Expert Consensus Document on Pulmonary Metastasectomy

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Pulmonary Metastasectomy Expert Consensus Statements

1. When caring for patients with cancer and pulmonary oligometastases, pulmonary metastasectomy (PM) should be considered within a multidisciplinary team (MDT) and carefully individualized.
2. In oncologically and medically appropriate non-small cell lung cancer (NSCLC) patients, tissue from PM should be sent for genomic/molecular analysis, including programmed death-ligand 1, to guide future therapies.
3. In oncologically and medically appropriate patients, PM can be considered with a preference for minimally invasive surgery (MIS) because of shortened postoperative recovery and lessened effect on quality of life.
4. If goals of R0 and pulmonary parenchymal sparing are not accomplishable by MIS but lend themselves to open approaches (thoracotomy, sternotomy, or clam shell), open techniques are appropriate.
5. Pneumonectomy to accomplish PM is discouraged except in carefully selected patients undergoing MDT management.
6. Although the absolute number of pulmonary metastases is not a direct contraindication to PM, candidate selection for PM is best suited to patients harboring 3 or fewer pulmonary metastases.
7. Lymph node (LN) sampling/dissection concomitant with PM should be considered, because pulmonary metastasis accompanied by mediastinal LN metastasis predicts poor survival.
8. Thermal ablation or stereotactic ablative body radiotherapy (SABR) is reasonable therapy for patients with pulmonary oligometastases, particularly for patients considered high risk for resection or who refuse resection.
9. Outside of clinical research, isolated lung perfusion is not warranted for management of pulmonary metastases.
10. In colorectal cancer patients, PM can be considered within an MDT construct with systemic therapy before or after PM.
11. In renal cell carcinoma patients, PM can be considered within an MDT construct.
12. In malignant melanoma patients, PM can be considered within an MDT construct.
13. In sarcoma patients, PM can be considered within an MDT construct.
14. PM in management of primary head and neck cancer can be considered in the context of a disease-free interval (DFI) exceeding 12 months, ability to completely resection, and absence of LN metastases.
15. When managing nonseminomatous germ cell tumors (NSGCTs), PM is indicated for all residual lung abnormalities $\geq$ 10 mm after platin-based chemotherapy with normalized serum tumor markers (STMs) suspected of containing teratoma.
16. When managing NSCGTs, contralateral lung abnormalities can be observed if histology of unilateral PM demonstrates complete tumor necrosis.

The Society of Thoracic Surgeons Executive Committee approved this document.

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17. When managing NSGCTs, PM is indicated for select patients with limited number of lung abnormalities after first-line or second-line platin-based chemotherapy suspected of containing viable nonseminomatous cancer or malignant transformation of teratoma into non-germ cell cancer, or both.
18. In breast cancer patients, PM can be considered within an MDT construct.

Introduction

PM has long been practiced, albeit in the face of a large literature with low level of evidence. Recognizing a need for some standardization, The Society of Thoracic Surgeons (STS) Work Force of Evidence Based Surgery formed a task force and subjected "pulmonary metastasectomy" to STS expert consensus development process. The task force membership included thoracic surgery, medical, and radiation oncology. The following is the resulting expert consensus, not rising to the level of guidelines due to the flawed supporting literature.

PM Literature Characteristics

Since 1980, greater than 1,000 publications addressed PM, without a single randomized controlled trial. Most of the studies are surgical series, usually from a single institution, and include single or multiple pathologies. The pool of patients from which metastasectomy patients derive is not reported, allowing no comparative survival analysis. Historical controls are used or metastatic disease survival is assumed to be zero, a contention not supported by the literature. Yet metastasectomy is infrequently performed (1% to 6.5%) when sizable populations of cancer patients are reported [1–3]. Thus, surgical case series manifest inherent selection bias and do not clarify the role of metastasectomy in prolongation of survival or cure. The literature is further hampered by inconsistent or absent description of other local or systemic therapies and variable length of follow-up.

Finally, the literature fails to distinguish between prognostic (indolent disease that will do well with any or no treatment) or predictive features (discriminate "likely" vs "unlikely" to benefit from a particular treatment). PM candidate predictive features include uncontrolled primary malignancy, nonpulmonary metastatic sites, non-R0 resection, and positive mediastinal LNs, all of which are usually considered operative contraindications, furthering the selection bias of surgical series [4, 5].

A few registry articles (eight in total) have largely defined practice. The most influential reported 5,206 patients with multiple pathologies from the International Registry of Lung Metastases (IRLM) [6], without a denominator of cancer patient population from which the metastasectomy patients derived (Table 1).

Table 1. General Characteristics of the Pulmonary Metastasectomy Literature

No randomized controlled trials
Pervasive selection bias
No comparative survival analysis
Inconsistent description of accompanying local or systemic therapies
Variable follow-up length
Fails to distinguish between prognostic or predictive characteristics
Does not clarify the role of pulmonary metastasectomy in prolongation of survival or cure

Methodology

The Expert Consensus Task Force on Pulmonary Metastasectomy was enlisted by the STS Workforce on Evidence Based Surgery to provide clinically relevant guidance to clinicians despite the above-stated limitations of the PM literature. Relevant literature was searched for in MEDLINE for articles published in English since 1990, using Medical Subject Heading terms "lung neoplasms + secondary," "metastasectomy, "pneumonectomy," "thoracotomy," and "thoracic surgery, video assisted," combined with a variety of primary neoplasm sites. Authors were free to select relevant articles for inclusion at their discretion. A systematic review was not performed owing to the overall lack of control groups.

Consensus statements were developed using a modified Delphi method. The proposed statements were subject to a vote using a 5-point Likert scale. An 80% response rate among the authors was required, and statements in which 75% of respondents selected "agree" or "strongly agree" were considered to have reached consensus. Three statements did not achieve 75% agreement after the first round of voting, and after minor revisions, were included after a second round of voting. The American College of Cardiology Foundation/American Heart Association classification system used in clinical practice guidelines to rate the strength, and level of evidence was not used for this report because the expert consensus process adopted by STS results in opinion statements rather than formal recommendations.

Overall Conceptual Framework of Treatment and the Role of PM

The focus of this effort is the role of resection (or ablation) of pulmonary metastases from an extrathoracic primary cancer. PM inherently involves application of a local therapy in a nonlocalized disease setting. Defining the clinical setting and the goals of treatment is important.

In patients who have isolated pulmonary metastases from an extrathoracic primary cancer, PM assumes the primary disease site is controlled and there are no other systemic metastases. It is generally accepted that undertaking PM makes little sense if other sites of disease are unaddressed. We acknowledge that this widely held consensus is based on rationale alone (no data are

available for PM in the face of multiple unaddressed other metastatic sites). However, this represents an "unopposed rationale," because it is hard to come up with a rationale to support the converse. (There are credible variations to this concept regarding timing: sometimes the sequence of PM may vary relative to achieving control of the primary site or other metastases [eg, liver and pulmonary metastases from colon cancer], but the fundamental concept of only undertaking PM in a setting where all known sites of disease are definitively addressed is unchanged.) This report does not address the situation of a "rogue metastasis," a site of metastasis that is not responding while other sites appear to be well controlled and quiescent (but still present). This is an emerging topic with its own complexities and beyond the scope of this report.

A simple physical concept of the process of metastasis is widely pervasive, involving anatomic and mechanical aspects of the vascular and lymphatic system as determinants of how metastasis occurs (hematogenous or lymphatic dissemination). Although simple and appealing, this concept is countered by many observations [7]. Different primary tumors exhibit a predilection for particular metastatic sites. In addition, circulating tumor cells in the bloodstream are commonly present, even in early-stage cancer patients who never subsequently develop metastases.

A large body of literature demonstrates that metastasis is an intricate multistep process [8, 9]. During this process, the cancer cell is transformed into different phenotypes (epithelial to mesenchymal transformation and back again) [10]. Tumor cells are present simultaneously in many different forms and heterogeneous subpopulations and can exist for a long time in a dormant state within permissive niches. The various steps are influenced by tumor cell–intrinsic genetic and epigenetic determinants as well as a complex array of tumor-host interactions (eg, a permissive microenvironment, angiogenesis, and tumor characteristics blocking activation of host immune response) [11, 12]. In the face of this large body of evidence, we must be careful not to adhere dogmatically to a simple physical concept of how metastasis occurs that is clearly an oversimplification.

