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 PD-L1 to guide future therapies.

3. In oncologically and medically appropriate patients, PM can be considered with a preference for minimally invasive surgery (MIS) due to shortened postoperative recovery and lessened impact on quality of life.

4. If goals of R0 and pulmonary parenchymal sparing are not accomplishable via MIS but loan themselves to open approaches (thoracotomy/sternotomy/clam shell), open techniques are appropriate.

5. Pneumonectomy to accomplish PM is discouraged except in carefully selected patients undergoing multidisciplinary management.

6. Although absolute number of pulmonary metastases is not a direct contraindication to PM, candidate selection for PM is best suited to patients harboring ≤ 3 pulmonary metastases.

7. LN sampling / dissection concomitant with PM should be considered since pulmonary metastasis accompanied by mediastinal LN metastasis predict 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 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 a MDT construct with systemic therapy before or after PM.

11. In renal cell carcinoma patients, PM can be considered within a MDT construct.

12. In malignant melanoma patients, PM can be considered within a MDT construct.

13. In sarcoma patients, PM can be considered within a MDT construct.

14. PM in management of primary head & neck cancer can be considered in the context of DFI >12 months, ability to completely resection and absence of LN metastases.

15. When managing nonseminomatous germ cell tumors, PM is indicated for all residual lung abnormalities after platin-based chemotherapy with normalized STM suspected of containing teratoma.

16. When managing nonseminomatous germ cell tumors, contralateral lung abnormalities ≤ 10 mm can be observed if histology of unilateral PM demonstrates complete tumor necrosis.

17. When managing nonseminomatous germ cell tumors, PM is indicated for select patients with limited number of lung abnormalities after first or second-line platin-based chemotherapy suspected of containing viable nonseminomatous cancer and/or malignant transformation of teratoma into non-germ cell cancer.

18. In breast cancer patients, PM can be considered within a MDT construct.

Introduction

Pulmonary metastasectomy (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.

Pulmonary metastasectomy literature characteristics

Since 1980, greater than 1000 publications addressed pulmonary metastasectomy, without a single randomized controlled trial (RCT). The overwhelming majority is surgical series, usually single institution, and includes 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 (1-6.5%) 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 which 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, non-pulmonary metastatic sites, non-R0 resection and positive mediastinal lymph nodes (LNs), all of which are usually considered operative contraindications, furthering the selection bias of surgical series. [4,5]
A few registry articles (8 in total) have largely defined practice. The most influential reported 5206 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

General Characteristics of the PM Literature
No RCTs
Pervasive selection bias
No comparative survival analysis
Inconsistent description of accompanying local or systemic therapies
Variable follow up length
Fail to distinguish between prognostic or predictive characteristics
Does not clarify the role of PM 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 in order to provide clinically-relevant guidance to clinicians in spite of the above-stated limitations of the PM literature. Relevant literature was searched for in MEDLINE for articles published in English since 1990, using MeSH terms "lung neoplasms + secondary," "metastasectomy, "pneumonectomy," "thoracotomy," "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 due 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 five-point Likert scale. An 80% response rate amongst 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 ACCF/AHA classification system used in clinical practice guidelines to rate the strength and level of evidence was not utilized for this paper, as 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 non-localized disease setting. It is important to define the clinical setting and the goals of treatment.

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 it makes little sense to undertake PM if there are other sites of disease unaddressed. We acknowledge that this widely held consensus is based on rationale alone (no data is available for PM in the face of multiple unaddressed other metastatic sites). However, this represents an "unopposed rationale," as 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 [e.g., 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 paper 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 paper.

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). While simple and appealing, this concept is countered by many observations [7]. Different primary tumors exhibit a predilection for particular metastatic sites. Additionally, circulating tumors 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 (e.g. a permissive microenvironment, angiogenesis, 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 vs an indolent tumor. Simple definition of the rate of achieving long-term DFS would be clinically useful (even without a no treatment [i.e. 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; it 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, breast cancer), the time of cancer diagnosis, interval between primary tumor resection (disease free interval, DFI), presence of other metastatic sites and type of prior systemic therapy impact decisions about PM. Patients with the smallest disease burden at initial diagnosis, longer interval since 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, 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 number of metastases. When these criteria are achieved, the tail or flattening of OS curves in contemporary reports include colorectal (OS 20-52% at 7-9 yrs)[13, 14], renal cell carcinoma (OS 33% 7 yrs) [15], melanoma (OS 14% 10 yr)[16], soft tissue sarcoma (OS 11- 23% 7-11 yrs) [17, 18], head and neck squamous cell cancer (OS 18% 13 yrs) [19], breast cancer (OS 40% at 18 yrs) [20] and hepatocellular carcinoma (OS 38% over 10 yrs) [21].

