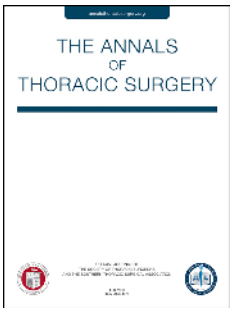

The Society of Thoracic Surgeons 2026 Expert Consensus on the Multimodal Treatment of Pleural Mesothelioma

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The Society of Thoracic Surgeons 2026 Expert Consensus on the Multimodal Treatment of Pleural Mesothelioma

Short Title: Treatment of Pleural Mesothelioma

Jeffrey B. Velotta, MD,[1,2,3] Anja C. Roden, MD,[4] Jonathan Rice, MD, PhD,[5] Charles B. Simone, MD,[6,7] Bansari Upadhyay, BS,[8] Pallavi Sood, PhD,[8] Daniel L. Miller, MD,[9] R. Taylor Ripley, MD,[10] Andrea Wolf, MD, MPH,[11] Bryan M. Burt, MD,[12] Samuel S. Kim, MD,[13] Isabelle Opitz, MD,[14] Hedy L. Kindler, MD,[15] Harvey I. Pass, MD,[16] J. W. Awori Hayanga, MD, MPH,[17] Valerie Rusch, MD,[18] Raphael Bueno, MD[19]

[1]Divison of Thoracic Surgery, Kaiser Permanente, Oakland, CA, United States

[2]Department of Surgery, University of California, San Francisco School of Medicine, San Francisco, CA, United States

[3]Department of Clinical Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA, United States

[4]Department of Laboratory Medicine and Pathology, Mayo Clinic Rochester, Rochester, MN, United States

[5]Division of Cardiothoracic Surgery, Department of Surgery, University of Arizona, Tucson, AZ, United States

[6]New York Proton Center, New York, NY, United States

[7]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, United States

[8]The Society of Thoracic Surgeons, Chicago, IL, United States

[9]Section of Thoracic Surgery, Department of Surgery, Medical College of Georgia, Augusta, GA, United States

[10]Division of Thoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX, United States

[11]Department of Thoracic Surgery, The Icahn School of Medicine at Mount Sinai, New York, NY, United States

[12]Division of Thoracic Surgery, Department of Surgery, University of California, Los Angeles, CA United States

[13]Division of Thoracic Surgery, Canning Thoracic Institute, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

[14]Department of Thoracic Surgery, University Hospital Zurich and University of Zurich, ZH, Switzerland

[15]Section of Hematology/Oncology, University of Chicago Medicine, Chicago, IL, United States

[16]Department of Cardiothoracic Surgery, NYU Langone Health, New York, NY, United States

[17]Department of Cardiovascular and Thoracic Surgery, West Virginia University, Morgantown, WV, United States

[18]Thoracic Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY, United States

[19]Division of Thoracic Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

Corresponding Author

Jeffrey B. Velotta, MD, FACS, Division of Thoracic Surgery, Kaiser Permanente Oakland Medical Center, 3600 Broadway, 3rd Floor, Suite 38, Oakland, CA 94611; Email: jeffrey.b.velotta@kp.org

The STS Executive Committee approved this document.

ABSTRACT

BACKGROUND: Pleural mesothelioma (PM) is a rare and complex thoracic malignancy for which treatment regimens continue to evolve. The role of surgery in the management of PM is controversial. We reviewed contemporary literature to provide consensus recommendations from an expert multidisciplinary panel on the multimodal treatment of PM with an emphasis on surgical intervention in order to update management pathways.

METHODS: An international, multidisciplinary panel developed PICO-based (Population, Intervention, Comparator, Outcomes) questions and conducted a comprehensive literature review to identify relevant literature. Consensus statements were developed using a modified Delphi process with at least 75% agreement over three voting rounds.

RESULTS: A total of 13 PICO questions were developed, and detailed summary statements were provided for each PICO subtopic based on systematic literature review and multidisciplinary expert panel discussion. There was strong consensus that accurate diagnosis depends on adequate pleural biopsy specimens and that clinical evaluation should include at a minimum CT and PET imaging. Therapeutic decisions should be discussed by a multidisciplinary tumor board including thoracic surgeons with expertise in PM treatment. If surgical resection is deemed appropriate, it should be part of a multimodal treatment plan. Pleurectomy/Decortication (P/D) or Extended Pleurectomy/Decortication (EPD) is strongly favored over Extrapleural Pneumonectomy (EPP) as the approach to resection.

CONCLUSIONS: This STS Expert Consensus Document includes contemporary treatment recommendations for PM based on systematic literature review and multidisciplinary expert panel discussion and provides a management framework for practicing thoracic surgeons.

Abbreviations and Acronyms

AATS	American Association for Thoracic Surgery
ACS CoC	American College of Surgeons Commission on Cancer
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
EACTS	European Association for Cardio-Thoracic Surgery
EBUS	Endobronchial Ultrasound
EBUS-TBNA	Endobronchial Ultrasound-Transbronchial Needle Aspiration
ECD	Expert Consensus Document
EORTC	European Organization for Research and Treatment of Cancer
EPD	Extended Pleurectomy/Decortication
EPP	Extrapleural Pneumonectomy
ERS	European Respiratory Society
ESTS	European Society of Thoracic Surgeons
EUS-FNA	Endoscopic Ultrasound-Fine Needle Aspirate
FDG-PET/CT	Fluorodeoxyglucose Positron Emission Tomography
GTSD	General Thoracic Surgery Database
IASLC	International Association for the Study of Lung Cancer
IMRT	Intensity-Modulated Radiation Therapy

LN	Lymph Node
LOS	Length of Stay
MARS	Mesothelioma and Radical Surgery
MCR	Macroscopic Complete Resection
MTB	Multidisciplinary Tumor Board
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
OS	Overall Survival
P/D	Pleurectomy/Decortication
PET/CT	Positron Emission Tomography–Computed Tomography
PICO	Population, Intervention, Comparator, Outcome
PICLN	Posterior Intercostal Lymph Nodes
PM	Pleural Mesothelioma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RCT	Randomized Controlled Trial
RATS	Robotic-Assisted Thoracic Surgery
SBRT	Stereotactic Body Radiation Therapy
STS	The Society of Thoracic Surgeons
SUVmax	Maximum Standardized Uptake Value

TNM Tumor, Node, Metastasis

VATS Video-Assisted Thoracic Surgery

WFEBS Workforce on Evidence-Based Surgery

The Society of Thoracic Surgeons (STS) Task Force on General Thoracic Surgery and STS Workforce on Evidence Based Surgery (WFEBS) assembled a multidisciplinary panel composed of thoracic surgeons, medical oncologists, radiation oncologists, and thoracic pathologists with expertise in treating Pleural Mesothelioma (PM). PM is a rare thoracic malignancy that is still associated with a poor overall survival (OS). Historically, surgical resection was considered a mainstay treatment, but recently, the benefit of surgery has been called into question. A recent randomized controlled trial (RCT) on mesothelioma and radical surgery (MARS-2) published by Lim et al. 2025 concluded that patients with PM who underwent neoadjuvant platinum-based chemotherapy followed by extended pleurectomy/decortication (EPD) had worse OS compared to those treated with chemotherapy alone.[1] However, while MARS-2 was a multicenter RCT, the results remain controversial because of concerns regarding study design, lack of complete preoperative staging, and postoperative morbidity. Therefore, this STS multidisciplinary expert panel was formed to review the published literature regarding the multimodal management of PM, including surgical resection, in order to provide a management framework for practicing thoracic surgeons.