Historically, the goal of PM has been cure. This concept would require definitive treatment of all sites of disease and be measured by long-term survival without recurrence, the rate of disease-free survival (DFS). There is no clear definition of what time frame should be considered to represent "long-term" survival, and in fact, this may be different in a rapidly growing versus an indolent tumor. A simple definition of the rate of achieving long-term DFS would be clinically useful, even without a no-treatment (ie, no PM) comparison group. However, DFS can be a difficult outcome measure if one considers the possibility that repeat resection of a recurrence may still achieve cure. One can argue that overall survival (OS) might approximate DFS and cure, but we must recognize that this is imperfect, especially when one is considering indolent tumors and in the context of other non-PM therapies (for which information is scarce).

In practice, PM is never considered abstractly in isolation. PM is always in the context of the possibility of systemic therapy, which may be an alternative, or an adjunct preceding or following PM. This creates difficulty in defining the role of PM and creates variability in the treatment approach, which may affect outcomes.

In cancers that commonly metastasize to the lung (colorectal cancer, renal cancer, melanoma, germ cell tumors, and breast cancer), the time of cancer diagnosis, interval between primary tumor resection (DFI), presence of other metastatic sites, and type of prior systemic therapy affect decisions about PM. Patients with the smallest disease burden at the initial diagnosis, longer interval since the primary therapy, best response to prior systemic treatment, and preserved performance status might derive the greatest likelihood of benefit from PM.

Is PM Associated With Cure?

PM appears to provide long-term survival (OS and DFS) or "cure" across multiple pathologies with adherence to historically accepted surgical principles, including control of the primary cancer, absence, or less commonly, control of extrathoracic metastasis, complete resection (R0), and ability to tolerate the resection. Less commonly reported criteria include LN involvement, DFI, and the number of metastases. When these criteria are achieved, the tail or flattening of OS curves in contemporary reports include colorectal (OS, 20% to 52% at 7 to 9 years) [13, 14], renal cell carcinoma (OS, 33% at 7 years) [15], melanoma (OS, 14% at 10 years) [16], soft tissue sarcoma (OS, 11% to 23% at 7 to 11 years) [17, 18], head and neck squamous cell carcinoma (HNSCC; OS, 18% at 13 years) [19], breast cancer (OS, 40% at 18 years) [20], and hepatocellular carcinoma (OS, 38% over 10 years) [21].

Is PM Associated With Prolonged Survival (Without Cure)?

Assessment would involve OS of patients undergoing PM compared with a similar cohort not undergoing PM. Assessing this requires not just a survival rate but a also comparable comparison group, which makes acquiring evidence for prolongation of survival difficult. When reported, OS is larger than DFS, implying a possible survival prolongation from PM: colorectal—9-year OS 52%, DFS 38% [12], 7.5-year OS 20%, DFS 17.5% [13]; soft tissue sarcoma—7-year OS 23%, DFS 8%; [16] hepatocellular carcinoma—10-year OS 38%, DFS 30% [21].

In the case of lung cancer, so-called oligometastatic disease is difficult to reliably distinguish from second primary disease unless the lesions are pathologically distinct [22]. Absence of involved LNs, development of cancer within prior areas of likely precancer, lack of other metastatic sites, and interval between the primary and secondary tumor diagnosis may suggest a second primary rather than metastatic disease [23]. Resection of true second primaries has a high likelihood of cure, so when in doubt, pursue resection [24]. Small series have shown 5-year survivals in the 40% range independent of the pathologies in patients where synchronous lung cancers

were removed, suggesting that even with oligometastatic cancer at presentation, resection may be of benefit [25].

PALLIATION. No data exist for PM for symptom palliation. PM as palliation of symptoms is rare, because pulmonary metastases seldom cause symptoms. It stands to reason that PM can be considered in symptomatic patients otherwise fit to undergo resection and that situations such as painful, obstructing, or bleeding metastases might be candidates for removal or ablation, if safe to do so. Rarely, symptoms may result from airway obstruction (often amenable to endobronchial palliative measures).

Multidisciplinary Care/Therapy: Whether, When, and How to Integrate PM With Systemic Therapy

MDT management should be the hallmark of both treatment and patient selection. The timing of metastasectomy vis-à-vis systemic therapy is complex and requires expert input, as does the risk/benefit assessment of local therapies, including surgical resection versus SABR/stereotactic body radiotherapy, versus percutaneous ablation versus systemic therapy alone. An anecdotal literature supports metastasectomy for diseases prone to indolent progression, such as some sarcomas, renal carcinoma, some melanomas, lung cancers, carcinoid tumors, and colorectal carcinomas. Surgery is preferred in patients who will tolerate resection for tumors such as germ cell cancers, where residual disease may be primarily teratoma but may devolve into malignant tissue if left in situ. Surgery is preferred for patients with chemoradiotherapy-insensitive disease such as renal cell carcinoma and melanoma.

The advent of targeted therapies and immunotherapy has changed the landscape in those latter tumor types substantially in recent years, but although responses to immunotherapy can be prolonged and significant, they still apply only to the minority of patients (major response in approximately 20%). Responses to targeted therapies are more common, but of shorter duration, so PM remains a consideration. The timing of resection and the role of neoadjuvant or adjuvant systemic therapy, or both, is poorly informed by the literature.

In the clinical scenario of isolated pulmonary metastases, the medical oncologist's role is to estimate overall prognosis, assess the utility of systemic therapy, and provide input on the necessity, intent, and timing of resection. Important factors to consider are status of the primary, recurrence-free survival, natural history of the disease, pathology, genotype, and availability of effective systemic treatment. An initial course of immunotherapy or targeted therapy may be appropriate for some diseases (melanoma or renal cell cancer), reserving resection as consolidation to render a patient disease free or as salvage in case of symptomatic resistant disease [26].

There is growing interest in controlling metastatic sites with local measures, which is an active area of research [27, 28]. Especially in cases of actionable molecular alterations, a large portion of patients continue systemic therapy despite radiographic progression, assuming an established global benefit [29]. In these patients, focus is shifting to the treatment of individual metastatic sites in combination with ongoing systemic treatment. However, there is generally limited value in "adjuvant" therapy—especially chemotherapy—for a patient rendered disease free through resection (eg, in cases of colorectal cancer or sarcoma).

There is no literature guidance regarding timing of PM relative to completion of systemic therapy or safe duration of cessation of wound healing inhibiting targeted therapy before surgery. A common anecdotal practice is to achieve "maximal" systemic control before PM. If serial imaging a few weeks apart shows stable response without further shrinkage and functional status is good, PM or ablation is performed soon thereafter. Most tyrosine kinase inhibitors used in lung cancer have minimal effect on wound healing. In the case of driver mutations, interrupting therapy is undesirable. Hence endothelial growth factor receptor tyrosine kinase inhibitors, for example, are generally interrupted only 1 to 2 days before surgery and resumed 1 or 2 days after.

Consensus Statements

1. When caring for patients with cancer and pulmonary oligometastases, PM should be considered within a MDT and carefully individualized.
   Strongly Agree: 92% Agree: 8% Neutral: 0% Disagree: 0% Strongly Disagree: 0%
2. In oncologically and medically appropriate NSCLC patients, tissue from the PM should be sent for genomic/molecular analysis, including programmed death-ligand 1 to guide future therapies.
   Strongly Agree: 67% Agree: 8% Neutral: 8% Disagree: 17% Strongly Disagree: 0%

Evaluation of a Patient Being Considered for PM

Selection/Exclusion of Patients for PM

In patients who have isolated pulmonary metastases from an extrathoracic primary cancer, PM assumes the primary disease site is controlled and there are no other systemic metastases, or if present, are being actively managed. No evidence defines "oligometastatic" disease or adequate DFI generalizable to all metastatic pathologies.

Imaging Modalities

Imaging of the patient considered for PM does not differ from that of a patient evaluation for resectability of primary lung cancer. Number, location, and technical resectability of metastases are best evaluated by chest computed tomography (CT). Extrathoracic disease is evaluated by positron emission tomography (PET) scan if the primary was avid (many renal cell carcinomas are not).

Risk Assessment

Operative "risk" is defined by hospital mortality or morbidity. Risk assessment of the patient considered for PM does not differ from that of a patient evaluation for medical operability of primary lung cancer. Clinical

evaluation delineating dyspnea, performance status, and exercise capacity supported by pulmonary function testing (spirometry and diffusion capacity) suffice. If lack of clarity regarding medical operability results, further testing is warranted (stair climbing, 6-minute walk test, and cardiopulmonary exercise testing). The same variables accepted as defining risk for anatomic pulmonary resection of primary lung cancer apply to PM (Fig 1).

