Current Indications for Pulmonary Metastasectomy

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KEYWORDS

• Metastases • Metastasectomy • Pulmonary nodule • Oligometastases
• Lung resection

KEY POINTS

- Eligibility for pulmonary metastasectomy includes confirming operative candidacy, complete resection of metastases with surgery, and control of the primary cancer.
- Positive prognostic factors include longer disease-free interval, lack of lymphadenopathy, single metastatic nodule, and certain primary histologies, such as nonseminomatous germ cell tumor.
- Parenchymal preserving techniques (wedge resection and segmentectomy) via minimally invasive surgery is the preferred method for surgical metastasectomy if feasible.
- Nonoperative techniques include stereotactic body radiation therapy, radiofrequency ablation, and microwave ablation.

INTRODUCTION

With its large surface area and blood flow, it is not surprising that the lung is one of the most common site of metastases. Accordingly, pulmonary metastasectomy has been long practiced in the field of oncology ,with one of the first reports from 1882[1] reviewing the removal of lung sarcoma metastases. Since initial reports, the field has advanced, with the International Registry of Lung Metastases in 1991 reporting on 5206 metastasectomy cases, with an overall 5-year survival of 13% to 36%, depending on primary tumor biology.[2] More recently a European Society of Thoracic Surgeons (ESTS) international work group evaluated the outcomes of pulmonary metastasectomy[3] and reported similar results. Definitive recommendations are limited due to lack of robust studies and randomized controlled trials. Selection bias among retrospective studies, variable adjuvant therapies, and variable follow-up length are consistent limitations.[4] The absence of a standard-of-care approach underscores the importance of multidisciplinary review and case-by-case consideration when evaluating a patient for pulmonary metastasectomy (**Fig. 1**).

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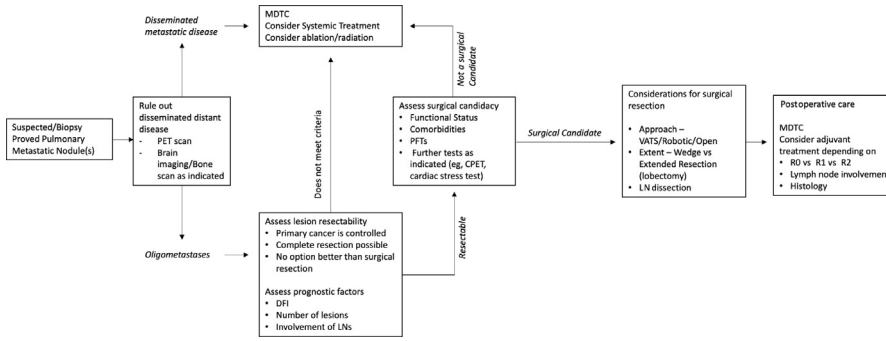

Fig. 1. Approach to the pulmonary metastases. CPET, cardiopulmonary exercise testing; MDTC, multidisciplinary tumor conference; PFTs, pulmonary function tests.

This review explores work-up of pulmonary metastases, principles for resection eligibility, outcomes of different primary histology, and alternatives to surgical resection. The goal is to attempt to create evidence-based guidelines to help guide management.

PATIENT ASSESSMENT

Evaluation of the patient with pulmonary metastases begins with a targeted history and physical examination. Generally, pulmonary metastases are asymptomatic and specific symptoms may well indicate advanced disease. However, 15% to 20% of patients can present with symptoms that include cough, hemoptysis, chest pain, or postobstructive pneumonia.[5,6] Symptoms and signs of distant metastatic disease also must be elicited. Smoking history and use of pertinent medications, including anticoagulants and steroids, are critical part of the medical history, specifically, prior history of venous thromboembolism—a frequent comorbid disease in this population.

Physical examination should focus on overall status, cardiopulmonary assessment, lymph node (LN) basin examination, and abdominal examination focusing on hepatospenomegaly.