METHODS

WRITING GROUP COMPOSITION: STS WFEBS, in collaboration with the Task Force on General Thoracic Surgery, convened an international, multidisciplinary expert panel which included thoracic surgeons, radiation oncologists, pathologists, and medical oncologists with recognized expertise in the multimodal management of PM. The expert panel convened monthly by virtual meetings to plan, review, and advance this expert consensus document. All expert panel members completed conflict-of-interest disclosures prior to initiation of the project; these disclosures were reviewed by the project chairs and WFEBS leadership. No major conflicts were disclosed that were deemed to adversely influence the development of this manuscript. All members were duly required to adhere to the STS Evidence Based Surgery clinical practice document development policies.

PROJECT SCOPE: The writing group formulated a series of clinical research questions using the PICO (Population, Intervention, Comparator, Outcomes) framework.[2] The PICO-based research questions focused on the diagnosis, evaluation and treatment of patients with PM. The PICO research questions are listed in Supplementary Appendix 1.

EVIDENCE IDENTIFICATION: A medical librarian developed a comprehensive PubMed search strategy. Searches were limited to English-language human studies published from 2011 to 2024 involving adults (≥18 years) with PM who underwent surgery. . Additional studies were identified through hand searches by the expert panel. The detailed search strategy is provided in Supplemental Table 1.

STUDY SCREENING AND SELECTION: Following removal of duplicate records, a total of 1,057 citations were imported into Covidence,[3] an online screening platform for structured screening. Screening occurred in two stages: initial review of titles and abstracts, followed by full-text evaluation based on predefined criteria. Studies were deemed eligible if they included the target population (adults ≥18 years with PM) and addressed the relevant interventions, comparators, and outcomes defined in the PICO questions (Supplementary Appendix 1). Studies were excluded if they were in non-English languages, involved animal or preclinical models; or consisted of grey literature (abstracts only, dissertations, white papers), case studies/case reports, editorials, letters, or commentaries without original data. Two reviewers independently assessed each full-text article, resolving any discrepancies by discussion. Ultimately, 116 studies met eligibility criteria and contributed to the development of consensus statements. The study selection process is detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart[4] in Figure 1. The hierarchy of evidence utilized for this expert consensus document was from highest to lowest strength: systematic reviews and meta-analyses, randomized controlled trials, and cohort studies and case-control studies.

CONSENSUS STATEMENT DEVELOPMENT AND VOTING: Guidelines from the American Association for Thoracic Surgery (AATS), European Association for Cardio-Thoracic Surgery (EACTS), European Society of Thoracic Surgeons (ESTS), and STS were followed to develop the consensus statements.[5] The modified Delphi method was used to formulate and refine consensus statements. Expert panel members rated each statement on a 5-point Likert scale (1 = strongly agree, 2 = agree, 3 = neither agree nor disagree, 4 = disagree, 5 = strongly disagree). Statements were included only if they achieved at least 75% agreement, defined by the selection of either "agree" or "strongly agree." All expert panel members participated in the voting process, and consensus on all statements was achieved after three rounds of voting. Voting outcomes are provided in Supplemental Table 2.

STS NATIONAL DATABASE: Data from the STS General Thoracic Surgery Database (GTSD) were reviewed pertaining to adults aged 18–90 years who underwent a surgical procedure for PM between January 1, 2015 and December 31, 2025. A total of 630 procedures were performed. Pleurectomy/decortication (P/D) accounted for the majority at 86% (541 cases), whereas extrapleural pneumonectomy (EPP) represented the remaining 14% (89 cases). Figure 2 displays the percentage distribution of patients by type of operation. Patients who underwent more than one of the listed procedures were included in each corresponding category. The specific inclusion criteria and harvest codes used to identify these cases are provided in Supplemental Table 3.

APPROVAL PROCESS: After the writing group completed the manuscript, it was reviewed and approved by the STS WFEBS, the STS Council on Quality and Research, and the STS Executive Committee. The manuscript was subjected to a two-week public comment period before submission to the *Annals of Thoracic Surgery* for peer review.

RESULTS

DIAGNOSIS AND WORKUP

STATEMENT 1.1: Adequate tissue sampling to establish the histological diagnosis and define the PM subtype (and grade for epithelioid tumors) is critical because they directly influence treatment decisions. If a diagnosis of PM is suspected based on patient history and/or imaging, surgical biopsy is recommended.

PM is a rare cancer that can be difficult to diagnose and challenging to treat. Classification into one of the three subtypes—epithelioid, biphasic, and sarcomatoid—as well as grading of epithelioid mesotheliomas, is based on histologic patterns and features. Accurate classification is imperative, as histologic subtype is an established prognostic factor in PM and dictates treatment recommendations. Surgical biopsy increases the accuracy of subtype determination compared with image-guided core biopsies.[6] In patients with a free pleural space, biopsy is best performed via a minimally invasive procedure with the minimum number of small ports (e.g., Video-Assisted Thoracic Surgery (VATS) or Robotic-Assisted Thoracic Surgery (RATS)). In patients with a fused pleural space, direct open pleural biopsy with partial single rib resection may be necessary. With either approach, the smallest number (usually 1 or 2) and size incisions should be used. Full thoracotomy as well as extensive pleurectomy to establish a diagnosis should be avoided .

STATEMENT 1.2: Surgical pleural biopsies, either by open or minimally invasive techniques, should minimize the number of incisions (ideally 1) and be in line with potential future thoracotomy incision(s). For patients who are likely to undergo surgical management of PM, future incisions should be taken into consideration when performing a pleural biopsy to establish the diagnosis. Careful planning of the biopsy incision can help limit disease seeding into additional surgical sites that may not be included in a subsequent thoracotomy incision.[7]

STATEMENT 1.3: The accuracy of histologic classification improves with the number of tissue blocks examined, supporting the practice of obtaining multiple biopsies from different disease locations to enhance diagnostic yield.

The diagnosis and subtype classification of PM are based on histological patterns. Due to intratumoral heterogeneity, biopsy findings may not fully accurately represent the histology of the entire tumor. This can lead to a change in subtype diagnosis following resection. Consequently, the accuracy of histologic classification increases with the number of tissue blocks examined.[8,9] In addition, a diagnosis of pleural mesothelioma in situ requires multiple biopsy pieces as similar findings can be focally seen in patients with diffuse mesothelioma.[9]

STATEMENT 1.4: A pleural biopsy is indicated in a patient with clinical suspicion of having mesothelioma, even in the setting of negative pleural cytology, due to the low sensitivity of cytology in detecting PM.

A diagnosis of PM can be made on pleural fluid. However, the sensitivity of pleural fluid is lower than that of a biopsy with reported sensitivity of 30% to 75% even though the specificity has been reported to be 99% to 100%. In general, only epithelioid mesotheliomas shed into pleural fluid. Therefore, the biphasic nature of PM usually cannot be established, and sarcomatoid or desmoplastic mesotheliomas are usually not diagnosed on the basis of pleural fluid samples. In addition, a diagnosis of PM in situ cannot be made on pleural fluid cytology alone, and requires adequate pleural tissue specimens only obtained with a pleural biopsy. If pleural fluid results are negative despite high clinical suspicion for PM, pleural biopsy is advised.[8,9]

STATEMENT 2.1: A PET/CT scan should be performed in patients with PM to accurately stage the patients and to guide the needs for additional invasive diagnostic procedures.