Recurrent Disease/Repeat PM

Patients by definition have metastatic disease from the beginning, and factors to consider are the same with recurrent pulmonary metastases after resection. These include duration of the DFI, overall prognosis, expected benefit of medical treatment, and the patient's symptoms. With subsequent recurrences, DFI tends to shorten, symptoms worsen, and the value of medical treatment is less. Cure is highly unlikely in these situations, and palliation with prolongation of survival are the hoped for treatment goals.

Surgical Objectives

An indisputable objective of PM is diagnosis when metastasis has not been previously pathologically confirmed. If PM is considered therapeutic (cure or long-term palliation), objectives include R0 resection, pulmonary parenchymal sparing, defining extent of disease (lymphadenectomy), and, rarely, relief of symptoms. Inability to achieve the primary goal of R0 resection precludes PM as therapy.

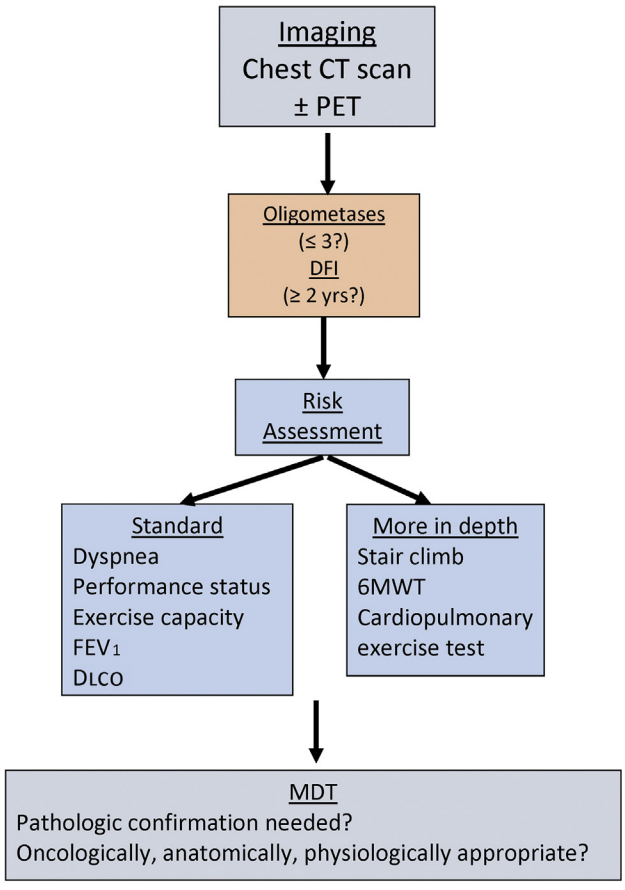

Fig 1. Evaluation for pulmonary metastasectomy. (CT = computed tomography; DFI = disease-free interval; DLCO = diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume in the first second; MDT = multidisciplinary team; PET = positron emission tomography; 6MWT = 6-minute walk test.)

Safety: Surgical Morbidity and Mortality

PM is safe. Accumulated reports totaling 6,122 patients [6, 30–32] demonstrate less than lobectomy (wedge resections and segmentectomy) is the most common resection technique, used in 4,644 patients (75%). Lobectomy, and seldom, pneumonectomy, was used in the remaining 25%. Perioperative safety is reflected in this preference for pulmonary parenchymal sparing. Operative mortality in these reports was 1.1% (71 patients), and morbidity, when reported [30–32], was 11% (102 of 916 patients). Average length of stay was 4.8 to 7.3 days [30, 31].

Technical Aspects of Surgical PM (Fig 2)

Extent of Resection

The necessity of achieving an R0 resection determines the extent of resection. Less than lobectomy is the dominant technique, allowing pulmonary parenchymal sparing. Lobectomy is occasionally indicated. Pneumonectomy is rarely appropriate and questionable as a technique in this patient population.

Surgical Approach

Historically, manual palpation has been touted as required to "find" all the metastases when multiple are present on radiographic studies. However, modern day CT scanning has very high resolution, and CT is likely able to identify most lesions, and if not all lesions, at least lesions that would be palpable. Localization of lesions can be difficult if they are small and multiple, and certainly manual palpation adds tactile feedback that is otherwise limited with thoracoscopic approaches. Finger palpation through port sites or utility incisions as well as indirect palpation of the lung using instruments, such as a ring forceps, can aid in finding lesions using minimally invasive thoracoscopic techniques, but close attention to the

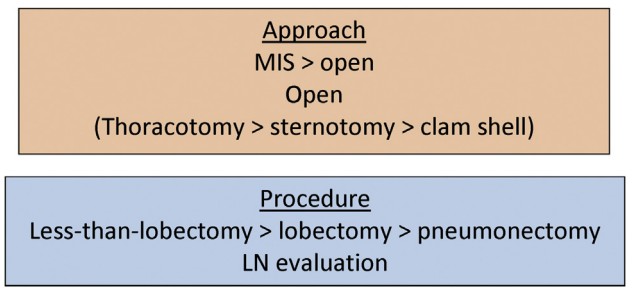

Fig 2. Surgical techniques for pulmonary metastasectomy. (LN = lymph node; MIS = minimally invasive surgery.)

CT scan and the anatomy of the lung real-time is as valuable. The literature describes multiple localization techniques, including percutaneous coils, wire localization, agar injection, and dyes, among others, but there are little data proving cost-effectiveness, and this will likely remain an individual preference in the near future and limited by the experience of the specialists applying different techniques. DFS does not appear to be affected by approach, at least for colorectal metastases [33].

When an open technique is needed, usually for multiple or difficult to locate lesions, a decision remains about the best open approach. Single-lung ventilation with high oxygen concentrations should be avoided in patients who have been exposed to bleomycin, which is often the case with testicular cancer. If bilateral metastases are present, a clamshell incision (bilateral sternothoracotomies) with short intermittent apneic periods, while using a fraction of inspired oxygen of 40% or less, should be considered to avoid the risk of pulmonary fibrosis. Bilateral lesions can be approached through staged thoracotomies, thoracoscopies, or median sternotomy if all lesions can be completely resected from this incision. A sternotomy is usually well tolerated and can avoid the need for longer periods of single lung ventilation requiring a high fraction of inspired oxygen.

Consensus Statements

3. In oncologically and medically appropriate patients, PM can be considered with a preference for MIS owing to the shortened postoperative recovery and lessened effect on short-term quality of life.
   Strongly Agree: 75% Agree: 8% Neutral: 17% Disagree: 0% Strongly Disagree: 0%
4. If goals of R0 and pulmonary parenchymal sparing cannot be accomplished by MIS but lend themselves to open approaches (thoracotomy, sternotomy, or clam shell), open techniques are appropriate.
   Strongly Agree: 83% Agree: 17% Neutral: 0% Disagree: 0% Strongly Disagree: 0%
5. Pneumonectomy to accomplish PM is discouraged except in carefully selected patients undergoing multidisciplinary management.
   Strongly Agree: 62% Agree: 30% Neutral: 8% Disagree: 0% Strongly Disagree: 0%
6. Although the absolute number of pulmonary metastases is not a direct contraindication to PM, candidate selection for PM is best suited to patients harboring 3 or fewer pulmonary metastases.
   Strongly Agree: 33% Agree: 42% Neutral: 8% Disagree: 8% Strongly Disagree: 8%

LN Management

In patients harboring pulmonary metastases from an extrathoracic solid organ, intrathoracic LN involvement often portends a worse prognosis [34, 35]. Historically, thoracic surgeons uncommonly perform mediastinal LN dissection in the setting of metastatic disease. The IRLM included 5,206 patients with varying pathology and reported metastasis to mediastinal or hilar LNs in 5% of patients (11% germ cell tumors, 8% melanomas, 6% epithelial tumors, and 2% sarcomas). Mediastinal LN sampling was discretionary, and LNs were assessed in only 4.6% of patients [6]. Since 1997, more surgical oncologists perform LN assessment during PM, but systematic mediastinal lymphadenectomy remains controversial. During a 2008 survey of the European Society of Thoracic Surgeons, 55% indicated that they regularly sample mediastinal nodes at the time of metastasectomy, whereas 33% avoided nodal dissection [36]. Although current evidence suggests intrathoracic LN status is an important predictive factor in PM, there are no randomized data answering whether mediastinal lymphadenectomy has a therapeutic effect.

The frequency with which pulmonary metastases can metastasize to regional LNs is unclear but appears to be influenced by tumor histology (higher in colorectal, breast, and renal cell carcinoma and less in sarcoma and melanoma). Autopsy series demonstrated a 33% incidence of mediastinal LN metastases in patients with nonpulmonary carcinoma [37]. The incidence of intrathoracic LN metastases at the time of PM for colorectal cancer is higher than other epithelial pathologies and ranges from 12% to 44% [38, 39].

