Hybrid approaches to pulmonary metastasectomy: a narrative review

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Background and Objective: Pulmonary metastasectomy (PM) is a common surgical resective procedure performed by thoracic surgeons to improve long-term survival in selected patients with metastatic tumors in the lung. In the past, thoracotomy was the preferred surgical approach but in recent years, treatment options have expanded to include minimally invasive approaches, thermal ablation therapy, stereotactic body radiation therapy (SBRT), and combinations of these techniques. With rapid advances in chemotherapy, immunotherapy, and molecular-targeted therapy, thoracic surgeons should review the indications and approaches to pulmonary metastases. This article aims to review the evolution of PM and the different modalities currently available to the stage IV patient.

Methods: A narrative review of the literature from 1959 to 2023 was conducted using a variable combination of the following terms: "lung metastasectomy" or "pulmonary metastasectomy", "thoracic surgery" or "lung surgery", "radiosurgery" or "stereotactic ablative radiotherapy" or "stereotactic body radiotherapy", "chemotherapy" and "ablation". Hand searching and citation chaining were used to include relevant articles that were not indexed in the initial search strategy. Included articles were those of human subjects and published in English language.

Key Content and Findings: A hybrid approach to PM brought about by interdisciplinary collaboration between the fields of thoracic surgery, interventional radiology, radiation oncology and medical oncology has expanded the indications for which this potentially curative procedure can be applied.

Conclusions: Open and minimally-invasive surgical resection, ablation, SBRT, chemotherapy, immunotherapy and targeted therapy can be used synergistically when applied in combination to provide local and systemic control of oligometastases. A highly individualized and multidisciplinary approach has the potential to maximize survival outcomes in patients with pulmonary metastases.

Keywords: Pulmonary metastasectomy (PM); oligometastases; hybrid approaches

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Introduction

Background

The concept of oligometastases was first proposed as a compromise between the contiguous Halsted theory and the systemic hypothesis of tumor progression, as an early state where metastases are limited in number and location and therefore, still susceptible to curative intent strategies like surgery and ablation (1). Almost three decades have passed since the term oligometastases was coined but its numerical definition, by the number of metastatic lesions and the number of organs involved, remains arbitrary. Treasure proposed that oligometastases is merely a "framing disease" conveying a therapeutic opportunity rather than an objective oncologic diagnosis (2). For the thoracic surgeon, the consensus as to "how many" lung metastases warrant an attempt for local control still hasn't been reached, with some advocating local treatment for as much as 20 metastases (3). As we explore the range of curative and palliative treatment options available from open to minimally-invasive surgery, interventional radiology, radiation and medical oncology, it is important to keep in mind which patients in the spectrum of localized to regional to widely disseminated cancer are candidates for metastasectomy, but this is beyond the scope of this review. Surely, the addition of different modalities has expanded the coverage of treatment for oligometastases.

Rationale and knowledge gap

The lung is the second most common site of metastases from all types of primary cancers and thoracic surgeons have long been invested in the treatment of pulmonary metastases. The landmark 1997 publication from the International Registry of Lung Metastasectomy showed potentially curative treatment especially in patients with completely resectable lesions, disease free interval ≥36 months and single metastasis only (4). To date, the literature on pulmonary metastasectomy (PM) for all types of primary cancers metastatic to the lungs such as colorectal cancers, osteosarcomas, gynecological and kidney cancers have been reported but these observational studies, although showing favorable results with complete resection, are limited by patient selection bias putting into doubt the evidence that PM is the best treatment for pulmonary metastases (5,6). In 2015, the Pulmonary Metastasectomy versus Continued Active Monitoring in Colorectal Cancer (PulMiCC) trial attempted to establish once and for all the survival benefit of PM for advanced colorectal cancer but was prematurely terminated because of poor patient recruitment. Despite its limited sample size, the study was able to determine that 5-year overall survival with PM versus active monitoring was only 38% *vs.* 29% (7). Banking on studies showing long-term survival in select patients undergoing complete resection of metastatic foci, we continue to develop means to establish superior local control in the cancer patient with spread to the lungs.