PET/CT scan plays a critical role in the initial evaluation of PM, providing staging accuracy that surpasses conventional imaging and directly informs the need for invasive diagnostic procedures. FDG-PET/CT scan

reliably identifies occult metastatic disease, including extrathoracic and mediastinal nodal involvement, which may be underestimated on a CT scan alone. Flores et al. reported that PET imaging can detect unsuspected distant metastases and correlates with nodal disease burden, demonstrating value in directing surgical decision-making and avoiding non-therapeutic surgery.[10] Contemporary data confirm high diagnostic accuracy for metastasis detection occurring in approximately 10% of patients, with PET/CT altering management in up to 40% of patients and identifying mediastinal nodal disease missed on CT.[11,12] Quantitative PET parameters, including Maximum Standardized Uptake Value (SUVmax), metabolic tumor volume, and total lesion glycolysis, correlate with tumor burden and biological aggressiveness, reinforcing the role of PET imaging in preoperative risk stratification and prognostication.[13-16] PET/CT scans provide an integrated metabolic and anatomic assessment that enhances staging precision and guides the selective use of mediastinoscopy, Endobronchial Ultrasound (EBUS), or exploratory laparoscopy when PET findings suggest potential nodal or distant spread.[11,12] This evidence supports the routine use of PET/CT scans in newly diagnosed PM patients to optimize staging and invasive procedural planning.

STATEMENT 2.2: Invasive staging evaluation including EBUS/mediastinoscopy and/or laparoscopy improve detection of occult metastasis missed on conventional imaging and can be considered for optimal initial evaluation of the extent of disease.

Invasive staging adds clinically meaningful information beyond CT and PET/CT scans in potentially resectable PM. Cervical mediastinoscopy detects occult mediastinal nodal metastases that are poorly predicted by imaging or nodal size. Nodal positivity strongly correlates with worse postoperative survival; therefore, preoperative pathologic nodal assessment is important for surgical selection.[17,18] Endoscopic nodal staging further increases yield: Endoscopic Ultrasound-Fine Needle Aspirate (EUS-FNA) and Endobronchial Ultrasound-Transbronchial Needle Aspiration (EBUS-TBNA) can safely sample N2/N3 stations and identify metastatic nodes despite negative imaging.[19,20] In contemporary practice, EBUS-

TBNA prevented unnecessary surgical intervention in nearly one-fifth of patients evaluated for trimodality therapy, highlighting its impact on eligibility decisions.[21] Because nodal spread can be patchy and involve stations accessible by either mediastinoscopy or endoscopic ultrasound, combining techniques offers broader coverage when a curative-intent operation is being considered.[18,21] Likewise, laparoscopy improves detection of transdiaphragmatic or peritoneal disease that conventional imaging often misses. The foundational manuscript by Conlon et al. demonstrated that laparoscopy revealed occult peritoneal/diaphragmatic extension in half of the patients with equivocal CT findings, avoiding nontherapeutic thoracotomy.[22] More recently, routine diagnostic laparoscopy found peritoneal disease in approximately 17% of surgical candidates, with most cases being PET/CT-negative, confirming that minimally invasive abdominal staging refines initial extent-of-disease assessment and surgical planning.[23]

STATEMENT 3.1: Discussion of specific treatment options for patients with PM should be presented in a multi-disciplinary conference with expertise in thoracic oncology.

Multidisciplinary Tumor Board (MTB) or discussion in a multidisciplinary team setting is strongly recommended for patients with PM.[24-26] The team should have experience in managing PM and should ideally comprise radiation oncologists, thoracic surgeons, medical oncologists, radiologists, pathologists, and pulmonologists. The MTB should review the pathologic and radiologic evidence for the diagnosis and risk stratification, make recommendations regarding treatment, and encourage the recruitment of appropriate patients into clinical trials.[24] Successful treatment of patients with PM requires accurate diagnosis and staging and careful planning of therapy with multiple modalities that may include surgery, systemic therapy, and/or radiation.[27] Thus, multidisciplinary experts are required to define an optimal strategy for each individual patient. If a center lacks expertise in one or more areas and/or experience with PM, the patient should be referred to a high-volume center with relevant expertise.[28]

STATEMENT 3.2: Discussion in multidisciplinary tumor board for PM should involve a thoracic surgeon with sufficient expertise in the surgical treatment of PM.

The role of curative-intent surgery has been questioned after the results from the MARS2 trial demonstrated that OS for patients with PM who received two cycles of platinum-pemetrexed chemotherapy followed by EPD was associated with a 9% risk of mortality at 90-days postoperatively and that OS was not superior to treatment with chemotherapy alone.[29] Experts from different disciplines, however, agree that in selected patients, curative-intent surgery may offer benefit (see PICO 4) and thus, it is critical that a dedicated thoracic surgeon with expertise in PM contributes to the MTB discussion.[30-32] If a center lacks expertise in the management of PM, consultation with a multidisciplinary team at a high-volume center of excellence in PM should be considered.[28] Given the rarity of PM, referral to a high volume thoracic surgeon with expertise in PM should be considered.

MULTIMODAL MANAGEMENT

STATEMENT 4.1: Patients should be evaluated for surgical resection at high volume centers with extensive experience treating PM.

Current joint guidelines from the European Respiratory Society (ERS), the European Society of Thoracic Surgeons (ESTS), the EACTS, and the European Society for Radiotherapy and Oncology (ESTRO) (2020) recommend that surgery for PM be performed in high-volume centers, within clinical trials, and as part of a multidisciplinary treatment approach.[33] The American Society of Clinical Oncology (ASCO) 2025 similarly recommends that surgery is best performed at centers with documented low morbidity and mortality within the context of multimodality therapy and preferably within clinical trials.[34] In addition, the updated 2026 National Comprehensive Cancer Network (NCCN) guidelines also emphasize that PM patients should be evaluated by surgeons with specific experience in managing PM.[26]

Multiple centers from the United States, Europe and Japan have reported optimal surgical outcomes for PM patients when operations are performed at high-volume centers .[27,30,35-38] A recent report emphasized that PM patients who underwent surgical evaluation and treatment at PM regionalized centers of excellence were more likely to undergo surgical resection and had better OS.[39]

For centers offering neoadjuvant therapy to PM patients, optimal anesthetic management is critical because a high intraoperative fraction of inspired oxygen and/or barotrauma can trigger postoperative ARDS.[40] The management of patients following EPP and EPD is particularly challenging and a center's experience plays a crucial role. Centers with less than five EPPs per year have a significantly higher incidence of postoperative ARDS. Centers offering extracorporeal life support programs may provide more experience and data in managing such patients.[41] Analyses of the STS database also show that surgical resection volume significantly influences morbidity and mortality after PM surgery in univariate analysis.

STATEMENT 4.2: Cardiopulmonary function, nutritional levels, and performance status must be considered acceptable for surgical resection by the thoracic surgeon.