A subjective impression of the patient's functional status can be achieved by enquiring about activities of daily living (ADLs) and instrumental activities of daily living. Scores, such as the Eastern Cooperative Oncology Group Performance Status, and Karnofsky performance scale, originally validated for suitability of systemic therapy, also can be used to complement assessment of performance status in the oncology patient.[7] Formal testing, such as 6-minute walk, shuttle walk, and stair climb, provide objective measurements for performance status, lung resection reserve, and a real-time objective assessment of physiologic reserve.[8]

RADIOLOGIC STUDIES

Pertinent imaging includes high-resolution computed tomography (CT) scan with 1-mm to 2-mm slices for assessment of pulmonary nodules and a PET scan to rule out other distant metastases. The sensitivity of PET scan varies according to histology of pulmonary metastasis. In a series by Fortes and colleagues,[9] PET scan was found positive for two-thirds of pulmonary metastases. This varied from 44% for sarcoma to 71% for renal cell carcinoma.[9,10] In general, approximately 3 out of 4 patients with

pulmonary metastatic disease have other distant metastasis.[11] Completion of staging for metastatic disease in addition to PET scan can be supplemented with bone scan. Additional brain imaging, such as CT brain or magnetic resonance imaging brain, can be tailored to the histology of pulmonary disease.

The presence of hilar or mediastinal LN metastases is associated with poor prognosis. Presence of lymphadenopathy should prompt invasive mediastinal staging (mediastinoscopy or endobronchial ultrasound-guided fine-needle biopsy). Preoperative confirmation of malignant metastatic LNs does not necessarily preclude surgical resection of the pulmonary tumor(s) but the additional metastatic burden reduces the chance for a complete resection and requires careful multidisciplinary consideration before proceeding.[12]

Standard criteria used for pulmonary resection should be applied in the setting of pulmonary metastasectomy (adequate spirometry and gas exchange). Most metastasectomies are nonanatomic resections, although, depending on location, some may require lobectomies or other extended resections. Postoperative predictive forced expiratory volume in the first second of expiration and diffusion capacity for carbon monoxide above 60% generally are satisfactory to proceed with resection. Values between 30% and 60% should prompt further testing, such as shuttle walk or stair climb tests and/or perfusion-ventilation scan, for further evaluation. Values less than 30% should employ cardiopulmonary exercise testing for further evaluation.[13] Thorough risk stratification becomes increasingly important as a patient's fitness declines.

ELIGIBILITY FOR PULMONARY METASTASECTOMY

Although there is a lack of strict criteria in selecting for pulmonary metastases resection, there are a few agreed-on tenets.[14] (1) First and foremost, the patient should be a fit candidate to undergo surgical resection. (2) Once surgical eligibility is confirmed, the primary cancer must be either controlled or controllable. (3) Ideally, there should be no extrathoracic metastasis; however, if present it also must be resectable or already resected successfully. (4) Surgery should completely resect the pulmonary metastases. Patients with R1 or R2 resection have poor longer-term prognosis and an incomplete resection subjects patients to the unnecessary risk of surgery with no benefit.[12] (5) Furthermore, there should be no better proved treatment option than operative intervention existing to treat the metastasis. In current times of evolving targeted, immune, and chimeric T-cell therapy, this is perhaps the most important consideration.

PROGNOSTIC FACTORS

Primary tumor histology is the most important prognostic factor for overall survival (OS) after pulmonary metastasectomy. Germ cell tumor metastases are associated with excellent long-term outcomes, reflected by approximately 70% 5-year survival and approximately 60% 10-year survival.[2]

Disease-free interval (DFI) between primary tumor control and emergence of metastasis is an important but somewhat confounded risk factor. Several studies indicate that a longer DFI interval is associated with improved outcomes after resection. It is unclear if the indolent nature of the tumor biology associated with a longer DFI is truly responsible for the better outcomes rather than the actual disease-free time frame. In addition, the definition of DFI is somewhat variable among studies, making simple comparisons challenging. There is no consensus on minimum DFI to rule in or rule out metastasectomy. Very short intervals or synchronous metastases warrant

consideration of systemic therapy and a period of observation to rule out emergence of other distant metastases. Increasing numbers of metastatic nodules and in some studies the laterality can portend a poor prognosis. Incomplete resection or positive surgical margins are nearly universally associated with poorer survival,[12] as discussed later.