PM is a common surgical resection procedure performed by thoracic surgeons which can improve long-term survival in selected patients with metastatic tumors in the lung. The oncological criteria for PM are: (I) the primary malignancy is controlled or controllable; (II) extrapulmonary metastasis is absent; (III) the lung foci must be resectable without compromising lung function; and (IV) the patient is in good physical condition to undergo surgery (8). Historically, surgery was performed when no alternative treatment options were available that would render a lower morbidity rate. In the present era, remarkable advances in immunotherapy and molecular-targeted therapy have been made available for systemic control of various cancers like the breast, lung, renal cell carcinoma and gastrointestinal stromal tumor (GIST) while stereotactic body radiation therapy (SBRT) has been found to provide favorable local control of pulmonary metastases (9-11). With tremendous strides in interventional radiology and radiation and medical oncology, the procedure originally performed exclusively by thoracic surgeons has now more than ever, inevitably emphasized the necessity of a multidisciplinary approach. Regardless of technique, the oncologic principles remain the same—to eliminate all lung metastases to promote cytoreduction while preserving lung function. It is with this background that thoracic surgeons should reassess the surgical approach to PM.

Objective

The aim of this article is to review the past and current approaches to PM with particular emphasis on the role of multimodal treatment and their application in a hybrid manner. We present this article in accordance with the Narrative Review reporting checklist (available at https://vats.amegroups.com/article/view/10.21037/vats-23-28/rc).

Methods

Scopus and MEDLINE via PubMed database were searched to identify relevant studies from 1959 to 2023 with the theme under review. Our search included the following

Table 1 The search strategy summary

Items	Specification
Date of search	January 14, 2023 to March 30, 2023
Databases and other sources searched	Scopus and MEDLINE via PubMed database
Search terms used	"lung metastasectomy" or "pulmonary metastasectomy", "thoracic surgery" or "lung surgery", "radiosurgery" or "stereotactic ablative radiotherapy" or "stereotactic body radiotherapy", "chemotherapy" and "ablation"
Timeframe	1959–2023
Inclusion and exclusion criteria	Inclusion: full text available in English, from 1959 to 2023
	Exclusion: irrelevant to primary search terms, unavailable in English, animal studies, studies including patients with history of other organ metastases
Selection process	J.O.G., J.L.J.D., J.M.C.C. reviewed all candidate articles and selected studies for inclusion based on verbal consensus and the above predefined inclusion and exclusion criteria. Hand searching and citation chaining were used to include relevant articles that were not indexed in the initial search strategy

key words variably combined: "lung metastasectomy" or "pulmonary metastasectomy", "thoracic surgery" or "lung surgery", "radiosurgery" or "stereotactic ablative radiotherapy" or "stereotactic body radiotherapy", "chemotherapy" and "ablation". Hand searching and citation chaining were used to include relevant articles that were not indexed in the initial search strategy. Studies were deemed eligible if they pertained to human subjects and was published in English. Studies were excluded if the language of study was not in English, included animal subjects, or included patients with history of other organ metastases. A summary of the search strategy is simplified in *Table 1*.

Iterations of surgical PM: open and minimally-invasive techniques

The first successful PM for renal cell carcinoma reported by Barney and Churchill in 1939 established metastasectomy as a viable treatment, with the hopes of providing long-term survival up to 5 years after surgery (12). In 2017, a systematic review on the long-term outcomes of surgical PM renal cell carcinoma noted a 5-year overall survival at 43% (13). In 2012, a meta-analysis attempting to identify the risk factors for survival in colorectal cancer patients with lung metastases cited a 27–68% 5-year overall survival rate in patients who were able to undergo complete resection (14). In the same year, a systematic review detailing outcomes of patients undergoing PM for soft tissue and bone sarcoma, on the other hand, cited a 5-year overall survival of 34% and 25%, respectively but the authors specifically stated that this survival advantage cannot be solely attributed to the role of PM (15). Given this survival advantage, thoracic surgeons continue to practice PM.

The accepted present criteria for selecting patients for surgical metastasectomy have not drastically changed since Thomford proposed them in 1965 (8). In current practice, however, lesions affecting both lungs are already acceptable candidates for bilateral PM done either in the same operative setting or as a staged procedure (16-19). Consensus regarding the limit of metastatic lesions to be resected still has not been established, but it is postulated that prognosis and number of metastatic lesions are inversely proportional with best results achieved with 1–2 lesions only (20-22).