In these retrospective series, mediastinal LN metastases were a significant negative indicator for survival. Hamaji and colleagues [39] reported outcomes of 319 patients who underwent mediastinal LN assessment during PM for colon cancer, where 5-year survival was 48% in the LN-negative group and 21% in the LN-positive group. The location of intrathoracic LNs (hilar or mediastinal) did not influence survival [39]. In a larger retrospective series of 883 patients undergoing PM for an array of pathologies, 3-year survival for patients with LN metastases was 38% compared with 69% in LN-negative disease [35].

As surgeons select appropriate patients for pulmonary metastasectomy, the presence of intrathoracic LN involvement with lung metastases gives reason to pause. Published retrospective series across varying pathologies universally document worse survival in patients harboring intrathoracic LN metastases. This has prompted a call for more thorough preoperative evaluation of patients. In 2010, the European Society of Thoracic Surgeons argued for mediastinal LN sampling before metastasectomy and suggested that best practice would be to exclude patients from PM with thoracic nodal disease [40]. The counter argument is that LN assessment allows for stratification of patients across different treatment strategies. For example, patients who undergo curative PM with LN-negative disease may be better suited for an observation strategy, whereas those with LN-positive disease might benefit from systemic treatment. As more effective systemic therapies evolve, patients may evolve to consideration of interval PM of residual or oligoresistant disease in the lungs.

DOES MEDIASTINAL LYMPHADENECTOMY IMPROVE SURVIVAL? The therapeutic effect of routine LN dissection during PM remains poorly defined. Published retrospective series reporting outcomes in patients undergoing systematic LN

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dissection during the time of PM have inadequate control groups. Winter and colleagues [41] performed a matched-pair analysis of 110 patients who underwent mediastinal LN dissection during PM for renal cell carcinoma compared with 111 patients with no LN assessment. Analysis showed a trend toward improved survival ($p = 0.068$) in patients undergoing LN dissection. Patients in their study who harbored intrathoracic LN metastases had a significantly shorter median survival than patients without LN metastasis (19 vs 102 months, $p < 0.001$).

WHO SHOULD UNDERGO MEDIASTINAL LN DISSECTION? In patients considered for PM, thoracic surgeons will often perform mediastinal LN dissection in the presence of suspicious LNs found on radiographic imaging. Despite diagnostic quality of CT chest and PET, LN metastases can be missed. Seebacher and colleagues [42] reported 209 patients who were routinely evaluated with CT and PET before pulmonary resection and underwent regional lymphadenectomy (n = 158) or LN sampling (n = 112) during PM for varying histologies. The authors observed unexpected intrathoracic LN metastases in 17% of patients, particularly with breast and renal cell pathology. In view of the prognostic significance of unexpected LN involvement, the authors recommended routine LN dissection for all patients undergoing PM.

Conclusion

Recurrent observations can guide practice. Because the incidence of intrathoracic LN metastases occurs in up to 44% of pulmonary metastases patients [39, 41] (where detection with CT chest or PET can be falsely negative), systematic LN dissection or sampling at the time of PM seems reasonable. Even patients with only 1 pulmonary metastasis can have involved intrathoracic LNs. Further justification of LN assessment includes setting expectations with patients and establishing whether adjuvant therapy is imminent or whether an observation strategy can be used in LN-negative disease. Establishing specific recommendations for the use of intrathoracic LN assessment across individual histologies (epithelial cancers, sarcomas, germ cell tumors, renal cell cancers, and melanoma) is not warranted given the data paucity.

Consensus Statement

7. LN sampling/dissection concomitant with PM should be considered because pulmonary metastasis accompanied by mediastinal LN metastasis predicts poor survival.

   Strongly Agree: 39% Agree: 38% Neutral: 23% Disagree: 0% Strongly Disagree: 0%

Nonsurgical Local Treatment Modalities for Pulmonary Metastasis

Role of Thermal Ablation and SABR

For this review, only studies with 20 or more patients, a minimum reported 3-year OS, and studies with mixed pathology, colorectal or sarcoma metastases (representing the largest reports allowing results to be more easily compared against studies involving surgical resection) were included. No randomized studies exist.

THERMAL ABLATION. Thermal ablation techniques include radiofrequency ablation (RFA), microwave, and cryotherapy. A number of systems are available for each modality. No studies compare the available systems. Although most centers are migrating toward using microwave for lung ablation, no studies have compared modalities. Finally, concerning pulmonary metastases, all of the studies fulfilling the inclusion criteria used RFA.

Smaller tumor size has been demonstrated to be important when using RFA [43]. Studies using RFA for pulmonary metastases used variable inclusion criteria, with some studies including tumors with diameters up to 80 mm [44]. Successful ablation of large tumors is unlikely, and inclusion will adversely affect results.

The largest report of ablation for pulmonary metastases included 566 patients, with 293 colorectal patients and 51 with sarcoma metastases [45]. The authors demonstrated that the primary disease location, DFI, size, and number of metastases were associated with OS on univariable and multivariable analysis. Addressing specifically patients with colorectal metastases, size (>2 cm) and number of metastases (>3) were both significantly associated with poorer survival.

A confounding issue of many studies of pulmonary metastases ablation is that only medically inoperable or patients in whom other treatment modalities had failed were included. Despite this, survival results (Table 2) are comparable to those after surgery. A prospective open-label study from Australia reported 148 non-resectable patients with colorectal metastases [50]. Median survival was 51 months, and 5-year survival was 45%.

Studies of sarcoma generally included smaller numbers of patients. In a report of 20 patients with metastases sized 2 cm or less, 3-year survival was 85% [52]. In the above large French study of 566 patients, there were 51 sarcoma patients [44]. Although this study included tumors up to 70 mm, 3-year survival for sarcoma patients was still acceptable at 58%.

STEREOTACTIC ABLATIVE BODY RADIOTHERAPY. The utility of SABR for medically inoperable lung cancer patients has been described [53]. It is not surprising that investigators report the use of SABR for pulmonary metastases patients. Lesion size, location (central vs peripheral), and number of metastases are important considerations from a technical and safety standpoint. However, all studies are small, and none report long-term outcomes (Table 3).

A study by Nuyttens and colleagues [54] reported 30 patients with 57 pulmonary metastases. Large peripheral tumors received 60 Gy (3 fractions), small peripheral tumors received 30 Gy (1 fraction), and central tumors received 60 Gy (5 fractions), illustrating the challenges in delivering SABR to patients with multiple tumors. At a median follow-up of 36 months, 4-year survival was 38%. Treatment was well tolerated, with 5 patients (16%) reporting acute grade 3 toxicity.

Table 2. Survival After Thermal Ablation for Pulmonary Metastases

First Author [Reference]	Year	Patients (No.)	Modality	Pathology	Median Follow-Up (months)	Median OS (months)	3-year OS (%)	5-year OS (%)	Tumor size, mm Median (range)
Ferguson [46]	2015	157	RFA	Colorectal	28	33.3	44	19.9	38[a]
de Baere [45]	2015	566	RFA	Mixed	35.5	62	67.7	51.5	15 (4–70)
Wang [47]	2015	67	RFA	Mixed	24	24	46.4	14.3	Max 50
Petre [48]	2013	45	RFA	Colorectal	18	46	50	NR	Max 35
Von Meyenfeldt [44]	2011	45	RFA	Mixed	22	55	69	NR	16 (5–80)
Matsui [49]	2015	84	RFA	Colorectal	37.5	67	65	51.6	15 (5–35)
Palussière [50]	2011	29	RFA	Sarcoma	50	NR	65.2	NR	Max 40
Chua [51]	2010	148	RFA	Colorectal	29	51	60	45	Max 50
Koelblinger [52]	2014	22	RFA	Sarcoma	20	51[a]	85	NR	7 (5–20)

[a] Mean data

Max = maximum tumor diameter; NR = not recorded; OS = overall survival; RFA = radiofrequency ablation.

Another study reported 95 patients with 134 metastases [55]. Patients with up to 4 metastases were included. Median survival was 38 months, and 3-year survival was 56.2%. There was no grade 4 or higher complications. Univariate analysis demonstrated the number of metastases and use of prior chemotherapy affected outcome.

Navarria and colleagues [56] reported 76 consecutive patients of variable histology with 118 lung lesions. Eligible patients had up to 5 tumors treated. Dose prescription varied for central and peripheral tumors as well as for larger versus smaller tumors. Although 80% of patients presented with grade 1 pulmonary toxicity (mostly radiation fibrosis in <25% of the lung), no grade 2 or higher pulmonary toxicity was reported. Survival at 3 years was 73%. The same group also reported a study of 28 patients with 51 sarcoma metastases [57]. There was no grade 3 or higher acute toxicity, and 5-year survival was 60.5%. This compares well to the 5-year survival reported in Table 2 for ablation of sarcoma metastases.