OPERATIVE TECHNIQUES FOR PULMONARY METASTASECTOMY

Initial limitations of imaging propagated the need for open surgery and bimanual palpation of pulmonary nodules. McCormack and colleagues[15] performed initial video-assisted thoracoscopic surgery [VATS] resections based on the preoperative radiological evaluation; then, a thoracotomy was performed with bimanual palpation for completeness. They found that 56% of patients had additional metastatic lesions detected after VATS on bimanual palpation.[15] Other studies have demonstrated 16% to 46% of lesions identified on palpation that were not evident on preoperative CT scans.[16,17] Long and colleagues[18] have attempted bilateral hand-assisted thoracoscopy through a single sternocostal incision. They found 53% of patients with bilateral metastases were noted to have only unilateral disease on preoperative staging.

In all of these studies, however, not all additional lesions are malignant, and, in addition, there is no proved survival benefit with the resection of small lesions undetected by CT scan. Furthermore, modern high-resolution CT scanning with 1-mm slices has vastly improved detection of subcentrimeter nodules, with sensitivity of 97% and negative predictive value of 96%,[19] obviating bimanual palpation.

Current studies demonstrate comparable rates in survival and cancer recurrence between VATS and open techniques of between 30.6% and 69%.[20,21] Given no apparent survival difference, the clinical significance of resection of radiologically undetected metastases is questionable. Thoracoscopic methods have demonstrated improved pain scores and shorter length of stay. Minimally invasive methods also aid in resection of bilateral lesions, and may simplify future re-resection, and generally are the standard of care for pulmonary metastasectomy.

Preservation of uninvolved pulmonary parenchyma is a key consideration. To this end, nonanatomic (wedge) resection to negative margins is the most common intervention. For patients with several foci that are being targeted, multiple stapled wedge resections within the same lobe can lead to significant distortion of the lobar architecture and consume a significant amount of uninvolved parenchyma. Consequently, fine-tip electrocautery resection is an alternative that is commonly considered during open techniques for patients with higher-burden (resectable) disease when stapled resection may not be ideal. The small parenchymal defects created can be suture repaired after hemostasis is obtained.[22] Central lesions or multiple metastases in 1 lobe may warrant a lobectomy. The indication for a more extensive resection, however, requires review in a multidisciplinary manner. The need for a pneumonectomy is not an absolute contraindication; however, it is associated with significant risk and is accompanied by variable long-term survival. Careful patient selection is key and may be considered in a patient with a soft tissue or bone tumor primary, a long DFI, and a central tumor.[23]

The need for routine lymphadenectomy during pulmonary metastasectomy is debatable and the practice of thoracic surgeons is variable.

In the International Registry of Lung Metastases published in 1997, only 5% of the patients had LN metastases reported, but LN dissection was performed in a minority of patients.[2] Recent single-institution reports have challenged these numbers. Hamaji

and colleagues[24] described 500 pulmonary metastasectomy patients, of whom 319 received LN dissection. Positive LN metastases were found in 12.5% (40/319).[24] In another study of 270 resections by Seebacher and colleagues,[25] the incidence of LN involvement was 17%. Unexpected LN involvement was found in 36% of patients with breast cancer, in 21% with renal cell carcinoma, and in 9.2% with colorectal cancer. In an ESTS survey, 55% of surgeons indicated they sampled LNs, 13% completed a lymphadenectomy, and 3.2% did not remove any LNs.[26]

