) occurring in the pulmonary system (1,32,33). Despite its responsiveness to systemic therapy compared to the rest of the NRSTS family, complete resection of metastatic disease is often recommended for synovial sarcoma (1). Slightly less than one-half of patients develop pulmonary metastases, emphasizing the importance of surgical resection (1). Stanelle *et al.* (34) compared a series of 41 patients with metastatic synovial sarcoma and found that those undergoing metastasectomy had an associated 5-year OS of 24%. Spillane *et al.* (33) similarly found an increase in OS of 17% among patients undergoing pulmonary metastasectomy compared to all patients. Taken together, these authors felt that metastasectomy was associated with survival benefits for children with synovial sarcoma if complete resection could be achieved.

Other NRSTS tumors such as chondroma sarcoma, malignant fibrous histiocytoma, and alveolar soft part sarcoma are also capable of metastasizing to pulmonary sites. Outcomes for these tumors are difficult to draw conclusions on given their rarity and resultantly few published series. Older series that examined a heterogeneous group of NRSTS including these types have ascribed greater disease control associated with pulmonary metastasectomy (35,36). However, survival outcomes were difficult to ascertain for different tumor subtypes. Kayton *et al.* (37) examined 20 patients with alveolar soft part sarcoma of which 14 were diagnosed with pulmonary metastases during their disease follow-up. OS at 5 years was 83% in this cohort, which led the authors to recommend metastasectomy for patients with pulmonary disease at presentation (37). Ultimately, more series with specific attention paid to outcomes after pulmonary metastasectomy are needed for patients with these rare tumor subtypes to draw more definitive recommendations on this procedure's utility.

Operative strategy

Historically, open thoracotomy was undertaken for all cases of oncologic resection in children. Over the last few decades, minimally invasive surgery has become increasingly utilized for various procedures in adults and children and has disseminated to more frequent applications in pediatric oncology (38). The advantages are well known and include decreased post-operative pain, shorter hospital stay, and reduced tissue trauma (*Figure 1*) (38). Specifically, important benefits of thoracoscopy include reducing musculoskeletal complications associated with traditional thoracotomy such as chest wall deformities and scoliosis, which can occur in up to 30% of pediatric patients undergoing thoracotomy (38). Advantages associated with thoracotomy include the ability to evaluate the entire lung as well as the chance to directly palpate suspicious lesions and resect. This is particularly important for osseous tumors such as osteosarcoma that have a calcific matrix and can be felt in lesions as small as 1 mm, sometimes referred to as deposits (4). Osteosarcoma metastases in particular pose a diagnostic challenge given that they can frequently present with atypical radiological features or are unable to be adequately visualized even with high resolution computed tomography (CT) modalities as

demonstrated in previous retrospective series (39-41).

VATS utilization increased rapidly from 2006 to 2009 and has plateaud in recent years (6). Challenges associated with VATS include reduced tactile feedback, smaller body size in pediatric patients, and limited working space (38). Despite the increased use of VATS for resection of lung metastases, controversy revolves around its inability to palpate lesions that can be missed on preoperative imaging such as those associated with osteosarcoma (6). Given the discordance between preoperative imaging detection of pulmonary metastases and intraoperative palpation of small deposits, this can be a contraindication for VATS in patients with osteosarcoma (41). For patients with other malignancies and concomitant solitary lung metastasis, Markowiak *et al.* demonstrated the equivalence of VATS for pulmonary metastasectomy to thoracotomy by providing evidence that an open approach with palpation of the lung showed no advantage in surgical outcome or survival (42). Traynor *et al.* (6) concluded VATS approaches for pulmonary metastasectomy resulted in fewer complications and shorter length of stay (LOS) in a nationwide sample of children even after controlling for resection extent, age and primary cancer.

As technology advances, combinations of approaches or adjunctive intraoperative imaging techniques may hold potential to augment the utility of VATS. Hybrid procedures combining VATS and lateral mini-thoracotomy to allow for manual palpation to perform multiple resections of pulmonary metastases has been described as a safe method to utilize the benefits of an open procedure while still accruing the reduced postoperative complication profile and LOS associated with VATS in adult series (43,44). In 1996, Gilbert *et al.* demonstrated VATS to be safe and complement open thoracotomy in children with osteosarcoma requiring pulmonary metastasectomy (45). With the increasing number of metastatic lesions, the use of stapler devices can be contraindicated with a higher number of resections and achieving a precision resection with VATS can be both time consuming and technically demanding (43,46). Laser-assisted resection may help to overcome some of these challenges and will require further study with regards to longer term OS and DFS prior to pediatric applications (47,48). Gow *et al.* (5) later illustrated that minimally invasive thoracoscopic ultrasound can be utilized to assist VATS to guide resection of deep pulmonary nodules intraoperatively for patients with osteosarcoma and other primary tumor types. Similarly, thoracoscopic resection of preoperatively localized small lung nodules via both CT-guided needle hook wire placement and microcoils has demonstrated as safe and effective in children (7,49,50). A recent survey of the American Pediatric Surgical Association reported that localization strategies are more frequently used by surgeons who prefer thoracoscopy for resection of pulmonary metastasis in children with osteosarcoma (51). Another emerging adjunct to guide visualization and resection strategies intraoperatively is using indocyanine green (ICG) fluorescence. To date, only case reports have demonstrated this application for pulmonary metastasectomy in the pediatric population (52,53). Furthermore, robotic-assisted thoracoscopic surgery (RATS) has rapidly gained utilization for oncologic resections in adults with beneficial results (54). No prospective pediatric series have yet to be performed with regards to RATS for pulmonary metastasectomy but may be an area of future investigation. Future studies are needed to determine if long term outcomes and relapse rates mirror the promising short-term results associated with newer approaches.

Conclusions

Metastatic disease for children continues to be associated with poor prognosis and survival compared to those with isolated primary tumors. Knowledge of the efficacy of pulmonary metastasectomy for pediatric solid tumors has significantly evolved over the past few decades. Although advancements in understanding the indications and outcomes associated with specific tumor histologies have been achieved, its role for primary tumors that are historically responsive to systemic therapy remains to be fully characterized. Additional research and data are necessary regarding the long-term outcomes associated with specific tumor histologies responsive to pulmonary metastasectomy.

Despite unique advantages and comparable post-operative outcomes of VATS with open thoracotomy, the use of VATS among pediatric surgeons has plateaued in recent years. This trend may be associated with limited prospective data regarding the long-term outcomes associated with open thoracotomy versus VATS for pulmonary metastasectomy in the pediatric population. The advent and role of hybrid VATS approaches including minithoracotomy may also help bridge the gap for oncologic applications such as these and be explored in future work. Areas of further study regarding its utilization should include whether indications for VATS in pulmonary metastasectomy can be expanded as well as potential

intraoperative imaging adjuncts to guide resection as well as newer resection devices. Although significant strides in technological advancements for VATS continue to be made in adult patients, much remains to be studied to evaluate outcomes for pulmonary metastasectomy in this vulnerable patient population.

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Footnote

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