The way in which thoracic surgeons practice PM remains to be highly variable. Both median sternotomy and thoracotomy for open resection of pulmonary metastases have been advocated with the advantages of each approach being disputed. Roth *et al.* reported on resection of pulmonary metastases secondary to soft-tissue sarcomas using both open approaches and concluded that median sternotomy resulted in detection of unsuspected bilateral metastases and avoidance of a second operative procedure (23). Bilateral anterior thoracotomies with a transverse sternotomy or the clamshell incision has also been described as an open method for bilateral PM (24).

Video-assisted thoracoscopic surgery (VATS) resection as a diagnostic and therapeutic technique has gained popularity over the recent years due to its superior functional outcomes. VATS showed the benefits of a less invasive approach which is obvious immediately after surgery: a better physical performance one month after the operation, a reduced length of hospital stay, a shorter duration of chest tube drainage and the use of epidural analgesia only, compared to an open approach (25-28). While thoracotomy provides the opportunity to discover non-imaged pulmonary nodules, only 6.9% of patients with solitary lesions on the computed tomography (CT) scan have more than one lesion when explored (29,30). VATS, although mostly indicated for diagnosis of indeterminate nodules, may be utilized for definitive treatment when only one small peripheral lesion is present on chest CT (31,32). VATS was the procedure of choice in patients with a peripheral solitary pulmonary nodule, however, in patients with multiple and deeply located lung metastases, thoracotomy was necessary to allow palpation of the lung. Despite the emergence of high-resolution chest CT, palpation of the lung remains to be necessary (29-32). However, according to the 2019 Expert consensus on PM, in cases where complete and parenchymal-sparing surgical resection is not achievable via minimally-invasive techniques, open surgery is still appropriate (33).

Moving forward from the surgical incision, even techniques to achieve precise tumor excision have not been standardized. For metastatic lesions presenting as peripheral nodules, wedge resection with adequate margins is employed as a parenchymal-sparing technique. Anatomical resections for complete excision of centrally located or bulky tumors, as well as multiple synchronous lesions in one segment or lobe may be addressed by segmentectomy or lobectomy. The incidence of pneumonectomy for PM is cited at 1.16% and continues to decline due to the availability of modern therapeutic alternatives (34,35). Apart from wedge resections, segmentectomies, lobectomies and pneumonectomies, the addition of clamps and stapling devices, electrocautery, photothermal laser, and energy-emitting devices have expanded the thoracic surgeon's armamentarium. The "circular clamp" technique used custom-built forceps designed to clamp centrally located nodules to avoid bleeding during the excision and to allow accurate suturing after the excision (36). Metastases located in areas where a stapler cannot be applied like nearby bronchi or blood vessels can be excised by laser (37). Photothermal laser resection with the application of neodymium-doped yttrium aluminium garnet (Nd:YAG) can provide precise tumor excision with 2–3 mm tumor margins and 5 mm rim of necrosis from laser energy dispersal (38-40). It is able to conserve normal lung parenchyma and does not distort the native lung configuration even in cases with multiple target lesions. In fact, it has been employed for as many as 20 metastases (3). Other alternative techniques have been proposed in order to save as much normal surrounding lung tissue such as: cautery resection (precision resection), LigaSure systemTM, ultracision HarmonicTM scalpel, and saline enhanced thermal sealing system (38). Local recurrence rate with electrocautery is slightly higher (51.2%) compared to laser (11.7%) and conventional wedge resection techniques with the use of clamps (8.3%) but was noted to have no significant difference (P=0.318) (39-41). There are no longer term studies detailing the rate of local recurrence with the use of these energy devices, which may be an area of future study.

The role of interventional radiology in PM

Image-guided needle biopsy via ultrasound (US) or CT and bronchoscopy has made interventional radiology a key player in the diagnosis and determination of pulmonary metastases. Furthermore, rapid advances in interventional radiology and the application of modalities such as needle-guided localization and radiofrequency ablation (RFA) have made interventional radiology a catalyst in minimally-invasive therapeutic treatment (42,43).