Is PM associated with prolonged survival (without cure)?

Assessment would involve overall survival of patients undergoing PM compared with a similar cohort not undergoing PM. The fact that to assess this requires not just a survival rate but a comparable comparison group makes it difficult to acquire evidence for prolongation of survival. When reported, OS is larger than DFS, implying a possible survival prolongation from

PM: colorectal - 9 yrs OS 52%, DFS 38%[12], 7.5 yrs OS 20% DFS 17.5%; [13] soft tissue sarcoma – 7 yr OS 23% DFS 8%; [16] hepatocellular carcinoma – 10 yr 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 pre-cancer, lack of other metastatic sites and interval between primary and secondary tumor diagnosis may suggest second primary rather than metastatic disease. [23] Resection of true second primaries have a high likelihood of cure, so when in doubt, pursue resection. [24] Small series have shown 5 years 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, since 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**

Multi-disciplinary team (MDT) management should be the hallmark of both treatment and patient selection. The timing of metastasectomy vis a vis systemic therapy is complex and requires expert input as does the risk/benefit assessment of local therapies, including surgical resection vs stereotactic ablative body radiation (SABR) / stereotactic body radiation therapy (SBRT), vs percutaneous ablation vs 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, 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 while 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 as well as the role of neoadjuvant and/or adjuvant systemic therapy 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 and genotype, and availability of effective systemic treatment. An initial course of immunotherapy or targeted therapy may be appropriate for some diseases (melanoma, 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 cases, 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 (e.g. 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 prior to surgery. A common anecdotal practice is to achieve "maximal" systemic control prior to 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 (TKIs) used in lung cancer have minimal effect on wound healing. In the case of driver mutations, it's undesirable to interrupt therapy. Hence EGFR TKIs, for example, are generally interrupted only a day or 2 prior to surgery and resumed a day or 2 after.

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.

   Strongly Agree: 92% Agree: 8% Neutral: 0% Disagree: 0% Strongly Disagree: 0%

2. In oncologically and medically appropriate non-small cell lung cancer (NSCLC) patients, tissue from PM should be sent for genomic/molecular analysis including PD-L1 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 CT. Extrathoracic disease is evaluated by 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, diffusion capacity) suffice. If lack of clarity regarding medical operability results, further testing is warranted (stair climbing, 6 minute walk test, cardiopulmonary exercise testing). The same parameters accepted as defining risk for anatomic pulmonary resection of primary lung cancer apply to pulmonary metastasectomy. Figure 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 worse and value of medical treatment 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 complete resection (R0), 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. Figure 2.

Safety: surgical morbidity & mortality

PM is safe. Accumulated reports totaling 6122 patients [6, 30-32] demonstrate less-than-lobectomy (wedge resections, 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 4.8-7.3 days. [30, 31]

Technical aspects of surgical PM

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, 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 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, dyes, etc, but there is little data proving cost-effectiveness and likely this will 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 as to the best open approach. Single lung ventilation with high oxygen concentrations should be avoided in patients who have been exposed to bleomycin (often the case with testicular cancer). If bilateral metastases are present, a clamshell incision (bilateral sternothoracotomies) with short intermittent apneic periods while using an FiO2 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 FiO2.

Consensus Statements:

3. In oncologically and medically appropriate patients, PM can be considered with a preference for minimally invasive surgery (MIS) due to shortened postoperative recovery and lessened impact 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 are not accomplishable via MIS but loan themselves to open approaches (thoracotomy/sternotomy/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 absolute number of pulmonary metastases is not a direct contraindication to PM, candidate selection for PM is best suited to patients harboring ≤ 3 pulmonary metastases.

   Strongly Agree: 33% Agree: 42% Neutral: 8% Disagree: 8% Strongly Disagree: 8%

Lymph node (LN) management (Lanuti)

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 5206 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 only 4.6% of patients had LNs assessed. [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 33% incidence of mediastinal LN metastases in patients with non-pulmonary 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 12-44%. [38, 39] In these retrospective series, mediastinal LN metastases were a significant negative indicator for survival. Hamaji and colleagues reported on 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 to 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 prior to 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, those 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 oligo-resistant 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 dissection during the time of PM have inadequate control groups. Winter et al performed a matched pair analysis of 110 patients who underwent mediastinal LN dissection during PM for renal cell carcinoma compared to 111 patients with no LN assessment. [41] Analysis showed a trend toward improved survival ($p=0.068$) in patients undergoing LN dissection. It should be noted that patients who harbored intrathoracic LN metastases in this study 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 CT chest and PET, LN metastases can be missed. Seebacher et al. reported on 209 patients routinely evaluated with CT and PET prior to pulmonary resection and underwent regional lymphadenectomy (n=158) or LN sampling (n=112) during PM for varying histologies. [42] 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. Since 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 one single 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 employed 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, melanoma) is not warranted given the data paucity.