LN metastases clearly can complicate pulmonary metastatic disease. The specific risks for concomitant LN disease are difficult to quantify aside from primary histology. How the number and size of the metastases are associated with risk of LN involvement is unclear.[27] LN involvement is a risk factor for worse survival; positive LN sare associated with a 0% to 24% 5-year survival, whereas negative LNs have a 24.7% to 50% 5-year survival.[28] The prognostic value of specific LN station is unclear. One study demonstrated an approximately 64-month survival with N1 disease, approximately 33-month survival with N2 disease, and an approximately 21-month survival with N3 disease.[29] Other studies, however, demonstrate no survival differences between involvement of any of these stations.[30]

The remaining question when investigating LNs in the context of pulmonary metastasectomy is performing a lymphadenectomy or LN sampling. Extrapolating results from the lung cancer study by American College of Surgery Oncology Group Z0030 showing no difference between the 2, most clinicians would agree that LN sampling might be sufficient for diagnostic information, although therapeutic implications remain nebulous.[31]

TUMOR-TYPE SPECIFIC OUTCOMES

Several studies on pulmonary metastasectomy combine histologies. Tumor type, however, exerts significant influence on outcomes after metastasectomy. First-time metastasectomy is established but recurrent pulmonary metastasis, which meets resection eligibility, also should be treat surgically.[32] Overall, the true survival benefit from resection of pulmonary metastasis is debatable due to lack of controls. Some experts may argue that prolonged survival after metastasectomy is observed due to a favorable patient selection (better tumor biology and patient characteristics).

Germ Cell Tumors

Pulmonary metastasectomy for germ cell tumor, specifically nonseminomatous germ cell tumor (NSGCT), is associated with excellent, if not one of the best, outcomes among primary histology. NSGCT pulmonary metastases are initially treated with systemic therapy because they are chemosensitive.[33] Persistent disease results in approximately 10% of these lesions progressing to surgical resection. A recent series by Kesler and colleagues[34] examining 159 pulmonary resections demonstrated a 68% 5-year OS. Residual disease was an important factor in decreased survival. Overall, almost 75% of patients had a benign transformation (52.7% of patients had a teratoma and 21.5% necrosis) and 25% had persistent malignancy (15% residual NSGCT and 10.1% degenerative non–germ cell cancer).[34]

Colorectal

Metastatic colorectal cancer has significant organ tropism for the lungs. This, combined with the high prevalence of colorectal cancer, makes pulmonary metastasectomy a common indication. Hepatic metastasectomy in selected patients has been

well established in the literature. Pulmonary metastasectomy for colorectal metastases has also been widely practiced, although the survival benefit is debated. Estimated 5-year survival is 32% to 54%.[35] Studies of prognostic markers are ongoing in order to select patient who will receive the most benefit. KRAS and mBRAF mutations are associated with poorer outcomes, such as early pulmonary recurrence, more diffuse pulmonary disease, and decreased survival.[36]

Sarcomas

Sarcomas are histologically diverse and survival comparisons of pulmonary metastasectomy remains controversial among each subtype. Smaller series do not demonstrate significant survival difference[37,38] yet other series show a comparable median survival of 27 months for patients with osteosarcoma and approximately 42 months for patients with soft tissue sarcoma.[39] In 62% of patients with metastatic sarcoma, the lung was the sole metastatic site,[40] and, because sarcoma is relatively resistant to chemotherapy or radiotherapy, resection often becomes the principal treatment of patients. Outcomes for osteogenic sarcoma metastasectomy range from 35% to 50% 5-year survival. A recent study by Kim and colleagues[38] demonstrated 5-year OS of 50%. DFI less than 12 months, positive margin, and more than 2 lesions of size greater 3 cm were associated with worse survival.

In soft tissue sarcomas, a large series of 225 patients demonstrated a 5-year survival of 38%,[41] although up to 50% survival with careful patient selection has been noted.[42] Again longer disease-free survival and fewer nodules were associated with better survival.

Breast

Pulmonary metastasis is found in approximately 7% to 24% of breast cancer patients.[43] In addition to short DFI, fewer metastatic lesions, and complete resection, patients with hormone receptor–positive disease appear to have a more favorable outcomes (77% 5-year survival vs 12% in receptor-negative patients).[44] A large meta-analysis of 1937 patients yielded a 5-year survival of 46% after pulmonary metastases resection[45] versus 16% in patients with limited metastasis to lung treated with systemic therapy.[46] Similar to other studies, a direct comparison is challenging due to selection bias.