Patients with PM who are considered for surgical resection, including EPP, EPD or P/D, must be thoroughly evaluated to determine suitability for operative intervention. These operations are extensive and require prolonged postoperative recovery as well as the need for additional systemic therapy. Therefore, stringent patient selection is essential. Surgical candidacy should be evaluated by thoracic surgeons with experience in treating PM. Optimal cardiopulmonary reserve, acceptable nutritional status, and appropriate functional performance have been shown to be positive factors for PM patients undergoing surgery.[42-46] Performance status, in particular, has been demonstrated to be an independent prognostic indicator of OS .[47]

STATEMENT 4.3: Tumor histologic subtype (i.e. epithelioid histology) and locoregional disease have favorable survival outcomes when surgery is performed in a multimodal fashion.

Several retrospective studies suggest that, among patients with PM who undergo curative intent surgical resection (EPP or EPD)- epithelioid histology is consistently associated with longer median OS relative to the biphasic or sarcomatoid subtypes.[27,36,39,48-50] Because non-epithelioid histologies (sarcomatoid and biphasic tumors) are associated with poorer outcomes, the potential incremental benefit of resection for these histologies may be limited outside of highly selected circumstances or clinical trials.[27,51,52]

Beyond histologic subtype, multiple factors significantly influence OS when assessing surgical candidacy, including tumor stage (T and N classification), gender, age, and the intent of surgery.[39] Additionally, tumor grade and presence of necrosis may provide prognostic information and further refine risk stratification beyond histology. Rosen et al. 2018 showed significant OS differences in epithelioid PM patients when stratified by nuclear grade and necrosis, in which the best OS were observed in the following order: Nuclear grade I tumors without necrosis (OS=29 months), nuclear grade I tumors with necrosis and grade II tumors without necrosis (OS=16 months), nuclear grade II tumors with necrosis (OS=10 months) and nuclear grade III tumors (OS=8 months).[53] In addition, in a recent systematic review, Schulte et al. further verified that tumor grade and presence of necrosis have an independent prognostic significance in epithelioid PM patients, in which the goal would be to further subtype and grade epithelioid PM histology to enhance surgical selection.[54]

Increasing nodal stage is associated with inferior outcomes and may influence surgical selection.[27,49,55,56] In a recently updated database analysis from 2013 to 2022 in the International Association for the Study of Lung Cancer (IASLC) 9th Edition Tumor, Node, Metastasis (TNM) staging edition for PM, a significant survival advantage was noted for N0 disease compared to N1 and N2 disease.[55] Altogether, when deciding appropriate surgical candidates, epithelioid histology and

locoregional disease have favorable survival outcomes when surgery is performed in a multimodal fashion.

STATEMENT 5: Patients who are undergoing surgery as part of a multimodal strategy may be offered neoadjuvant (or adjuvant) systemic therapy as determined by a multidisciplinary team based on clinical scenario and institutional expertise.

According to recent and foundational clinical series, perioperative systemic therapy is a core element of multimodality management for selected patients with resectable PM, but the timing (neoadjuvant vs adjuvant) should be individualized following discussion by a multidisciplinary team. Induction platinum–pemetrexed–based chemotherapy has been widely used before EPP or P/D to treat occult micrometastatic disease early, and potentially facilitate macroscopic complete resection (MCR) in expert centers.[57-59] However, national and institutional data indicate that routine neoadjuvant therapy for all candidates may not be optimal: A large comparative outcomes analysis showed OS to be similar for induction-then-resection versus resection-then-postoperative chemotherapy, but postoperative outcomes were worse after induction, supporting selective rather than universal neoadjuvant use.[60] Complementing this finding, an institutional National Cancer Database(NCDB) intention-to-treat study found that neoadjuvant chemotherapy did not improve survival over immediate surgery and was associated with inferior post-resection survival, likely reflecting progression during induction or reduced physiologic reserve at operation.[61] Since neoadjuvant therapy can lead to attrition from progression or declining fitness, some institutions favor upfront lung-sparing resection for limited disease with postoperative chemotherapy when rapid cytoreduction is prioritized.

Prospective RCTs emphasize the appropriateness of flexibility in sequencing treatment. In the European Organization for Research and Treatment of Cancer (EORTC) 1205 randomized phase II trial of EPD with three cycles of cisplatin–pemetrexed given either pre- or postoperatively, EPD achieved high

MCR rates and extremely low perioperative mortality. Chemotherapy completion was higher in the neoadjuvant arm, but OS was comparable between the two strategies. Thus, no preferred sequence emerged.[62] Radiotherapy can similarly be integrated either immediately before or after surgery in high-volume centers. Long-term outcomes with neoadjuvant versus adjuvant pleural intensity-modulated radiation therapy (IMRT) were comparable, underscoring that local experience and logistics can appropriately drive sequence selection.[63] Finally, perioperative immunotherapy is emerging as another systemic option: neoadjuvant nivolumab with or without ipilimumab was feasible. Most patients proceeded to surgery and optional adjuvant therapy afterwards, further supporting MDT-driven personalization of perioperative systemic therapy.[64] Collectively, these studies justify offering neoadjuvant or adjuvant systemic therapy around surgery, with timing tailored to stage, histology, patient fitness, and institutional outcomes.

STATEMENT 6: Patients who receive upfront surgery for PM should be considered for adjuvant systemic therapy.

As stated previously, equipoise exists regarding whether to offer neoadjuvant or adjuvant systemic therapy in PM patients who undergo maximal surgical cytoreduction. This decision should be individualized and made in the context of a multidisciplinary team (discussed in PICO 5). Since neither EPP nor EPD is expected to achieve a microscopic complete resection in this disease, adjuvant systemic therapy is recommended.[26,34,65]

STATEMENT 7.1: P/D or EPD is recommended in patients with PM who undergo surgery with curative intent.

For more than three decades following Butchart's seminal small series reporting the use of EPP for PM, EPP was considered standard surgical management for this disease because it allowed complete resection of all gross tumor.[66] This coincided with an era when staging for PM was imprecise, prognostic

factors poorly defined, and chemotherapy and radiotherapy largely ineffective. In centers of excellence, operative mortality for EPP was about 6% and median OS after EPP ranged from 22 months (stage I) to less than 1 year (stage IV).[57,67-70]

In 2008, Flores et al. reported a retrospective multicenter study comparing outcomes after P/D versus EPP in 663 patients.[49] By multivariable analysis controlling stage, histology, gender and multimodality therapy, EPP was associated with significantly worse OS. Though initially controversial, this publication led to reconsideration of the role of EPP. Additional retrospective series confirmed that P/D and EPD were associated with lower operative mortality (4% or less), and equivalent or better OS than after EPP.[49,71] The prospective, multicenter "MARS1" feasibility trial of 50 patients randomized to neoadjuvant chemotherapy followed by EPP versus chemotherapy alone added further impetus to abandoning EPP as the main approach to resection for PM. In this study, reported by Treasure and colleagues in 2011, only 16 of 24 assigned patients underwent EPP, and 3 of the 16 patients (19%) died postoperatively.[71] OS was significantly worse among patients who underwent EPP versus those managed non-surgically.[71] While by no means a definitive clinical trial, it contributed to the enthusiasm for lung-sparing operations and P/D and EPD gradually became accepted as the preferred approach to resection of PM. Improvements in the technical conduct of these operations now routinely enable MCR of tumor in most patients similar to what can be achieved after EPP. Furthermore, contemporary national practice patterns from the STS GTSD verify that P/D now predominate over EPP (Supplemental Table 3).