Consensus statement:

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

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

Nonsurgical local treatment modalities for pulmonary

Role of thermal ablation and SABR

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

Thermal ablation

Thermal ablation techniques include radiofrequency ablation (RFA), microwave and cryotherapy. There are a number of systems available for each modality. No studies compare

the available systems. Although, most centers are migrating towards using microwave for lung ablation, there are no studies comparing modalities. Finally, concerning pulmonary metastases, all of the studies fulfilling the inclusion criteria utilized 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 diameter 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 overall survival on both univariable and multivariable analysis. Addressing specifically patients with colorectal metastases size (>2cm) and number of metastases (>3), both were significantly associated with poorer survival.

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

Studies of sarcoma generally included smaller numbers of patients. A report of 20 patients with metastases 2cm 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 70mm, 3-year survival for sarcoma patients was still acceptable at 58%.

Stereotactic Ablative Body Radiation Therapy (SABR)

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 versus 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.

A study by Nyuttens et al. reported 30 patients with 57 pulmonary metastases. [54] Large peripheral tumors received 60Gy (3 fractions), small peripheral tumors 30 Gy (1 fraction) and central tumors 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 (16%) patients reporting acute grade 3 toxicity.

Another study reported 95 patients with 134 metastases. [55] Patients with up to 4 metastases were included. Median survival was 38 months. Three 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 impacted outcome.

Navarria et al reported 76 consecutive patients of variable histology with 118 lung lesions. [56] Eligible patients had up to 5 tumors treated. Dose prescription varied for central and peripheral tumors, as well as larger versus smaller tumors. Although 80 % of patients presented with grade 1 pulmonary toxicity (mostly radiation fibrosis in <25% of the lung), there was no grade 2 or higher pulmonary toxicity. 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 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 who failed prior therapies, considered non-surgical 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. Additionally we suggest that ablation /SABR be considered an option for patients who present with ipsilateral metastases after prior metastasectomy. The morbidity of re-operation is avoided, and it is likely that such patients are at risk for a 3rd recurrence.

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

Table 2: Survival after Thermal Ablation for Pulmonary Metastases

Author Year (n)	Number of patients	Modality	Pathology	Median Follow-up (months)	Median OS (months)	3-yr OS	5-yr OS	Median Tumor size (range) mm
Ferguson J 2015[46]	157	RFA	Colorectal	28	33.3	44%	19.9%	38*
De Baere T 2015[45]	566	RFA	Mixed	35.5	62	67.7%	51.5%	15(4-70)
Wang Y 2015[47]	67	RFA	Mixed	24	24	46.4%	14.3%	Max 50
Petre EN 2013[48]	45	RFA	Colorectal	18	46	50%	NR	Max 35
Von Meyenfeldt 2011[44]	45	RFA	Mixed	22	55	69%	NR	16(5-80)
Chua TC 2010[51]	148	RFA	Colorectal	29	51	60%	45%	Max 50
Matsui Y 2015[49]	84	RFA	Colorectal	37.5	67	65%	51.6%	15(5-35)
Palussière J 2011[50]	29	RFA	Sarcoma	50	NR	65.2%	NR	Max 40
Koelblinger C 2014[52]	22	RFA	Sarcoma	20	51*	85%	NR	7(5-20)

* = mean, Max=maximum tumor diameter, NR=not recorded

Table 3: Survival after SABR for Pulmonary Metastases

Author Year (n)	Number of patients	Pathology	Median Follow-up (months)	Median OS (months)	3-year survival	4-year survival	5 year survival
Nuyttens JJ 2015[54]	30	Mixed	36	36	NR	38%	NR
Wang Z 2015[55]	95	Mixed	17	38	56.2%	NR	NR
Navarria P 2015[57]	28	Sarcoma	21	27.8	NR	NR	43.3
Navarria P 2014[56]	76	Mixed	18	20	73%	NR	NR
Comito T 2014[58]	40	Colorectal	24	NR	58%	NR	NR
Aoki M 2016[60]	66	Mixed	31.7	NR	76%	NR	NR
Singh D 2014[61]	34	Mixed	16.7	NR	23%	NR	NR
Baschnagel AM 2013[62]	32	Mixed	27.6	40	63%	NR	NR
Fillipi A 2015[59]	40	Colorectal	20	46	NR	NR	39%

NR=not recorded

Consensus statement:

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 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 selectively delivering 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 impact 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 two pulmonary veins, and tolerance for hyperthermic conditions without significantly impairing systemic function. [64-66] Johnston 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. [67]