Since low-dose CT screening has made it possible to diagnose pulmonary nodules and ground-glass opacities as small as 0.3 cm, more creative techniques to sample these indeterminate lesions had to be invented. The instillation of dye, radio-opaque contrast, needles, coils, hook wires, and even radio frequency identification (RFID) tags through CT and bronchoscopy guidance has made it possible for invisible and impalpable nodules to be detected while performing minimally invasive surgery (44,45). RFID tags implanted via cone beam CT guided bronchoscopy have been reported to aid in the detection of nodules as small as 0.3 cm as deep as 2.6 cm from the pleural surface during VATS (46). Intraoperative lung ultrasonography performed via thoracoscopy has also been proposed as a substitute to palpation in the detection of pulmonary nodules but only limited experiences on VATS-US have been published (47-51). Another technique that is gaining traction is the use of near-infrared spectrometry or NIRS in combination with indocyanine green to detect occult nodules as small as 0.2 cm within 2 cm from the pleural surface (52,53). Precise localization of nodules that are undetectable by positron emission tomography (PET)-CT and manual palpation can now be performed without resorting to open thoracotomy.

Application of thermal energy in the form of cryotherapy, microwave ablation and RFA can be employed for nonsurgical local control of pulmonary metastases especially in patients who are poor operative candidates. The lung is particularly conducive to image-guided thermal ablation (IGTA) techniques due to the high contrast offered by the low density of air and high density of tumors, and the efficiency of heat delivery through the insulation provided by air (54,55). Commonly done under CT-guidance, percutaneous argon-based cryoablation has been proven as a safe alternative to resection of central and subpleural lung tumors while allowing assessment of the ablation zone or "ice ball formation" in real-time (56,57). In 2020, the Multicenter Study of Metastatic Lung Tumors Targeted by Interventional Cryoablation Evaluation (SOLSTICE) trial concluded that percutaneous cryoablation is safe (grade 3–4 adverse event rate 5.3%) providing an 85.1% and 77.2% local recurrence-free response rate (local efficacy) at 12 and 24 months, respectively (58). Similarly, the Efficacy of Cryoablation on Metastatic Lung Tumors with a 5-year follow-up (ECLIPSE) study demonstrated an 87.9% 3-year and 79.2% 5-year control rate after cryoablation (59).

Forms of thermal ablation include RFA and microwave ablation, which both destroy tumor cells by achieving lethal temperatures approximately 60 ℃. RFA creates heat through an electrical current and thus is only effective in tissues adjacent to the probe. The response to RFA of pulmonary tumors: a prospective, intention-to-treat, multicenter clinical trial (RAPTURE) study, found a 12-month local control rate of 88% (60). In 2015, a large series of 566 patients treated with RFA for lung metastases showed a 53.7% 3-year and a 44.1% 4-year local efficacy rate. Similar to cryoablation, RFA has low invasiveness that allows repeated procedure up to four times when needed (61). Microwave ablation, on the other hand, generates heat by applying an electromagnetic field to water molecules and is applicable to larger ablation volumes since it is not dependent on electrical conduction (54,61). Local control rate for microwave ablation is cited between 82.93% to 97.8% (62,63). IGTA via any of these techniques offers repeatability and parenchyma sparing. A systematic review of percutaneous ablation for PM showed a 12-month local control rate of 91% (64).

IGTA has been mentioned in conjunction with surgery. An earlier report combining CT-guided RFA in conjunction with surgical excision was performed to avoid a more invasive bilateral thoracotomy or a pneumonectomy (65). The image-guided combined ablation and resection in thoracic surgery (iCART) for the treatment of multiple metastases is a preliminary case series including four patients treated with microwave ablation and wire-guided surgery in the same operative setting, showcasing a highly personalized treatment approach for the patient with multiple lung metastases (66). A retrospective study involving seventeen patients who underwent hybrid surgical PM and RFA concluded that this approach, whether used concurrently or in sequence, can provide locoregional treatment in patients with multiple or bilateral lung metastases. No local recurrence was noted at median follow up 34 months. The small sample size and heterogeneity of patients included in this study leaves more to be investigated (67).