Regarding colorectal metastases, we included two studies. Overall survival in one study was 39% at 5 years and was 58% at 3 years in the second [58, 59].

FACTORS TO CONSIDER WHEN SELECTING THERAPY. The availability of thermal ablation and SABR provides additional tools for treating patients with pulmonary metastases. Generally, patients treated in these studies included patients in whom prior therapies failed, who were considered nonsurgical candidates, or who refused surgery.

In the absence of randomized comparisons with surgery (even for primary lung cancer), it is reasonable to reserve these therapies for such patients. In addition, we suggest that ablation/SABR be considered an option for patients who present with ipsilateral metastases after prior metastasectomy. The morbidity of reoperation is avoided, and such patients are likely at risk for a third recurrence.

SABR has a potential to affect pulmonary function in the long-term, particularly if multiple areas in the lung are treated. In addition, a larger number of thermal ablation studies provided follow-up beyond 2 years. For this reason, we favor ablation over SABR. However, ablation has been shown to be less effective for larger tumors in lung cancer patients, with higher local failures [43]. SABR would therefore be preferable for tumors larger than 3 cm (perhaps 2 cm) when resection is not an option (Fig 3).

Table 3. Survival After Stereotactic Ablative Body Radiotherapy for Pulmonary Metastases

First Author [Reference]	Year	Patients (No.)	Pathology	Median Follow-Up (months)	Median OS (months)	3-Year Survival (%)	4-Year Survival (%)	5-Year Survival (%)
Nuyttens [54]	2015	30	Mixed	36	36	NR	38	NR
Wang [55]	2015	95	Mixed	17	38	56.2	NR	NR
Navarria [57]	2015	28	Sarcoma	21	27.8	NR	NR	43.3
Navarria [56]	2014	76	Mixed	18	20	73	NR	NR
Comito [59]	2014	40	Colorectal	24	NR	58	NR	NR
Aoki [60]	2016	66	Mixed	31.7	NR	76	NR	NR
Singh [61]	2014	34	Mixed	16.7	NR	23	NR	NR
Baschnagel [62]	2013	32	Mixed	27.6	40	63	NR	NR
Filippi [58]	2015	40	Colorectal	20	46	NR	NR	39

NR = not recorded; OS = overall survival.

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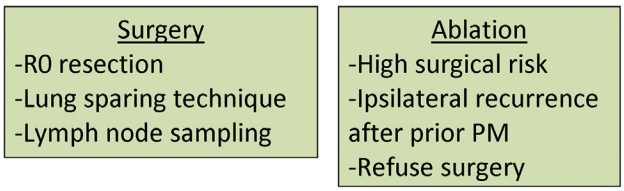

Fig 3. Pulmonary metastasectomy (PM) local therapeutic possibilities.

Consensus Statement

8. Thermal ablation or SABR is reasonable therapy for patients with pulmonary oligometastases, particularly for patients considered high-risk for resection or who refuse resection.

Strongly Agree: 58% Agree: 25% Neutral: 8% Disagree: 8% Strongly Disagree: 0%

Lung Perfusion for Metastasis

Isolated lung perfusion (ILP) is a surgical technique developed to deliver high-dose chemotherapy to the lung, minimizing systemic exposure by selectively delivering the agent though the pulmonary artery and selectively diverting venous effluent. ILP has the theoretical advantage of delivering high-dose drug treatment to the lung while limiting exposure of sensitive critical organs, thus avoiding severe complications. Moreover, ILP minimizes the effect of active drug loss from renal metabolism of the drugs [63]. The lung was identified as an ideal organ for isolated perfusion because of its symmetry, exclusive arterial supply from the pulmonary artery, venous drainage into 2 pulmonary veins, and tolerance for hyperthermic conditions without significantly impairing systemic function [64–66]. Johnston and colleagues [67] began research into ILP in 1983, investigating the toxicity and pharmacokinetics of doxorubicin in addition to the effect of hyperthermia on lung function and uptake of doxorubicin during ILP.

There are two perfusion techniques: a single pass and a recirculating blood circuit. The single pass removes the venous effluent after circulating the chemotherapeutic agent through the lung one time versus a recirculating blood circuit that collects the effluent and redelivers the drug to the lung. Technical variations include antegrade versus retrograde perfusion, blood flow occlusion techniques, endovascular blood flow occlusion, delayed clamp release, and selective endovascular pulmonary artery perfusion [68].

In 1995, Pass and colleagues [69] conducted a phase I trial looking at the safety and feasibility of ILP with tumor necrosis factor-α and interferon-γ in 15 patients. Three partial responses were seen within 8 weeks of ILP; however, new nodules or regrowth appeared 7 to 9 months postoperatively. The nonperfused side in all patients, exhibited stable or worsening disease by 8 weeks postoperatively [69]. In 1996, Ratto and colleagues [70] performed cisplatin-based ILP in 6 patients with lung metastases from sarcoma. The authors completed all procedures without complications intraoperatively and no intraoperative or postoperative deaths. In 2 of 6 patients, a "contusion syndrome" occurred—radiographic signs of interstitial and alveolar edema. At 13 months, 4 of 6 patients were alive without evidence of disease recurrence. One patient died of extrapulmonary metastases, and 1 patient had distant disease relapse. Chemotherapy toxicity occurred in none of the patients. In addition, they performed staged lung perfusion on 2 patients with bilateral disease and determined it was safe.

In a second human study performed by Schröder and colleagues [71], 4 patients with sarcoma lung metastases underwent ILP with high-dose cisplatin and hyperthermia. Two of these patients had bilateral disease. Three patients were alive and disease free at 12 months. The fourth patient died of cerebral metastases without evidence of local disease recurrence [71].

Burt and colleagues [72] conducted a phase I trial of ILP with doxorubicin for patients with unresectable sarcoma pulmonary metastases. Of 8 patients who were enrolled, 7 were treated with 40 mg/m^2 or less, and 1 patient received 80 mg/m^2. There were no perioperative deaths. Six patients died of disease on follow-up out to 28 months. Unfortunately, there were no partial or complete responses to treatment. Only 1 patient showed stabilization of the lesions in the perfused lung compared with the contralateral lung.

In 2004, Hendriks and colleagues [73] conducted a phase I trial for ILP with melphalan. There were 16 patients divided into eight groups, all of whom had pulmonary metastases from melphalan-sensitive tumors. There were no operative or postoperative deaths. Lung edema developed in 2 patients who received 60 mg melphalan at 37°C, and roentgenogram findings resembled a chemical pneumonitis. During long-term follow up, 7 of 16 patients had recurrent disease; 4 of 7 had disease outside of the lung, and 1 of 7 was in the previously perfused lung [73].

Complications of ILP have been limited to the lungs, with transient pneumonitis, pulmonary edema, and decreases in forced expiratory volume in 1 second and diffusion capacity of the lung for carbon monoxide. Significant systemic toxicity has largely been avoided, with the exception of reported doxorubicin cardiac toxicity [68].

Despite a handful of phase I clinical trials showing that ILP can be performed in humans, the results are mixed, and poor long-term survival in these patients is the most common outcome. Continued clinical development of ILP is controversial, considering the evolution of novel therapeutics such as biologic-targeted therapies and immunotherapy.

Consensus Statement

9. Outside of clinical research, ILP is not warranted for management of pulmonary metastases.

Strongly Agree: 75% Agree: 17% Neutral: 8% Disagree: 0% Strongly Disagree: 0%

Cancer Type-Specific Management of Pulmonary Metastases

Colorectal Cancer

A Surveillance, Epidemiology, and End Results database study observed that approximately 5% of colorectal cancer patients had lung metastasis at the initial staging. Incidence of lung metastases was higher among rectal primaries (5.6%) versus colon cancer (3.7%) [74]. Other studies report a 5% to 15% incidence of lung metastases, including metachronous disease [75]. Pulmonary metastases developed in only a small fraction of patients with colorectal cancer; however, because this malignancy is common, management of pulmonary metastases from colorectal cancer remains an important oncologic challenge.

Traditionally, the goal of PM in colorectal cancer is to achieve cure in a patient population in which metastatic disease usually connotes incurable. For example, Hou and colleagues [76] reported survival of colorectal cancer patients with lung metastasis managed with the inclusion of PM. Whether by thoracoscopic surgery or open surgery, the OS curve reached a plateau with long-term follow-up. The 5-year overall survival rate was 50% and 46% ($p = 0.251$) by thoracoscopy or open surgery, respectively. The 5-year DFS rate approximated 35% to 40% for both surgical groups.