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 which collects the effluent and redelivers the drug to the lung. Technical variations include antegrade vs 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 conducted a phase I trial looking at the safety and feasibility of ILP with TNF-α and interferon-γ in 15 patients. Three partial responses were seen within 8 weeks of ILP however new nodules or regrowth appeared 7-9 months postoperatively. In all patients the non-perfused side exhibited stable or worsening disease by 8 weeks postoperatively. [69] In 1996, Ratto and colleagues performed cisplatin based ILP in 6 patients with lung metastases from sarcoma. [70] The authors completed all procedures without complications intraoperatively and no intraoperative or postoperative deaths. In 2 of 6 cases 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 one patient had distant disease relapse. Chemotherapy toxicity occurred in none of the patients. Additionally, they performed staged lung perfusion on two patients with bilateral disease and determined it was safe. In a second human study performed by Schröder and colleagues, 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 from cerebral metastases without evidence of local disease recurrence. [71]

Burt and colleagues conducted a phase I trial of ILP with doxorubicin for patients with unresectable sarcoma pulmonary metastases. [72] Eight patients were enrolled, 7 patients were treated with 40 mg/m^2 or less and 1 patient received 80 mg/m^2. There were no perioperative deaths, 6 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 when compared to the contralateral lung.

In 2004, Hendricks and colleagues conducted a phase I trial for ILP with melphalan. There were a total of 16 patients divided into 8 groups, all of whom had pulmonary metastases from melphalan sensitive tumors. There were no operative or postoperative mortalities. Two patients who received 60 mg melphalan at 37^{o}C developed lung edema and x-ray findings resembling 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 FEV1 and DLCO. Significant systemic toxicity has largely been avoided with the exception of reported doxorubin 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, isolated lung perfusion 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 SEER database study observed approximately 5% of colorectal cancer at initial staging had lung metastasis. Incidence of lung metastases was higher among rectal primaries (5.6%) versus colon cancer (3.7%). [74] Other studies report a 5-15% incidence of lung metastases including metachronous disease. [75] In total a small fraction of patients with colorectal cancer develop pulmonary metastases; however, given 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 et al reported survival of colorectal cancer patients with lung metastasis managed with the inclusion of PM. [76] Whether by thoracoscopic surgery or open surgery, the overall survival curve reached a plateau with long-term follow-up. 5-year overall survival rate was 50% and 46% (P=0.251) by thoracoscopy or open surgery, respectively. The 5-year DFS rate approximated 35-40% 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 and/or a longer lifespan promote consideration of metastasectomy. Treasure et al in 2014, summarized the prior findings of the landmark IRLM. [77] Within the IRLM, colorectal cancer was the most common pathology. Lower survival was predicted by multiple metastases, CEA elevation and a shorter (or no interval i.e. 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 year 2000 were analyzed. Four factors were associated with poor survival:

1. short disease-free interval between primary tumor resection and development of lung metastases (HR 1.59, 95 % confidence interval [CI] 1.27-1.98)
2. multiple lung metastases (HR 2.04, 95 % CI 1.72-2.41)
3. involvement of hilar and/or mediastinal LNs (HR 1.65, 95 % CI 1.35-2.02)
4. elevated pre-operative carcinoembryonic antigen (CEA) (HR 1.91, 95 % CI 1.57-2.32).

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

Based primarily on retrospective reports of selected patients typically with oligometastatic lung disease, 5-year survival rates following PM ranged from 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 over 1300 PM patients from 11 publications, with 4 reports including patients managed with both liver and lung metastasectomy, stipulated inclusion criteria of publication after 1989, at least 40 patients and at least 20 months median follow-up. [79] The mean age ranged from 59 to 63 years. The majority of subjects within each series had a solitary lung metastasis (26-75%). In addition to 5-year survival rates of 33-65% in this review, thirty-day operative mortality rates were very low (0-2.4%). Long-term survival in this patient population reflects a combination of surgical resection and neo-adjunctive and/or adjunctive chemotherapy. It is unclear whether surgery or selection bias determined the long-term survival. [77]

Only a randomized clinical trial will definitively determine the value of PM for colorectal cancer. The PulMiCC study (NCT01106261), A Randomized Trial of PM in Colorectal Cancer, completed its feasibility phase with enrollment of 70 patients and in 2015 began the formal randomized phase III trial portion. [80] The UK-based, multi-center 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 endpoint of the phase III trial with secondary endpoints to include lung function, patient-reported quality of life and health economic assessment.

Perioperative systemic therapy

Without guidance of RCT evidence, a common practice approach relies on extrapolation from the more general colorectal cancer literature. Adjuvant chemotherapy provides a benefit in DFS and overall survival 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.