SBRT for lung oligometastasis

SBRT or stereotactic ablative radiotherapy (SABR) refers to the delivery of large, hypofractionated doses of external beam radiotherapy to a small, discrete treatment volume using a biologically effective dose of ≥100 Gy (68-70).

This ablative treatment approach was initially put to clinical use by a Swedish neurosurgeon, Lars Leksell, for the treatment of intracranial metastases (71). SBRT is the application of this technique to disease sites outside of the cranial vault.

SBRT is particularly viable in the case of pulmonary metastasis because lung tissue follows the parallel architecture model of radiobiology, which means functional damage will not occur until a critical number of alveolar subunits are inactivated by irradiation. This affords the ability to administer high doses of radiation without excessive risk of radiation pneumonitis, provided sufficient normal lung can be spared (72). Furthermore, prospective studies demonstrating the safety and efficacy of SBRT for inoperable early-stage non-small cell lung cancer have provided sound clinical evidence to support the use of SBRT in the setting of pulmonary oligometastasis (73-75).

The Stereotactic Ablative Radiation Therapy for the Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET) was a randomized, multicenter, open-label phase 2 study that assessed the impact of adding SBRT to palliative standard of care treatments on overall survival, progression free survival, toxicity, and quality of life in patients with a controlled primary tumor and up to 5 oligometastatic lesions (76). It was found that SBRT extended the median overall survival time from 28 to 41 months and significantly doubled the median progression free survival time from 6 to 12 months (76,77).

A multicenter LArge retrospectIve daTabase on the personalization of stereotactic ABlative radiotherapy use in lung metastases from colorectal cancer (The LaIT-SABR study) is the largest series including 1,033 metastases from colorectal cancer concluded that SABR offers a 75.4% 2-year local progression-free survival and may delay the progression to widely disseminated disease (78). These favorable results are also echoed in the population-based phase 2 SABR-5 trial which demonstrated a median progression free survival of 15 months and local control at 3 years of 87% among patients with oligometastatic disease treated with SBRT (79). A later report by Olson *et al.* showed the incidence of grade 3 or toxic effects was less than 5%. Furthermore, the rates of grade 2 or higher toxic effects (18.6%) were lower than previously published for SABR-COMET (29%) (80). On multivariate analysis, increasing tumor diameter, declining performance status, disease-free interval <18 months, 4 or more metastases at SABR, initiation or change in systemic treatment, and oligoprogression were significant independent predictors of progression free survival; while tumor diameter colorectal histology and "other" histology were associated with worse local control (79).

The Stereotactic ABlative Radiotherapy Before Resection to AvoId Delay for Early-stage LunG Cancer or OligomEts During the COVID-19 Pandemic or SABR-BRIDGE approach was developed during the early stages of the pandemic to avoid tumor progression that could result to unresectable disease (81). Neoadjuvant SABR followed by radical-intent surgery after 3–6 months as a hybrid approach can potentially provide local control and tumor sterilization with minimal toxicity but substantial evidence to support this hypothesis is still wanting. Given the scarcity of data on pathologic complete response (pCR) and underwhelming regional control and survival rates, current efforts are aimed at investigating a hybrid approach which involves the use of neoadjuvant SBRT followed by radical-intent surgery. This technique has the potential to grant improved outcomes while simultaneously providing data on tumor sterilization. The ongoing post-SBRT PM (PSPM) trial is currently examining the efficacy and safety of this method (82).

Taken together, available evidence shows that SBRT is a reasonable option for patients with oligometastatic cancer, with encouraging local control, progression free survival, overall survival rates, and toxicity profile (70). However, the decision to pursue this treatment should consider the institutions' local experience, tumor characteristics and patient preference.