Reported by Lim et al. 2024, the "MARS 2" prospective multicenter randomized clinical trial comparing perioperative platinum-based chemotherapy and P/D or EPD to chemotherapy alone, found that patients in the surgery arm of the study did not experience an improved OS and had diminished quality of life parameters relative to patients receiving chemotherapy only. This study sparked an international debate on whether there is any role for surgery in PM, even using lung-sparing

procedures.[29] Although stringently designed and conducted, the trial reflects limitations of the required pre-treatment staging (CT imaging only), and the challenges of reproducing in a multicenter setting the results seen in single institution studies from centers of excellence (e.g. 9% postoperative mortality at 90 days in MARS 2).[1,29] Overall, the MARS 2 results highlight the importance of careful patient selection, precise staging, meticulous surgical technique and perioperative care required to achieve optimal outcomes, even after P/D or EPD.

As discussed in other sections of this document, multiple prospective clinical trials have now shown the feasibility of combining surgical resection (EPP or P/D, EPD) with systemic therapy and/or radiation, delivered in either the neoadjuvant and/or adjuvant setting.[72] The operative approach may influence the patterns of disease progression. In prospective clinical trials, EPP and neoadjuvant or adjuvant hemithoracic radiation are associated with a low risk of local recurrence and mainly distant sites of disease progression, while intrathoracic recurrence is more common after P/D and EPD.[57,72]

STATEMENT 7.2: EPP may seldom be performed when the tumor is unresectable by P/D or EPD and the patient has favorable prognostic factors.

In patients with PM undergoing surgery, complete macroscopic resection occasionally may be better achieved by EPP than by P/D or EPD. An example is a tumor associated with a severely scarred and contracted underlying lung that fails to re-expand after decortication. Electing to proceed to EPP requires determination of acceptable performance status, has the cardiopulmonary reserve to tolerate the operation, and has favorable prognostic factors, e.g., pure epithelioid histologic subtype and absence of lymph node metastases. Systematic lymph node sampling or dissection with frozen sections to confirm that the nodes are benign help support an intraoperative decision to proceed to EPP. Performing an EPP leverages the potential advantages of a MCR against a potentially higher operative risk.

Some series indicate that performing an EPP in highly selected patients is acceptable usually within the context of multimodality therapy.[24] Analyses of the multicenter IASLC Mesothelioma Database (retrospectively collected data) utilizing the 7th edition of the PM staging system showed that patients who had stage I tumors experienced a better OS after EPP than after P/D.[73] However, this advantage was not seen in more advanced disease and other factors were prognostically more significant in multivariable analyses. A prospective single institution trial by de Perrot et al. 2016 of accelerated hemithoracic radiation followed by EPP in 62 patients reported an operative mortality of 1.6% and a median OS of 36 months.[72] Krug et al. 2009 reported a prospective Phase II multicenter trial of neoadjuvant chemotherapy followed by EPP and adjuvant hemithoracic radiation.[74] Of 57 patients considered for surgery, 54 underwent EPP with 2 postoperative deaths (3.7%).

Thus, in contemporary practice, EPP is no longer the procedure of choice for PM but, in highly selected situations, may be the most appropriate technical option if performed with acceptably low risk.

STATEMENT 8.1: When indicated, surgery for PM should include lymph node assessment.

When surgery is undertaken for PM, systematic lymph node sampling and/or dissection should be incorporated. Past studies reported that accurate nodal staging is central to prognosis and treatment selection because nodal metastasis consistently identifies a higher-risk group. In the seminal trimodality series from Brigham and Women's Hospital, Sugarbaker et al. 1999 showed that metastatic extrapleural nodes independently doubled the relative risk of death after EPP firmly establishing node status as a key survival determinant.[69] Building on this finding, Flores and colleagues evaluated 348 resected patients having either EPP or P/D and demonstrated a clear prognostic gradient by nodal station: N0 or isolated N1 disease carried a median survival of 19 months, whereas N2 and/or internal thoracic node involvement reduced median survival to 10 months, with outcomes worsening as the number of involved N2 stations increased.[75] These data indicate that both the presence and extent/topography of

nodal spread meaningfully stratify prognosis, supporting routine mediastinal, hilar, and internal mammary nodal assessment at operation.

De Perrot et al. 2016 similarly reported that pathologic N2 disease reduced median survival from 29 to 10 months and was the only independent predictor of poor outcome in multivariable analysis.[72] Importantly, they reported a substantial false-negative rate with mediastinoscopy, with roughly one-third of clinically N0 patients harboring occult N2 metastases at resection, underscoring the need for intraoperative node sampling/dissection.[76] Martin-Ucar et al. 2007 focused on patients with pathologic N2 disease and showed comparably poor survival whether treated with EPP or P/D (≈15months), reinforcing that N2 involvement defines an advanced-risk cohort and should be identified accurately before and during surgery.[77] Contemporary population data confirm the staging issues: Verma et al. 2020 demonstrated occult nodal disease in clinically N0 patients and a 51% higher mortality hazard for pN+ versus pN0, advocating routine pathologic nodal staging in potentially resectable PM.[78] A recent narrative review further confirmed that imaging and even invasive preoperative techniques miss extra-mediastinal stations (e.g., internal mammary, peridiaphragmatic), making surgical lymphadenectomy the most reliable staging modality and essential for multimodality planning.[79]

STATEMENT 8.2: To optimize pathological staging information, sampling/dissection of lymph nodes should include hilar, mediastinal, as well as other lymph node stations relevant to PM including pericardial, diaphragmatic, intercostal, and internal mammary nodes.

Optimal pathological staging in PM requires a systematic lymph node evaluation that extends beyond routine mediastinal and hilar stations. The American Joint Committee on Cancer (AJCC)/IASLC 8th edition revised the nodal classification for PM, grouping ipsilateral bronchopulmonary, hilar, and mediastinal nodes together with additional pleural-drainage stations—specifically internal mammary, peridiaphragmatic/diaphragmatic, pericardial, and intercostal nodes—within the N1 category, reflecting

their shared regional drainage and prognostic relevance.[80] **This change underscores why surgical nodal sampling/dissection is mandatory and include these pleural nodal sites whenever feasible to optimize staging accuracy.**

Posterior intercostal lymph nodes (PICLN) exemplify the importance of expanding nodal assessment because they drain the posterior parietal pleura and chest wall and are a recognized pathway of regional spread.[81] Friedberg and colleagues demonstrated that PICLN metastases are independently associated with substantially worse progression-free and overall survival and add prognostic information beyond traditional nodal assessment, supporting routine harvest during cytoreductive surgery.[82] Berger et al. 2021 showed that preoperative CT has limited sensitivity and specificity for detecting malignant PICLNs; therefore, reliance on imaging alone risks understaging and reinforces the need for intraoperative sampling of the pleural nodal stations.[81]

A recent analysis of the IASLC database for the 9th edition of the staging system found no evidence warranting further modification of the N descriptors introduced in the 8th edition, confirming the ongoing relevance of comprehensive nodal evaluation.[55] Taken together, these data support lymph node sampling/dissection that includes mediastinal and hilar nodes as well as the pleural lymph nodes (pericardial, diaphragmatic/peridiaphragmatic, intercostal/posterior intercostal, and internal mammary stations) to maximize the accuracy of pathological staging in PM.