CLINICAL DATA AND PM. Patient selection is at the core of the literature addressing PM in colorectal cancer. Centers performing PM commonly use resectability and medical operability as the initial basis for considering PM. Characteristics predicting a lower risk for recurrent cancer or a longer lifespan, or both, promote consideration of metastasectomy. Treasure and colleagues [77] in 2014 summarized the prior findings of the landmark IRLM. Within the IRLM, colorectal cancer was the most common pathology. Lower survival was predicted by multiple metastases, carcinoembryonic antigen elevation, and a shorter or no interval (ie, synchronous metastases) DFI between primary resection and development of metastasis.

A systematic review and meta-analysis of risk factors for survival after PM in colorectal cancer was published in 2013 [78]. Approximately 3,000 patients from 25 studies published since 2000 were analyzed. Four factors were associated with poor survival:

1. short DFI between primary tumor resection and development of lung metastases (hazard ratio [HR], 1.59; 95% confidence interval [CI], 1.27 to 1.98);
2. multiple lung metastases (HR, 2.04; 95% CI, 1.72 to 2.41);
3. involvement of hilar or mediastinal LNs, or both (HR, 1.65; 95% CI, 1.35 to 2.02); and
4. elevated preoperative carcinoembryonic antigen (HR, 1.91; 95% CI, 1.57 to 2.32).

Interestingly, as other subsequent surgical series reported, a history of resected liver metastases (HR, 1.22; 95% CI, 0.91 to 1.64) did not achieve statistical significance as a poor predictor of survival. How such predictive indicators should be integrated into decision making regarding PM remains unclear.

Data primarily from retrospective reports of selected patients, typically with oligometastatic lung disease, show 5-year survival rates after PM of 30% to 60%. At least a few hundred studies of PM for colorectal cancer have been published, all with the failings discussed previously. A 2010 summary of more than 1,300 PM patients from 11 publications, with four reports including patients managed with both liver and lung metastasectomy, stipulated inclusion criteria of publication after 1989, at least 40 patients, and median follow-up of at least 20 months [79]. The mean age was 59 to 63 years. Most patients within each series had a solitary lung metastasis (26% to 75%). In addition to 5-year survival rates of 33% to 65% in this review, 30-day operative mortality rates were very low (0% to 2.4%). Long-term survival in this patient population reflects a combination of surgical resection and neoadjunctive or adjunctive chemotherapy, or both. Whether surgery or selection bias determined the long-term survival is unclear [77].

Only a randomized clinical trial will definitively determine the value of PM for colorectal cancer. The Randomised Trial of Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) study (NCT01106261), completed its feasibility phase with enrollment of 70 patients and began the formal randomized phase III trial portion in 2015 [80]. The United Kingdom-based, multicenter study plans to recruit 300 patients with colorectal adenocarcinoma and lung oligometastases who undergo clinical evaluation and MDT case review to determine appropriateness of PM. Candidates are offered study participation and randomized to PM or observation as part of their overall oncologic therapy. Overall survival is the primary end point of the phase III trial, with secondary end points to include lung function, patient-reported quality of life, and health economic assessment.

PERIOPERATIVE SYSTEMIC THERAPY. Without guidance of randomized controlled trial evidence, a common practice approach relies on extrapolation from the more general colorectal cancer literature. Adjuvant chemotherapy provides a benefit in DFS and OS in resected stage III and likely high-risk stage II colon cancer. Given the recurrence risk is even higher for resected stage IV colorectal cancer, many oncologists accept the use of chemotherapy in the setting of colorectal cancer PM using the same course of fluoropyrimidine or doublet fluoropyrimidine and oxaliplatin as used in resected stage III disease.

A large randomized clinical trial showed the use of perioperative adjunctive chemotherapy for resectable liver metastases in colorectal cancer is safe and prolongs DFS. No effect on OS was observed with longer follow-up [81, 82]. The European Organisation for Research and Treatment of Cancer (EORTC) 40983 study randomized 364 patients to liver metastasectomy only versus liver metastasectomy and perioperative chemotherapy with fluorouracil, folinic acid, and oxaliplatin (FOLFOX4 regimen) with median follow up of 8.5 years. The initial publication in 2008 [81] noted several versions of analysis,

but with all randomized patients analyzed, the absolute increase in rate of progression-free survival at 3 years was 7.3% (from 28.1% [95% CI, 21.3 to 35.5] to 35.4% [95% CI, 28.1 to 42.7]; HR, 0.79; 95% CI, 0.62 to 1.02; $p = 0.058$). Follow-up reporting in 2013, described a median survival of 61.3 months (95% CI, 51.0 to 83.4 months) and 5-year survival of 51.2% (95% CI, 43.6% to 58.3%) in the perioperative chemotherapy group, and median survival of 54.3 months (95% CI, 41.9 to 79.4 months) and 5-year survival of 47.8% (95% CI, 40.3% to 55.0%) in the surgery-alone group.

CURRENT CANCER MANAGEMENT SOCIETAL GUIDELINES. In the United States, the National Comprehensive Cancer Network Guidelines form the basis for clinical practice standards, particularly with more common cancers. The National Comprehensive Cancer Network Guidelines for colon cancer recommend for patients with resectable lung metastases in isolation or together with liver metastases to be considered for metastasectomy [83]. The strength of recommendation is category 2A ("Based upon lower-level evidence, there is NCCN [National Comprehensive Cancer Network] consensus that the intervention is appropriate."). No distinction is made regarding the strength of the recommendation in terms of synchronous or metachronous metastases.

The European Society of Medical Oncology consensus guidelines for the management of patients with metastatic colorectal cancer were updated in 2016 [84].

- For patients with oligometastatic disease, systemic therapy is the standard of care and should be considered as the initial part of every treatment strategy (exception: patients with single/few liver or lung lesions; see below).
- The best local treatment should be selected from a "toolbox" of procedures according to disease localization, treatment goal ("the more curative the more surgery"/higher importance of local/complete control), treatment-related morbidity, and patient-related factors, such as comorbidity/ies and age (Level IV, Grade B).

(Level of evidence [IV of I-V range]: Retrospective cohort studies of case-control studies. Grade of evidence [B of A-E range]: Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended.)

The United Kingdom National Institute for Health and Care Excellence addressed the role of resection for metastatic colorectal cancer that gives deference to an MDT assessment, presumably to enhance the likelihood of evidence-based medical decision making. In addition, systemic therapy is recommended as initial therapy [85].

Consensus Statement

10. In colorectal cancer patients, PM can be considered within an MDT construct, with systemic therapy before or after PM.
Strongly Agree: 92% Agree: 8% Neutral: 0% Disagree: 0% Strongly Disagree: 0%

Renal Cell Carcinoma

Approximately one-third of patients with renal cell carcinoma present with synchronous metastatic disease [86]. Surgical approach is typically thoracotomy, but approach did not affect long-term survival in a series of 191 patients if R0 resection was accomplished [87]. The extent of surgical resection varied from wedge to lobectomy. Reported 30-day perioperative mortality rates ranged from 0% to 2.1% [15, 88, 89]. Surgery-specific survival is confounded by inclusion of adjuvant chemotherapy, immunotherapy, or extrathoracic metastasectomies in many series [15, 88–92]. In reports over the past 15 years, median survival ranged from 21 to 44 months (Table 4).

Specific predictive factors examined include completeness of resection, DFI, number, size, and pulmonary location of metastases, age, tumor grade, and sex. In Hofmann and colleagues [97], there were no survivors at 5 years if resection was incomplete versus 39% at 5 years. They reported number of metastases and 5-year survival was 54.7% for 1 metastasectomy versus 32% for 2 to 6 metastases [97]. A Japanese single-institution case series of 25 patients over 10 years reported overall 3-year survival of 53% and 5-year survival of 35.5% with a 34-month median survival. Interestingly, DFI, location, and number of metastases, as well as completeness of resection, were not significant predictive indicators [93]. The number of metastases was not important in multivariate analysis of 105 patients, but nodal involvement was a negative predictive factor [89].

An Italian single-institution review of 48 patients between 1973 and 2008 reported the median survival was similar at 39 months and was 60% at 3 years, 47% at 5 years, and 18% at 10 years [94]. In a Mayo Clinic study reporting metastasectomy from multiple sites, completeness of resection was predictive: an incomplete PM negatively affected 5-year survival with a significant decrease from 73.6% to 12.95% at 5 years [92]. Similarly, the Cleveland Clinic in 2005 reported complete resection improved 5-year survival from 8% to 42% [15]. In two series of 105 and 191 patients, completeness of resection was important for survival, as was size of the lesions [87, 89].