The use of perioperative adjunctive chemotherapy for resectable liver metastases in colorectal cancer has been shown in a large randomized clinical trial to be safe and to prolong DFS. No impact on overall survival was observed with longer follow-up. [81, 82] The 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, 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% [95·66% CI 21·3–35·5] to 35.4% [28·1–42·7]; HR 0·79 [0·62–1·02]; p=0·058). Follow-up reporting in 2013, described a median survival was 61.3 months (95% CI 51.0-83.4) and 5-year survival of 51.2% (95% CI 43.6-58.3) in the perioperative chemotherapy group and median survival of 54.3 months (41.9-79.4) and 5-year survival of 47.8% (40.3-55.0) in the surgery alone group.

Current cancer management societal guidelines

In the United States the National Comprehensive Cancer Network (NCCN) Guidelines form the basis for clinical practice standards particularly with more common cancers. NCCN Guidelines for colon cancer recommend for patients with resectable lung metastases either 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 consensus that the intervention is appropriate."). No distinction is made regarding strength of recommendation in terms of synchronous or metachronous metastases.

The European Society of Medical Onocology 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 [IV, B].

(Level of evidence (IV out 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 UK National Institute for Health and Care Excellence (NICE) addressed the role of resection for metastatic colorectal cancer that gives deference to a 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 a MDT construct with systemic therapy before or after PM.

Strongly Agree: 92% Agree: 8% Neutral: 0% Disagree: 0% Strongly Disagree: 0%

Renal cell carcinoma

About one third of patients with renal cell carcinoma present with synchronous metastatic disease. [85] Surgical approach is typically thoracotomy but approach did not impact 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 thirty-day perioperative mortality rates ranged from 0 – 2.1%. [15, 88, 89] Surgery-specific survival is confounded by inclusion of adjuvant chemotherapy, immunotherapy or extra-thoracic metastasectomies in many series. [15, 88-92] In reports over the past 15 years, median survival ranged from 21 – 44 months. Table 4

Specific predictive factors examined include completeness of resection, DFI, number, size and pulmonary location of metastases, age, tumor grade and gender. In Hofmann et al, there were no survivors at 5-years if resection was incomplete versus 39% at 5 years. They reported number of metastases and a single metastasectomy 5-year survival was 54.7% versus 32% for 2-6 metastases. [97] In a Japanese single institution case series of 25 patients over ten years reported overall 3-year survival of 53% and 5-year 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] Number of metastases was not important in multivariate analysis of 105 patients but nodal involvement was a negative predictive factor. [89] A Italian single-institution review of 48 patients between 1973 and 2008, the median survival was similar at 39 months, the 3-year survival 60%, 5-year 47% and 10-year 18%. [94] In a Mayo Clinic study reporting metastasectomy from multiple sites, completeness of resection was predictive: an incomplete PM negatively impacted 5-year survival with a significant decrease from 73.6% to 12.95% at five 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 > 60 years old having 70% 5-year overall survival versus 37% if < 60. [96] Similarly older patients did better

in a series of multiple organ metastases. The 5-year DFS was 22%, lower than when compared to metastasectomies form other sites. [90] Gender and tumor grade were not significant predictive factors in a 1985-1999 German series. [87]

Table 4: Survival after PM in Renal Cell Carcinoma

Author (year)	Number of patients	Median survival (months)	Overall Survival (%)		
			3-year	5-year	10-year
Kawashima A et al (2011)[93]	25	33.9	53.3	35.5	NA
Kanzaki R et al (2011)[94]	48	39	60	47	18
Assouad J et al (2007)[95]	65	NA	NA	34.4	NA
Marulli G et al (2006)[96]	59	NA	63	53	NA
Murthy SC et al (2005)[15]	92	44.4	49	31	NA
Piltz S et al (2002)[89]	105	NA	54	40	33
Pfannschmidt J et al (2002)[87]	191	21.4	NA	41.5	NA

Consensus statement:

11. In renal cell carcinoma patients, PM can be considered within a 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. Historically, median survival only reached 6-8 months with an estimated 5-year survival < 5%. [98] The incidence of pulmonary metastases in patients diagnosed with melanoma ranges between 30-40%. The most common first visceral metastatic site for melanoma in large series is lung. [98] In an analysis of 1,158 patients harboring melanoma metastases in visceral sites, those with only lung metastases had improved survival compared to 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 to 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 impacted survival since 2011 where subgroups of patients can achieve 60% 2-year survival. [101] In an contemporary analysis of 441 patients with stage IV melanoma from 2011-2014, the best overall survival was observed in patients treated with metastasectomy as 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 1990's. [16, 103, 104] Several studies investigated the role of PM in advanced melanoma reporting 5-year survival rates of ~ 40% in highly selected patients with median follow-up of 18-55 months. [106, 106] Independent prognostic variables for improved overall survival in these series included: tumor doubling time > 60 days, tumor size < 2cm, 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 19% 5-year survival. [105] In 1720 patients with pulmonary metastases from melanoma, PM was performed on 318 patients. The greatest benefit of metastasectomy in the surgically treated patients was observed in patients who presented with a DFI of > 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 a MDT construct.