STATEMENT 9.1: MCR of all visible and palpable disease is recommended for patients who undergo surgery for PM.

Multiple studies from high volume PM centers have shown the benefit of MCR on OS for PM patients.[35,44,83-87] On the contrary, only one retrospective single institution study from Turkey concluded that MCR was not associated with improved survival in PM surgical patients following propensity score matching, in which median OS was similar between the MCR vs. non-MCR groups (13.3 vs. 14.2 months;

P=0.63).[88] However, the surgical groups studied included both P/D and EPP patients, which may have affected the OS based on surgical approach (14.2 months; P=0.63).[88] In summary, MCR of all visible and palpable diseases for patients who undergo surgery for PM is recommended.

STATEMENT 9.2: In some patients, resection of diaphragmatic involvement may be achieved without resection of the entire ipsilateral diaphragm.

In a subset of patients, a diaphragm-sparing approach may be considered if MCR can still be achieved. Arak et al. 2024 found that P/D (diaphragm-sparing) when compared to EPD (diaphragm resection with phrenectomy) had significantly reduced operative time, air leak duration, and length of stay (LOS), with no difference in OS.[89] Furthermore, Sharkey et al. 2016 found no evidence of diaphragm involvement in PM-resected specimens in 37.9% of patients, highlighting the possibility that P/D surgeries performed could in fact spare the diaphragm muscle without compromising MCR.[90] The IASLC Mesothelioma Task Force in 2019 proposed a system towards standardizing surgical-based treatments for PM and also advocated for preserving as much functional diaphragm muscle as possible.[91] In summary, in a certain subset of patients, resection of the disease involving the diaphragm may be achieved without resection of the entire ipsilateral diaphragm with the continued goal of MCR.

STATEMENT 9.3: Incomplete resection (also termed tumor debulking) of PM via any operative approach, including VATS, RATS, or thoracotomy to remove only part of the disease is not recommended.

Incomplete resection of PM, regardless of the operative approach, is not recommended. There have been no direct RCTs comparing partial or incomplete resection either by VATS, RATS, and/or thoracotomy to MCR by P/D and/or EPP. In contrast, as stated in Statement 9.1, multiple large institutional and retrospective studies have shown significant OS benefits when MCR was achieved in PM patients.[35,44,83-87] Furthermore, the 2026 NCCN guidelines for PM specifically state and recommend that the goal of surgery for PM is complete resection of all visible and palpable tumor.[26] In summary,

incomplete resection of PM in any operative approach, including VATS, RATS, or thoracotomy is not recommended.

STATEMENT 10.1: To support optimal multidisciplinary clinical care decisions and the performance of clinical trials, operative reports should use uniform nomenclature to describe the operation (P/D, EPD or EPP) and should reproducibly record each component of the operation. Ideally, this is best achieved through the use of a synoptic report form.

Surgical procedures for PM, particularly those performed with curative intent, have been far less standardized than operations for other thoracic malignancies, notably lung cancer resection. The lack of standardization is related to the variability of the cancer itself combined with variability in surgical techniques, lack of uniform nomenclature, and inconsistency in reporting technical details of the operation. Consequently, it is often difficult to assess surgical results and the impact of resection on oncologic outcomes within the context of multimodality therapy.

To support a universal language and shared understanding among PM surgeons across institutions, recommendations are that uniform nomenclature should be adopted. To standardize the terms to describe operations for PM, Rice et al. 2011 defined EPP, EPD, P/D, and partial pleurectomy.[92] This nomenclature should be used because it provides reproducible general definitions for the operation performed. However, as recommended by Friedberg et al., 2019 the findings at surgery, the technical details of these complex procedures and the extent of any residual tumor at the end of the operation are best recorded using a synoptic format.[91] This enables surgeons from different institutions to assess accurately the extent of resection and its impact on oncologic outcomes.

Synoptic operative reports that uniformly record surgical findings and technical details are known to provide more precise and complete information than traditional narrative reports (especially for cancer operations), and to facilitate data extraction for biostatistical analyses.[93] Published experience has shown that well-structured electronic synoptic operative reports with detailed drop-down menu options

and minimal free text, are not only precise but easy for surgeons to use. Synoptic operative reports have become a standard for accreditation of cancer programs by the American College of Surgeons Commission on Cancer (ACS CoC). The CoC has developed a synoptic operative report format for lung cancer resections but does not yet have one for PM. [94] The template shown in Supplementary Appendix 2 serves as an example for synoptic reporting in this disease.

STATEMENT 10.2: The operative report should describe the extent of pleural resection, along with the extent of chest wall, diaphragm, pericardial, lung, or other organ resection, if any. It should also record the extent of lymph node sampling or dissection, and when applicable, the extent and methods of reconstruction (e.g., chest wall, pericardium and/or diaphragm).

Curative intent operations for PM require not only removal of all pleural tumor but also potential resection of adjacent involved structures, e.g., lung, pericardium, diaphragm, and chest wall. The extent of resection and the need for reconstruction are highly individualized and depend on the stage of disease and the degree to which the individual primary tumor infiltrates adjacent organs. Thus, the operative report should systematically describe the extent of the tumor and record each component of the operation including the extent of pleural resection as well as resection of underlying lung, pericardium, diaphragm, chest wall and any other involved organs. The details of reconstruction, if any, should also be recorded.[91] Again, this information is most accurately captured in a synoptic operative report.

Lymph node metastases are known to have a significant adverse impact on OS in PM. The patterns of lymphatic drainage in PM differ from those seen in lung cancer with mediastinal lymph nodes more frequently involved than peribronchial and hilar lymph nodes.[75] Nodal metastases also occur in pleural-based locations not seen in lung cancer, e.g. internal mammary, peridiaphragmatic, pericardial fat pad, and posterior intercostal lymph nodes. Systematic lymph node sampling or dissection of these various nodal stations is required to provide accurate pathologic staging, to inform prognosis, and to plan

adjuvant therapy. As shown in Supplementary Appendix 2, synoptic reporting allows specific recording of the lymph node stations biopsied or removed.[55,95]

STATEMENT 10.3: The completeness of resection (MCR or gross residual disease) along with sites and extent of residual disease, if any, should be recorded in the operative report.

Contemporary treatment for PM is always multidisciplinary and frequently multimodal. Accurate documentation of surgical findings, including the extent of resection and residual sites of tumor (if any) at the end of the operation, informs decisions about adjuvant therapy. Therefore, all of these factors should be clearly documented in the operative report. Again, this information is best captured within a synoptic report as outlined in Supplementary Appendix 2.

R0 resection (complete resection with microscopically negative margins) is not possible in PM because the margins of resection include organs that cannot or should not be resected (e.g. esophagus, great vessels). However, a MCR (R1 resection) is usually feasible. In some patients, only a R2 resection (residual macroscopic disease) can be achieved. The operative report should clearly record whether a R1 or R2 resection was performed. If gross residual tumor remains at the end of the operation, the disease site(s) and tumor volume should be specified[91,95] (see Supplementary Appendix 2).