Regional and systemic medical therapies for lung metastases

Classically, systemic chemotherapy was the sole treatment option for patients with distant metastases. However, many patients will develop recurrent pulmonary metastases despite the use of systemic chemotherapy. Furthermore, chemotherapy is dose-limited because of its tendency to incite systemic toxicity. In 1959, Creech described a method of pulmonary perfusion of both lungs simultaneously with the use of two extracorporeal circuits. Heart-lung bypass was used between the vena cava and the femoral artery while blood from the left atrium flowed through a pump oxygenator and returned to the pulmonary artery by gravity, therefore completely excluding the pulmonic circuit (83). Krementz in 1986 reported on four patients who underwent lung perfusion with a good clinical response in one patient with epidermoid cancer involving the right main stem bronchus, extending into the trachea, the first clinical report of lung perfusion for the treatment of cancer (84). Isolated lung perfusion (ILuP), the intraoperative administration of chemotherapeutic agents through an isolated pulmonary circulation has been extensively studied in animal models since 1983 and phase II trials with agents such as melphalan has been proven to be safe and feasible in humans (85,86). ILuP was founded on the basic principles of isolated limb and liver perfusion and was touted to be an attractive and promising surgical technique for the delivery of high-dose chemotherapy with minimal systemic toxicity in experimental models and phase II human studies (87,88). In patients with stage IV colorectal carcinoma and sarcoma, ILuP with melphalan combined with PM showed comparable morbidity rates, length of stay with a local recurrence rate of 43% in 3 years (89). In theory, locoregional control should be superior with the combination surgical resection for gross disease and ILuP for micrometastasis. Building on this concept, selective pulmonary artery perfusion (SPAP) with blood flow occlusion (BFO), an endovascular technique for the delivery of high-dose chemotherapeutic agents to the ipsilateral pulmonary artery via femoral cannula, postulated to achieve tumor and nodal down-staging by enhancing drug delivery (90). Compared to ILuP, this less invasive procedure can be repeated multiple times and has shown promising results in rat models (91).

Modern medical treatments, particularly immunotherapy and targeted therapy such as v-raf murine sarcoma viral oncogene homolog B1 or BRAF and mitogen-activated extracellular signal-regulated kinase or MEK inhibitors for malignant melanoma and immune checkpoint inhibitors like programmed cell death ligand 1 or PD-L1 inhibitors for lung cancer, have revolutionized the current oncologic practice, as well (92,93). Initially these modalities were offered as last resort alternatives to those who are unable to undergo surgery, but some regimens have shown that they have survival rates paralleling and even surpassing that of radical resection (93). Immunotherapy and molecular-targeted therapy agents are currently being offered in the neoadjuvant and adjuvant setting for various cancers, but their role as neoadjuvant treatment for PM remains to be elucidated.

Future plans and studies needed

In summary, the data gathered in this review paint a clear picture of the time lag between large prospective studies that demonstrate the effectiveness of various approaches and the swift advancements in imaging technologies, surgical techniques, and medical treatments for metastasectomy. Identifying this knowledge gap can influence the direction of future research. Although incidental reports and retrospective studies offer some insight into the benefits of combined therapies involving surgical oncology, chemotherapy, and radiotherapy for pulmonary metastases, there is still a lack of clinical trials and large prospective studies investigating the application of these hybrid approaches and their comparison to the current standard of care. Clearly, further exploration is needed regarding indications, contraindications, timing, and sequencing of therapies, but the implementation of hybrid approaches for stage IV lung disease appears promising.

Conclusions

In conclusion, the management of pulmonary metastasis is continuously evolving, considering the rapidly changing landscape and the expanding range of options provided by surgery, interventional radiology, radiation oncology, and medical oncology. Open and minimally-invasive surgical resection, ablation, SBRT, chemotherapy, immunotherapy, and targeted therapy can be synergistically employed in combination to achieve local and systemic control of oligometastases. Furthermore, given the diverse nature of pulmonary metastases and the unique characteristics of each patient. An individualized and multidisciplinary approach has the best potential to optimize survival outcomes for our patients.

While this narrative review offers a general overview of the currently available modalities for patients with pulmonary metastases, there is still a need for a rigorous and comprehensive investigation as to how these therapeutic approaches function independently and in conjunction. Prospective and randomized controlled studies are required to validate the indications and technical considerations for each modality's application, particularly in the context of oligometastatic disease. Similarly, a comparative analysis that examines both short-term and long-term outcomes of the different interventions can assist clinicians and patients in decision-making and treatment planning. This underscores the importance of multidisciplinary collaboration, not only in patient care but also in research endeavors.

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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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