Strongly Agree: 75% Agree: 25% Neutral: 0% Disagree: 0% Strongly Disagree: 0%

Sarcoma

Approximately 20%-40% of sarcoma patients develop pulmonary metastases with disease progression, often with 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. Never the less, as with other pathologies, sarcoma PM is not common. Nationwide data from Iceland described 81 patients treated for sarcoma over a 24-year period, only 5 of whom (6.5%) underwent PM. [3]

Commonly reported data may identify several predictive indicators of increased survival, including: (1) metachronous versus synchronous, (2) DFI >12 months, (3) younger age, (4) limited number of metastases, (5) low pathologic grade, and (6) complete resection. [115-117] There is no agreed-upon number of lesions at which resection is thought to be futile, but it is likely more difficult to achieve complete resection or reach disease-free status with more lesions. Furthermore, timing of resection remains controversial. [118] Molecular markers as prognostic indicators has been reported, but is not widely adopted. [119]

Despite aggressive resection strategies, sarcoma patients with pulmonary metastases 5-year survival is only 30% - 50%. [3, 5, 108, 111, 115, 116, 121] Many patients experience pulmonary recurrence, although there are reports of “benefit” from a second PM. [111, 122]

There appears to be a small survival difference for different sarcomas, with gynecological sarcomas showing better survival than osteosarcomas, which in turn have slightly improved survival compared with other sarcomas. [123-125]

Combined treatment, that is, resection plus another local therapy (e.g. SABR), has been reported, and represents a trend in treating all metastases while reducing resection of pulmonary tissue. [126] ILP with high-dose chemotherapy at the time of resection has also been reported, with modest benefit. [127]

Consensus statement:

13. In sarcoma patients, PM can be considered within a MDT construct.

Strongly Agree: 92% Agree: 8% Neutral: 0% Disagree: 0% Strongly Disagree: 0%

Head & neck cancers

Even though the metastasis rate from head and neck squamous cell carcinoma (HNSCC) is low and depends on loco-regional control and LN status, the lungs account for up to 70-85% of HNSCC metastases. [128] Differentiating a primary lung squamous cell carcinoma (LSCC) from lung metastasis in a patient with HNSCC is challenging with the use of standard histopathology techniques. Both LSCC 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, [129] and microRNA profiling, [130] there is no gold standard to validate therapeutic approaches and potentially introduces selection bias in addressing the role of PM. [131-134]

There are approximately twenty retrospective reports over the past twenty years in which authors reviewed single institutional experience with PM alone. There are only two reports retrospectively comparing chemotherapy versus PM. [135, 136]

Positive predictive factors for PM alone include DFI, gender, age, site of origin of primary head and neck cancer and completeness of resection. In 1992 Finley et al reported no five-year survivors in 18 patients treated surgically if their DFI was < 1 year but concluded that resection of solitary metastases resulted in long-term survival. [137] Similar conclusions were reported by Wedman et al in describing 138 patients with pulmonary metastases from HNSCC, 21 of whom underwent PM. [138] There was a 59% 5-year survival 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 < 12 months was noted to be a negative prognostic factor in several small series, [133, 137, 139] while other studies state 24-26 months as the significant DFI resulting in more favorable outcome. [131, 134, 140, 141] Male gender has been found to be unfavorable. [131, 139]

Histologic origin of the metastases is important. HNSCC versus glandular tumors was a poor prognostic factor in a small series. [139] 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%. [140] However, the SCC patients had potentially confounding worse predictive factors such as non-R0 resection, shorter DFI (< two years) and older age. Similarly in two larger series completeness of resection translated into improved outcome [131, 135] but presence of nodal metastases was unfavorable. [131] The fact that metastases from SCC origin do worse than those from glandular may reflect sampling bias and difficulty in distinguishing them from primary LSCC which are potentially under-treated with suboptimal resection.

As mentioned above, resection versus chemotherapy with matched pair analysis concluded PM resulted in significantly better survival. PM lead to median survival was 19 versus 5 months [135] and overall 3-year survival of 68% versus 15%. [136]

Table 5: Survival after PM in Head & Neck Cancer

Author (year)	Number of patients	Median survival (months)	Overall Survival (%)	
			3-year	5-year
Yotsukura et al (2015)[134]	34	77	NA	NA
Miyazaki et al (2013)[136]	24	NA	68	NA
Haro et al (2010)[132]	21	NA	53.3	NA
Daiko et al (2010)[141]	33	21	43	NA
Winter et al (2008)[135]	67	19.4	NA	20.9
Shiono et al (2009)[131]	114	26	NA	26.5
Chen et al (2008)[139]	20	NA	NA	59.4
Nibu et al (1997)[142]	32	NA	NA	32