STATEMENT 11.1: PM patients with clinical ipsilateral mediastinal N1 nodal involvement based on imaging should undergo preoperative invasive mediastinal staging either by EBUS or mediastinoscopy.

Currently, preoperative CT chest with IV contrast and PET/CT scans are the recommended imaging modalities for preoperative clinical staging in PM. However, PM lymph node metastases differ in spread and location from NSCLC; therefore, whether invasive mediastinal staging either by EBUS and/or mediastinoscopy is routinely warranted in all patients is unknown. What is known is that positive lymph node status is associated with worse OS in PM.[55,79] Also, the total number of positive lymph nodes, lymph node involvement, and metastatic lymph node ratio are important prognostic factors.[96,97] There continue to be mixed results on the value of routine EBUS and/or mediastinoscopy in all PM patients

regardless of clinical imaging characteristics due to potential incongruity between preoperative invasive nodal staging results and final pathological nodal staging results.[76] This controversy is based on the lack of survival difference between whether the patient received preoperative EBUS and/or mediastinoscopy or not.[76] However, these studies were based on routine mediastinoscopy prior to EPP and are not the current more standardized approach of P/D. In addition, preoperative EBUS mediastinal staging in PM patients with positive N2/N3 disease prevented unnecessary surgery in 18.8% of patients with no EBUS-related complications.[21] In summary, the expert panel recommends preoperative invasive mediastinal staging by EBUS and/or mediastinoscopy when there is a high suspicion of at least N1 (ipsilateral) nodal involvement based on CT and/or PET CT scan.

STATEMENT 11.2: PM patients with confirmed ipsilateral N1 nodal stations based on EBUS/mediastinoscopy may be considered for surgery in the context of a multimodal treatment regimen.

The multimodal management involving surgery in PM patients with confirmed N1 disease (ipsilateral nodal stations on EBUS and/or mediastinoscopy) is complex due to a lack of large scale multicenter trials in this rare subpopulation. However, when considering surgery for node-positive disease, Martin-Ucar et al. 2007 found that PM patients with N2 disease who underwent P/D had acceptable survival rates (mean OS = 16 months) and decreased morbidity compared to EPP patients. In addition, current 2026 NCCN guidelines for surgical treatment state that if technically appropriate, P/D for advanced stage PM including N1 disease can reduce the risk for perioperative mortality and may be acceptable if MCR can be achieved or in the setting of excellent symptomatic control for recurrent pleural effusions.[26] Verma et al., after reviewing all clinically lymph node (LN)+ PM patients treated with all modalities including surgery, concluded that even though more advanced nodal disease is associated with worse prognosis, nodal status alone should not be an exclusion criterion for surgery and other important factors including age, performance status and histology should be taken into account when deciding whether surgery

should be offered in a multimodal approach.[78,79,98] In addition, data on LN+ PM patients from high volume PM centers have revealed acceptable survival numbers when surgery was utilized in a multimodal fashion. In particular, node-positive patients with epithelioid histology who achieved MCR showed favorable OS.[49,91,99] Recently, the IASLC Nodal staging manuscript noted OS >40% at three-years in patients who underwent surgery with positive N1 disease. In summary, PM patients with confirmed N1 (ipsilateral) nodal stations may be considered for surgery in a multimodal treatment regimen with emphasis on younger age, optimal performance status, epithelioid histology, and evaluation from a high-volume PM center.

STATEMENT 11.3: PM patients with preoperative clinical contralateral N2 or supraclavicular lymph node involvement confirmed either by EBUS/mediastinoscopy or incisional biopsy should generally not be considered for surgery.

PM patients with preoperative N2 contralateral or supraclavicular lymph node involvement either by EBUS or mediastinoscopy generally have very poor OS. Bille et al. 2024 reported significantly worse OS based on lymph node status after adjusting for age, gender, region, and histologic subtype with a median OS of 13.3 months for N2 tumors versus 23.2 months for N0 tumors.[55] The authors also noted significant differences in OS between N0 versus N1 (HR=1.31, p = 0.0009) and between N1 versus N2 (HR = 1.41, p = 0.0016) with clearly more inferior survival when N2 lymph nodes were positive compared to N1 lymph nodes. Furthermore, the 2026 NCCN guidelines state that if N2 disease is identified preoperatively, prognosis with surgery is diminished and that surgery should be considered in a clinical trial setting or at a center with extensive expertise in PM.[26] In summary, PM patients with N2 LN involvement should generally not be considered for surgery with the emphasis being placed for consideration of enrollment in clinical trials and further evaluation from expert high volume PM centers.

STATEMENT 12.1: Intra-operative regional adjuvant therapy may be considered during surgery for PM. Despite MCR, ipsilateral thoracic recurrences remain the most common site of recurrent disease.[100-103] Given that the major site of recurrence is local, intra-operative adjuvant therapy is commonly performed with the goal of decreasing the local recurrence rate. Multiple adjuvant therapies that are administered intra-operatively have been studied; yet, RCTs comparing therapies to one another or therapies to a no-therapy arm have not been performed. The most common intra-operative regional adjuvant therapies include chemotherapy, povidone-iodine, and photodynamic therapy.[69,100,104,105]

Intra-operative regional adjuvant chemotherapy has questionable benefit in prospective phase II studies.[100,103] These reports noted significant toxicity associated with intra-operative therapy. However, subgroup analyses and retrospective reports suggest that intra-operative chemotherapy may be beneficial for appropriately selected cohorts. The phase II study reported that the higher dose level was associated with a better survival rate.[103] This study also noted survival was associated with the expected prognostic factors including complete resection and epithelial histology. Additionally, a large retrospective series reported that adjuvant chemotherapy was associated with longer survivals in a lower risk cohort.[106] More recently, retrospective evaluation of hyperthermic pleural lavage with povidone-iodine noted no post-operative mortalities and minimal toxicity with survival rates that compare favorably to other strategies.[104]

Patients with PM have a high rate of local recurrences; therefore, intra-operative methods to decrease this rate are appealing. However, to date, an effective method has not been clearly defined. Both chemotherapy and povidone-iodine may provide benefit, but given the lack of proven benefit, methods to prevent adverse events with these therapies are critically important.

MANAGEMENT OF PLEURAL MESOTHELIOMA RECURRENCE

STATEMENT 13.1: Surgical resection should be considered for durable control of isolated recurrence (chest wall, pleura, etc.) following prior surgical resection.

Surgical resection remains an appropriate option to achieve durable local control for well selected patients who have isolated chest wall and/or pleural recurrences following prior surgical resection. Investigators from Brigham and Women's Hospital reported on their experience of 47 patients who had chest wall recurrences amenable to a second resection at a median of 16.1 months following EPP or P/D. Chest wall resection was shown to be safe and feasible, with survival following surgery correlated with the time from initial resection to chest wall recurrence.[107] Researchers from Hyogo College of Medicine in Japan evaluated 57 patients who developed recurrence following neoadjuvant chemotherapy and P/D. The 1-year post-recurrence survival rate for the whole cohort was 59.5%, with the 43 patients undergoing post recurrence treatment having a five-fold improvement in survival relative to best supportive care that included up to 2 additional cycles of chemotherapy. Three patients in that cohort underwent a salvage chest wall resection.[108] Investigators from University of Florence in Italy assessed 11 patients who experienced recurrences following EPP, 8 of whom underwent a second surgery with curative intent. Median survival after the second surgery was 14.5 months, with the investigators concluding that due to the limited survival, second operations are most appropriate in patients with isolated, symptomatic recurrences near vital organs who cannot undergo radiotherapy.[109]

The use of surgical resection for local control of isolated recurrences should be a multidisciplinary decision in conjunction with radiation and medical oncology. Such decisions should consider the extent and risk of the required resection, the likelihood of disease control, the general medical condition of the patient, the prognostic profile of the patient's tumor (e.g., histologic subtype) and alternative treatment options. Because resections for local recurrence may be technically and oncologically complex, they are best performed at centers of excellence for PM.