Age has been identified as positive predictive indicator. A previous citation reported age older than 60 years having a 5-year overall survival of 70% versus 37% if younger than 60 [96]. Similarly, older patients did better in a series of multiple organ metastases. The 5-year DFS was 22%, lower than when compared with metastasectomies from other sites [90]. Sex and tumor grade were not significant predictive factors in a 1985 to 1999 German series [87].

Consensus Statement

11. In renal cell carcinoma patients, PM can be considered within an MDT construct.
Strongly Agree: 92% Agree: 8% Neutral: 0% Disagree: 0% Strongly Disagree: 0%

Malignant Melanoma

Metastatic disease after initial treatment of malignant melanoma is found in approximately 30% of patients.

Table 4. Survival After Pulmonary Metastasectomy in Renal Cell Carcinoma

First Author [Reference]	Year	Patients (No.)	Median Survival (months)	Overall Survival		
				3-Year (%)	5-Year (%)	10-Year (%)
Kawashima [93]	2011	25	33.9	53.3	35.5	NA
Kanzaki [94]	2011	48	39	60	47	18
Assouad [95]	2007	65	NA	NA	34.4	NA
Marulli [96]	2006	59	NA	63	53	NA
Murthy [15]	2005	92	44.4	49	31	NA
Piltz [89]	2002	105	NA	54	40	33
Pfannschmidt[87]	2002	191	21.4	NA	41.5	NA

NA= not available.

Historically, median survival only reached 6 to 8 months, with an estimated 5-year survival of less than 5% [98]. The incidence of pulmonary metastases in patients diagnosed with melanoma ranges between 30% and 40%. The most common first visceral metastatic site for melanoma in large series is the lung [99]. In an analysis of 1,158 patients harboring melanoma metastases in visceral sites, those with only lung metastases had improved survival compared with other visceral sites [100]. Systemic therapy remains the mainstay for treatment in stage IV disease, but conventional chemotherapy and interleukin 2 have been toxic and disappointing. Historical data published in 1998 from the IRLM suggested PM for advanced-stage melanoma had the worst outcome compared with germ cell tumors, epithelial tumors, and sarcoma [6]. The probability of melanoma relapse in this surgical series (n = 328) was 64%, where 73% of relapses involved extrathoracic organs. Despite historical reports of poor prognosis for advanced melanoma, immune check-point inhibitors have greatly affected survival since 2011, where subgroups of patients can achieve 2-year survival of 60% [101]. In a contemporary analysis of 441 patients with stage IV melanoma from 2011 to 2014, the best overall survival was observed in patients treated with metastasectomy as the primary treatment with R0 intent [102].

Favorable outcomes resulting from surgical resection of distant melanoma metastases in selected patients have been demonstrated in surgical series dating back to the 1990s [16, 103, 104]. Several studies investigated the role of PM in advanced melanoma, reporting 5-year survival rates of approximately 40% in highly selected patients with median follow-up of 18 to 55 months [105, 106]. Independent prognostic variables for improved overall survival in these series included tumor doubling time exceeding 60 days, tumor size of less than 2 cm, number of lung metastases (≤1), complete resection, and the absence of extrapulmonary disease. Patients with multiple pulmonary metastases (>5) and no extrapulmonary disease were still able to achieve a 5-year survival of 19% [105]. In 1,720 patients with pulmonary metastases from melanoma, 318 patients underwent PM. The greatest benefit of metastasectomy in the surgically treated patients was observed in patients who presented with a DFI of more than 5 years and harbored no extrathoracic disease. Complete resection was accomplished in 249 (78%) of these patients [107].

In addition to the tenants of (1) primary site control, (2) no extrathoracic sites of disease, (3) "long" DFI, and (4) "limited" number of pulmonary metastases, within a paradigm of systemic immunotherapy for metastatic melanoma, anecdotally incomplete response of residual pulmonary metastases has been considered for PM.

Consensus Statement

12. In malignant melanoma patients, PM can be considered within an MDT construct.
Strongly Agree: 75% Agree: 25% Neutral: 0% Disagree: 0% Strongly Disagree: 0%

Sarcoma

Pulmonary metastases with disease progression develop in approximately 20% to 40% of sarcoma patients, often with the lung as the only site [108–114]. Because chemotherapy historically has limited response in sarcoma patients, PM is an accepted, even preferred, treatment for patients with lung lesions. Nevertheless, as with other pathologies, sarcoma PM is not common. Nationwide data from Iceland described 81 patients treated for sarcoma over a 24-year period, and only 5 (6.5%) underwent PM [3].

Commonly reported data may identify several predictive indicators of increased survival, including (1) metachronous versus synchronous, (2) DFI exceeding 12 months, (3) younger age, (4) limited number of metastases, (5) low pathologic grade, and (6) complete resection [31, 115, 116]. There is no agreed-upon number of lesions at which resection is thought to be futile, but achieving complete resection or reaching disease-free status is likely more difficult with more lesions. Furthermore, timing of resection remains controversial [117]. Molecular markers as prognostic indicators have been reported but not widely adopted [118].

Despite aggressive resection strategies, 5-year survival of sarcoma patients with pulmonary metastases is only 30% to 50% [3, 5, 108, 111, 115, 119, 120]. Many patients experience pulmonary recurrence, although there are reports of "benefit" from a second PM [111, 121].

There appears to be a small survival difference for different sarcomas, with gynecologic sarcomas showing

better survival than osteosarcomas, which in turn have slightly improved survival compared with other sarcomas [122–124].

Combined treatment, that is, resection plus another local therapy (eg, SABR), has been reported and represents a trend in treating all metastases while reducing resection of pulmonary tissue [125]. ILP with high-dose chemotherapy at the time of resection has also been reported, with modest benefit [126].

Consensus Statement

13. In sarcoma patients, PM can be considered within an MDT construct.
Strongly Agree: 92% Agree: 8% Neutral: 0% Disagree: 0% Strongly Disagree: 0%

Head and Neck Cancers

Even though the metastasis rate from HNSCC is low and depends on locoregional control and LN status, the lungs account for up to 70% to 85% of HNSCC metastases [127]. Differentiating a primary lung squamous cell carcinoma from lung metastasis in a patient with HNSCC is challenging with the use of standard histopathology techniques. Lung squamous cell carcinoma and HNSCC have features in common, including histology, epithelial cells of origin, and association with tobacco. Although attempts have been made to distinguish metastases from primary lung cancer using genomics, including loss of heterozygosity [128] and microRNA profiling [129], there is no gold standard to validate therapeutic approaches and potentially introduces selection bias in addressing the role of PM [19, 130–132].

There are approximately 20 retrospective reports over the past 20 years in which authors reviewed single-institutional experience with PM alone (Table 5). Only two reports have retrospectively compared chemotherapy versus PM [133, 134].

Positive predictive factors for PM alone include DFI, sex, age, site of origin of primary head and neck cancer, and completeness of resection. In 1992, Finley and colleagues [135] reported no 5-year survivors in 18 patients treated surgically if their DFI was less than 1 year but concluded that resection of solitary metastases resulted in long-term survival. Similar conclusions were reported by Wedman and colleagues [136] in describing 138 patients with pulmonary metastases from HNSCC, 21 of whom underwent PM. There was a 5-year survival of 59% in those undergoing lung resection compared with 4% for those who did not, concluding that a long but undefined DFI may select long-term survivors. A DFI of less than 12 months was noted to be a negative prognostic factor in several small series [131, 135, 137], whereas other studies state 24 to 26 months as the significant DFI resulting in more favorable outcome [19, 132, 138, 139]. Male sex has been found to be unfavorable [19, 137].

Histologic origin of the metastases is important. HNSCC versus glandular tumors was a poor prognostic factor in a small series [137]. In a larger study comparing PM for HNSCC versus glandular-origin head and neck tumors, the overall 5-year survival rate for the glandular tumors was 64% versus 34% [138]. However, the squamous cell carcinoma patients had potentially confounding worse predictive factors such as non-R0 resection, shorter DFI (<2 years), and older age. Similarly in two larger series, completeness of resection translated into improved outcome [19, 133], but presence of nodal metastases was unfavorable [19]. The fact that metastases from squamous cell carcinoma origin do worse than those from glandular may reflect sampling bias and difficulty in distinguishing them from primary lung squamous cell carcinoma, which are potentially undertreated with suboptimal resection.