Consensus statement:

14. PM in management of primary head & neck cancer can be considered in the context of DFI >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 (NSGCT)

The lung is the most common site of visceral metastases from hematogenous dissemination. In contrast to other solid neoplasms however, metastatic involvement of either the lung or mediastinum represents American Joint Committee on Cancer Stage III disease. [143] The paradigm of platin-based chemotherapy followed by surgery to remove residual disease for the treatment of NSGCT 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 prior to any thoracic surgical procedure, the pathologic findings of postchemotherapy retroperitoneal LN dissection (RPLND) as there is a high correlation between RPLND and lung pathology. [144, 145] Significantly elevated serum tumor markers (STM), alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (HCG), after chemotherapy have a high sensitivity for persistent NSGCT. [146] In the vast majority, STM normalize 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. [147]

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. It is estimated approximately 10-20% of all testicular NSGCT patients will have residual pulmonary disease following chemotherapy or subsequently manifest pulmonary disease during follow-up and warrant consideration of PM. [148, 149] In approximately one half of these cases, there is residual mediastinal disease, which 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 post-chemotherapy pulmonary abnormalities. In addition to testicular/RPNLD pathology containing teratoma and normalized STM, CT findings suggestive of pulmonary teratoma include a rounded and/or cystic appearance. While considered "benign", teratoma has local growth potential as well as malignant transformation, therefore surgery is recommended with high cure rates. [150-152] Moreover parenchymal sparing techniques involving "shelling out" of teratoma, is efficacious, avoiding large pulmonary resections. [148] If PM in one lung is pathologically complete tumor necrosis, abnormalities

in the contralateral lung are observed, as there is a 90% pathologic concordance between lungs. [153] 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 either elevated STM and/or testicular/RPNLD pathology. In these cases, PM is undertaken in select patients to remove a limited number of areas, as cure is possible but significantly lower as compared to PM for teratoma. [151, 154-156] In contrast to teratoma, which has low metabolic activity, PET imaging can be helpful to determine resectability in patients suspected of residual malignant disease. Standard wide local excision (wedge) is utilized. Adequate surgical margin less commonly requires anatomic pulmonary resection.

PM following platin-based chemotherapy in the treatment of NSGCT of testicular origin has high curative potential with five-year survival rates ranging from 59% to 94%. Although prospective randomized studies are lacking, high cure rates after PM generate a strong bias towards surgery. Prognostic factors include International Germ Cell Cancer Cooperative Group risk (low, intermediate, high) at 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 nonseminomatous germ cell tumors, PM is indicated for all residual lung abnormalities $\geq$ 10 mm after platin-based chemotherapy with normalized STM suspected of containing teratoma.

    Strongly Agree: 67% Agree: 25% Neutral: 8% Disagree: 0% Strongly Disagree: 0%

16. When managing nonseminomatous germ cell tumors, 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 nonseminomatous germ cell tumors, PM is indicated for select patients with limited number of lung abnormalities after first or second-line platin-based chemotherapy suspected of containing viable nonseminomatous cancer and/or malignant transformation of teratoma into non-germ cell cancer.

    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 7-24%. [157] The initial purpose of performing metastasectomy in most breast cancer

patients is to confirm the diagnosis, establish hormone receptor status, and to 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, 158-164] In a meta-analysis of 16 studies evaluating 1937 patients undergoing breast cancer PM, a 46% 5-year survival was reported. [165] Poor predictive factors were DFI < 3 years, incomplete resection, > 1 metastasis and negative hormone receptor status. In contrast, a 16% 5-year survival was reported in a case series of breast cancer patients with metastases limited to the lungs and treated with chemotherapy alone. [165] Similar to metastatic disease from other solid organs, PM of multiple or bilateral breast cancer metastases was associated with poor outcome. [167] 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 vs. multiple sites of disease. [20] The extent of pulmonary resection and approach does not appear to influence survival. [20, 167]

Since 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 et al examined medically treated patients with or without PM and found a significant survival improvement with the addition of PM (34 vs. 58 months). Five-year survival in the medically treated group compared to the surgical group was 11% vs. 36%, respectively. [162] Chemotherapy before or after PM did not influence overall survival in a cohort of 467 PM breast cancer patients. [158]

There is evidence suggesting employing PM in breast cancer patients harboring hormone receptor-positive (either ER or Her2-neu) disease appears to have a survival advantage over receptor negative disease (77% vs. 12%, 5-yr survival, respectively). [160] The presence of mediastinal LN metastases with breast cancer lung metastases portends a worse prognosis. [20, 168] 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. [169]

Consensus statement:

18. In breast cancer patients, PM can be considered within a 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/ societal guidelines, multidisciplinary and shared-decision making approach to patient care provides a framework for clinical care recommendations, even with a pure evidence-based approach is not possible.

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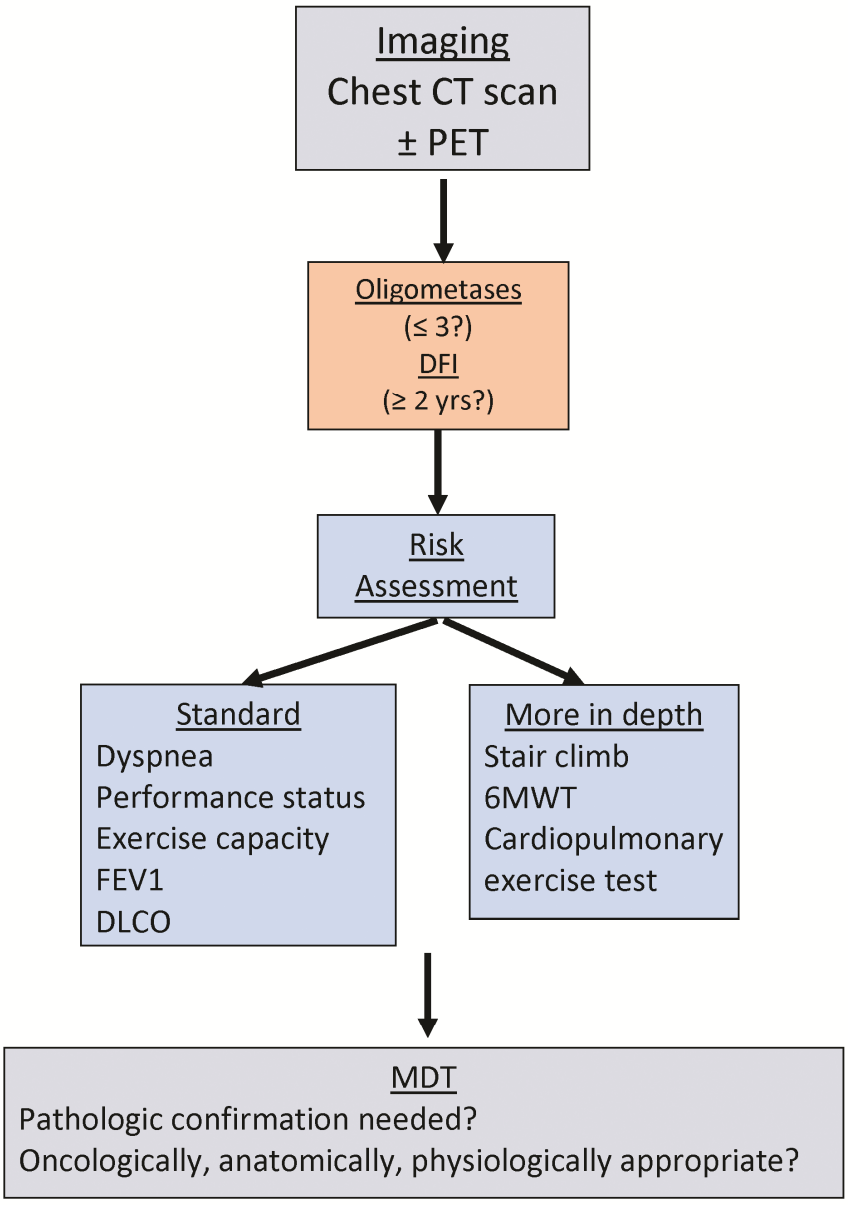
Figure legends

Figure 1 Evaluation for PM

Figure 2 Surgical Techniques for PM

Figure 3 PM Local Therapeutic Possibilities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± PET
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(≤ 3?)
DFI
(≥ 2 yrs?)
Risk
Assessment
Standard
Dyspnea
Performance status
Exercise capacity
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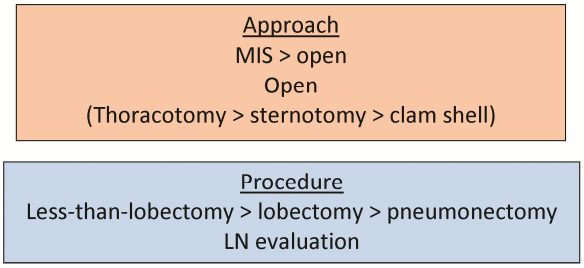
DLCO
More in depth
Stair climb
6MWT
Cardiopulmonary
exercise test
MDT
Pathologic confirmation needed?
Oncologically, anatomically, physiologically appropriate?



Surgery	Ablation
-R0 resection -Lung sparing technique -Lymph node sampling	-High surgical risk -Ipsilateral recurrence after prior PM -Refuse surgery