Melanoma

Lung is the most common visceral site for melanoma metastasis, and isolated metastases is associated with significantly higher survival in comparison to other visceral sites (liver and brain).[47] Survival at 5 years after metastasectomy is up to 40% in selected patients with small tumors (<2 cm) and a single metastatic lesion.[48] The advent of checkpoint inhibitors has drastically improved the outcomes of metastatic melanoma. In this context, pulmonary metastasectomy also can be considered for residual pulmonary metastasis after immunotherapy.[4]

Head and neck

The challenge in head and neck cancer metastases to the lung is distinguishing true metastasis from primary squamous lung cancer. With similar risk factors, histology, epithelial cell origin, and a lack of definitive techniques to differentiate the 2 different cancers, the outcomes of pulmonary metastasectomy for head and neck squamous cell cancers (HNSCCs) often is confounded with a primary lung squamous cell cancer.[49] A DFI less than a year is of especially poor prognosis, with 0% 5-year OS in some series.[50,51] In well-selected patients, 5-year OS up to 59% is reported.[52]

Retrospective studies matching surgical and nonsurgical treatment of HNCC metastasis demonstrate a survival advantage with longer median survival (19.4 months vs 5 months, respectively[53]). Therefore, HNSCC metastasis with DFI more than a year and other general favorable characteristics, including lack of LN involvement, should be considered for surgical resection.[4]

NONOPERATIVE TECHNIQUES FOR PULMONARY METASTASECTOMY

Surgery is the first-line approach for patients who can tolerate the resection and meet metastasectomy criteria. For those who are not deemed surgical candidates, however, ablative therapy presents an alternative option. Stereotactic body radiation therapy (SBRT), radiofrequency ablation (RFA), and microwave ablation (MWA) are the principal nonoperative ablative interventions.

Traditionally, radiation therapy has been employed in a palliative therapy role for lung metastases.[54] Retrospective reports, however, demonstrate a good control rate for stereotactic radiation in the pulmonary metastases setting as well with lesion control, observed in 75% to 90% patients[55] at 3 years. Direct comparisons between studies is difficult due to different histologies, varying total radiation doses, and fractions. Interpretation of OS also is challenging due to the selection bias within the cohort. One retrospective comparison[56] of 27 patients with 70-Gy SBRT and 31 resections for osteosarcoma metastasis demonstrated comparable OS between the 2 groups. No significant differences in OS and disease-free survival have been found when comparing SBRT and surgical metastasectomy.[57–59] Most institutions use certain criteria to consider SBRT for pulmonary metastases, such as poor surgical candidate, central lesions, and short DFI.

RFA utilizes an alternative current to cause coagulative necrosis. Pneumothoraces are a frequent complication reported in 25% to 40% of patients,[60,61] when applied to lung metastases. RFA is employed very selectively in lung tumors. Masses greater than 3 cm and those near blood vessels generally are avoided.[62,63] MWA uses much higher frequencies and hyperthermia to effect tumor ablation. As with SBRT, RFA and MWA are alternative options when eligibility for metastasectomy are satisfied but the patient is not a surgical candidate. Furthermore, these 2 ablative options can be used in a previously radiated field.

FUTURE DIRECTION

The only randomized controlled trial conducted (Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer[64]) was closed early due to recruitment issues. Although it was underpowered, the estimated 5-year survival rate was 38% for metastasectomy patients and 29% in the well-matched controls.[64] Prospective studies and trials that compare systemic and targeted therapies to ablation and surgical resection will be key in advancing the field. As the use of immunotherapy becomes more prevalent in locally advanced and metastatic cancer, its role in treatment of isolated lung metastases and oligometastases will become prominent, and treatment paradigms no doubt will need to be adjusted.

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