As mentioned above, resection versus chemotherapy with matched-pair analysis concluded PM resulted in significantly better survival. PM led to median survival of 19 versus 5 months [133] and overall 3-year survival of 68% versus 15% [134].

Consensus Statement

14. PM in management of primary head and neck cancer can be considered in the context of DFI exceeding 12 months, ability to completely resection, and absence of LN metastases.
Strongly Agree: 42% Agree: 42% Neutral: 8% Disagree: 8% Strongly Disagree: 0%

Nonseminomatous Germ Cell Tumors

The lung is the most common site of visceral metastases from hematogenous dissemination. In contrast to other

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Table 5. Survival After Pulmonary Metastasectomy in Head and Neck Cancer

First Author [Reference]	Year	Patients (No.)	Median Survival (months)	Overall Survival (%)	
				3-Year	5-Year
Yotsukura [132]	2015	34	77	NA	NA
Miyazaki [134]	2013	24	NA	68	NA
Haro [130]	2010	21	NA	53.3	NA
Daiko [139]	2010	33	21	43	NA
Winter [133]	2008	67	19.4	NA	20.9
Shiono [19]	2009	114	26	NA	26.5
Chen [137]	2008	20	NA	NA	59.4
Nibu [140]	1997	32	NA	NA	32

NA = not available.

solid neoplasms, however, metastatic involvement of the lung or mediastinum represents American Joint Committee on Cancer Stage III disease [141]. The paradigm of platin-based chemotherapy, followed by surgery, to remove residual disease for the treatment of NSGCTs is considered one of the most successful models of multimodality cancer therapy. Recommendations for postchemotherapy PM are based on multiple factors, including the serologic and radiographic response to chemotherapy, the presence or absence of teratomatous pathology in the orchiectomy specimen, and if performed before any thoracic surgical procedure, the pathologic findings of postchemotherapy retroperitoneal LN dissection (RPLND) because there is a high correlation between RPLND and lung pathology [142, 143]. Significantly elevated STMs α-fetoprotein and β-human chorionic gonadotropin after chemotherapy have a high sensitivity for persistent NSGCT [144]. STMs normalize in most patients after first-line chemotherapy, typically signifying resolution of the malignant nonseminomatous components with residual "benign" disease. Patients who demonstrate serologic progression of disease with persistent STM elevation after first-line chemotherapy are typically given second-line platin-based chemotherapy, including consideration of high-dose chemotherapy with autologous stem cell transplant [145].

Many patients with stage III disease will completely resolve or have only minor residual lung abnormalities (<10 mm) after cisplatin-based chemotherapy. Observation is then warranted. An estimated 10% to 20% of all patients with testicular NSGCT will have residual pulmonary disease after chemotherapy or subsequently manifest pulmonary disease during follow-up and warrant consideration of PM [146, 147]. In approximately one-half of these patients, there is residual mediastinal disease that also requires removal and needs to be part of surgical planning. Unfortunately, no accurate models exist for distinguishing complete tumor necrosis from remaining pathology for postchemotherapy pulmonary abnormalities. In addition to testicular/RPNLD pathology containing teratoma and normalized STMs, CT findings suggestive of pulmonary teratoma include a rounded or cystic appearance. Although considered "benign," teratoma has local growth potential as well as malignant transformation; therefore, surgery is recommended with high cure rates [148–150]. Moreover parenchymal-sparing techniques involving "shelling out" of teratoma are efficacious, avoiding large pulmonary resections [146]. If PM in 1 lung is pathologically complete tumor necrosis, abnormalities in the contralateral lung are observed, because there is a 90% pathologic concordance between lungs [151]. Less commonly, malignant residual disease in the form of persistent NSGCT or malignant transformation of teratoma into non-germ cell cancer is present and may be anticipated by elevated STMs or testicular/RPNLD pathology, or both. In these cases, PM is undertaken in select patients to remove a limited number of areas, because cure is possible but significantly lower compared with PM for teratoma [149, 152–154]. In contrast to teratoma, which has low metabolic activity, PET imaging can be helpful to determine resectability in patients when residual malignant disease is suspected. Standard wide local excision (wedge) is used. Adequate surgical margin less commonly requires anatomic pulmonary resection.

PM after platin-based chemotherapy in the treatment of NSGCT of testicular origin has high curative potential, with 5-year survival rates ranging from 59% to 94%. Although prospective randomized studies are lacking, high cure rates after PM generate a strong bias toward surgery. Prognostic factors include International Germ Cell Cancer Cooperative Group risk (low, intermediate, or high) at the time of presentation and histology of resected disease after chemotherapy (benign: necrosis/teratoma; malignant: persistent NSGCT/malignant transformation into non-germ cell cancer).

Consensus Statements

15. When managing NSGCTs, PM is indicated for all residual lung abnormalities ≥ 10 mm after platin-based chemotherapy with normalized STMs suspected of containing teratoma.
Strongly Agree: 67% Agree: 25% Neutral: 8% Disagree: 0% Strongly Disagree: 0%

16. When managing NSGCTs, contralateral lung abnormalities can be observed if histology of unilateral PM demonstrates complete tumor necrosis.
Strongly Agree: 46% Agree: 46% Neutral: 8% Disagree: 0% Strongly Disagree: 0%

17. When managing NSGCTs, PM is indicated for select patients with limited number of lung abnormalities after first-line or second-line platin-based chemotherapy suspected of containing viable nonseminomatous cancer or malignant transformation of teratoma into non-germ cell cancer, or both.
Strongly Agree: 67% Agree: 33% Neutral: 0% Disagree: 0% Strongly Disagree: 0%

Breast Cancer

The incidence of pulmonary metastases in patients diagnosed with breast cancer ranges between 7% and 24% [155]. The initial purpose of performing metastasectomy in most breast cancer patients is to confirm the diagnosis, establish hormone receptor status, and rule out other primary or metastatic cancers. Therapeutic PM in management of metastatic breast cancer is controversial. Breast cancer metastatic to lung is regarded as a systemic disease with no clear role for therapeutic PM. Despite this accepted practice pattern, several retrospective studies suggested a potential survival advantage in highly selected breast cancer patients undergoing PM for isolated or limited disease [6, 156–162]. A meta-analysis of 16 studies evaluating 1,937 patients undergoing breast cancer PM reported a 5-year survival of 46% [163]. Poor

predictive factors were DFI of less than 3 years, incomplete resection, more than 1 metastasis, and negative hormone receptor status. In contrast, a 5-year survival of 16% was reported in a case series of breast cancer patients with metastases limited to the lungs and treated with chemotherapy alone [164]. Similar to metastatic disease from other solid organs, PM of multiple or bilateral breast cancer metastases was associated with poor outcome [165]. This concept is emphasized by a report of 81 patients with metastatic breast cancer with improved overall survival (103 vs 37 months) in patients harboring a single versus multiple sites of disease [20]. The extent of pulmonary resection and approach does not appear to influence survival [20, 165].

Because many publications investigating the management of stage IV breast cancer with pulmonary metastases included patients on systemic therapy (hormonal, cytotoxic, or targeted), the true contribution of PM to long-term survival is unclear. Staren and colleagues [158] examined medically treated patients with or without PM and found a significant survival improvement with the addition of PM (34 vs 58 months). Survival at 5 years was 11% in the medically treated group compared with 36% in the surgical group [160]. Chemotherapy before or after PM did not influence overall survival in a cohort of 467 PM breast cancer patients [156].

There is evidence suggesting using PM in breast cancer patients harboring hormone receptor–positive (either estrogen receptor-positive or human epidermal growth factor receptor 2 [Her2]-neu) disease appears to have a survival advantage over receptor-negative disease, with 5-year survival of 77% versus 12%, respectively [158]. The presence of mediastinal LN metastases with breast cancer lung metastases portends a worse prognosis [20, 166]. However, a recent review concluded that in view of the present relatively good survival among patients with metastatic breast cancer, the added value of PM is unclear [167].

Consensus Statement

18. In breast cancer patients, PM can be considered within an MDT construct.
Strongly Agree: 58% Agree: 33% Neutral: 8% Disagree: 0% Strongly Disagree: 0%

Conclusion

Best practice for PM in cancer management remains uncertain. As with other areas of oncology care, physicians must hold themselves to evidence-based clinical standards, as best as possible, and avoid the trap of doing something because it can be done. The art of medicine is alive and well in many aspects of oncology care. Ideally, continual review of current oncologic literature, familiarity with national and societal guidelines, multidisciplinary, and shared decision-making approach to patient care provides a framework for clinical care recommendations, even when a pure evidence-based approach is not possible.

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