STATEMENT 13.2: Stereotactic body radiation therapy should be considered for isolated pleural recurrence.

Stereotactic body radiation therapy (SBRT) is another viable local therapy option for PM patients with isolated pleural recurrences. SBRT, typically delivered in five or fewer fractions to discrete tumor sites of up to 7 cm,[110] can achieve durable local control with low toxicity rates in patients with isolated pleural recurrences. Investigators from Milan, Italy reported on 37 patients treated to 43 pleural lesions with SBRT or hypofractionated radiotherapy. With relatively modest biologically effective doses, the local control rate at 1 year was 76% for the entire cohort, with improved local control among patients being treated with higher ablative SBRT dosing, and no grade ≥3 acute or late toxicities reported.[111] Among 25 sites treated with SBRT for 15 patients with PM, investigators from University of Pennsylvania reported a 2-year local control rate of 100% and 3-year local control rate of 87.5%, with no acute or late grade ≥3 SBRT-related toxicities.[112] In the largest series reported to date, researchers from Memorial Sloan Kettering Cancer Center reported on 44 patients who had 59 lesions treated. At 1 year, local control for the pleural lesions was 96.3%, and again no grade ≥3 acute or late toxicities were seen.[113] In summary, the literature suggests SBRT to be an extremely safe and very effective modality to achieve durable local control in patients with isolated pleural recurrences.

STATEMENT 13.3: Conventionally fractionated or mildly hypofractionated radiation therapy should be considered for diffuse and/or bulky pleural disease recurrence in well selected patients.

Beyond the established roles of conventionally fractionated or mildly hypofractionated radiation therapy for palliation or as an adjuvant or neoadjuvant modality in patients undergoing EPP or EP/D, radiotherapy can be considered as a salvage or definitive modality in patients with diffuse and/or bulky pleural recurrences. While high doses of radiation therapy for bulky PM disease were historically limited to delivery in patients having undergone EPP who are not at risk of developing radiation pneumonitis in the ipsilateral lung, the increased utilization of IMRT[114] has afforded for the safer delivery of

radiotherapy to larger volumes, even in patients with two intact lungs.[115] With its unique physical properties, proton therapy has further enabled the definitive treatment of larger or more diffuse PM recurrences and can better spare irradiation dose to the heart, esophagus, contralateral lung, liver, kidney and stomach, with early clinical reports showing excellent tumor control and low toxicity rates with proton therapy.[116-120] These advanced radiation modalities, including IMRT and proton therapy, can allow for safer radiation dose escalation, which can optimize tumor control for mesothelioma. Through its immunomodulatory role, radiation therapy delivered to salvage patients progressing while receiving systemic therapy may also allow for synergy with immunotherapy and the potential for abscopal responses.[121,122] Definitive-intent doses of radiation therapy, however, can be associated with high rates of pneumonitis, especially when large pleural recurrences or all pleural surfaces of the ipsilateral chest are being targeted, and such approaches should preferably be undertaken in high-volume mesothelioma centers of excellence or on a clinical trial. [121,122]

CONCLUSIONS

PM is a rare thoracic malignancy with complex treatment options. This expert consensus document highlights the most current interpretation of the literature on the multimodal management of PM by multidisciplinary experts with specific extensive experience treating PM. The goal of these statements on the multimodal management of PM is to provide clinicians, particularly thoracic surgeons, a practical framework on how to manage these complex patients. The authors understand the limited availability of high quality RCT evidence for this rare malignancy and that the final management recommendations are based on the panel's clinical experience treating PM as well as their interpretation of the data sources which does introduce some subjectivity and biases. In summary, PM patients should have confirmation of histologic subtype, thorough initial clinical staging, and expert multidisciplinary review of individual treatment options including whether or not consideration of surgical resection is appropriate.

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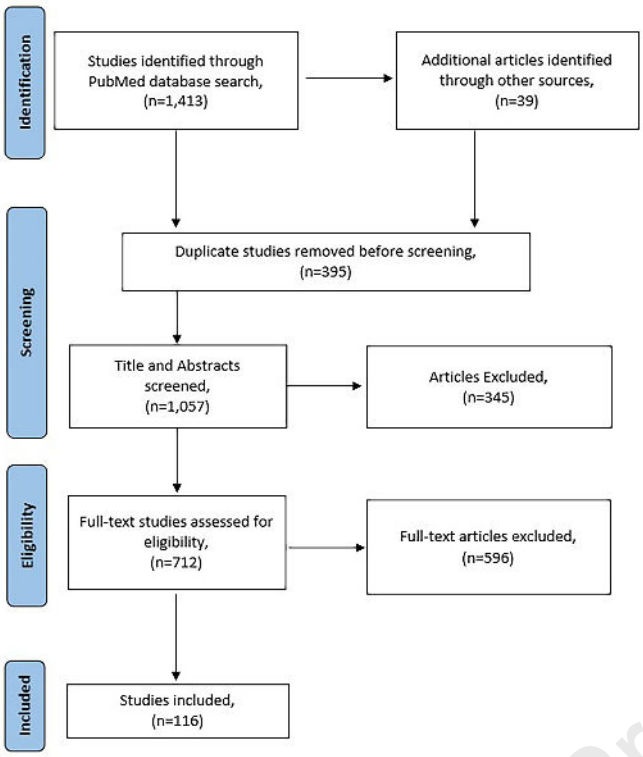
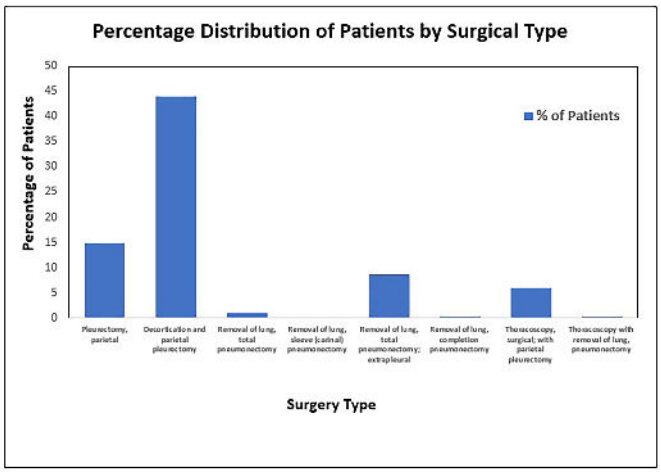
FIGURE LEGENDS

Figure 1: Illustrates PRISMA Flowchart for Study Identification and Selection Process.

Figure 2: Percentage distribution of patients represented by surgery type from January 1, 2015, to December 31, 2025 based on data from the STS General Thoracic Surgery Database (GTSD).





Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: