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Contemporary issues in the surgical management of pleural mesothelioma

Juuso Paajanen, MD, PhD[1], **Michael T. Jaklitsch, MD**[1], **Raphael Bueno, MD**[1]

[1]The Thoracic Surgery Oncology laboratory and the International Mesothelioma Program (www.impmeso.org), Division of Thoracic Surgery and the Lung Center, Brigham and Women's Hospital, and Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

Abstract

The surgical management of pleural mesothelioma (PM) can be divided into diagnostic, staging, palliation, and cytoreductive surgery. In the cytoreductive surgical setting, the combination of different treatment modalities has led to better outcomes than surgery alone. The scarcity of high-quality studies has led to heterogeneity in management of PM across the mesothelioma treatment centers. Here, we review the literature regarding the most important open questions and ongoing clinical trials.

Keywords

Mesothelioma; surgery; pleurectomy decortication; multimodality treatment

Introduction

Pleural mesothelioma (PM) is a rare, aggressive cancer, usually associated with prior asbestos exposure. The incidence is slightly under 1 per 100,000 persons in the US, with men showing an approximately five times higher incidence rate compared to women.[1] After a latency period of 15–50 years, a multifocal PM grows typically in the pleura and produces a rind that constricts lung, heart and mediastinum. Improvement of outcomes has proved to be challenging as the median overall survival (OS) has varied from 7 to 14 months with 5-year survival rate at 5 to 10% for decades.[2–4] PMs are divided into three histological subtypes, which are used for treatment decisions and have prognostic impact: epithelioid with epithelial-shaped cells, sarcomatoid with spindle-shaped cell, and biphasic (or mixed) with a mixture of the two types of cells.[5]

The management of PM consists of surgery, systemic therapies and radiotherapy (RT).[6,7] Surgical approaches are needed to obtain sufficient diagnostic pleural biopsies, for palliative therapies, and for cytoreductive surgery. The invasive growth of PM into the pleural cavity poses challenges for true microscopic negative margins (i.e., R0) resection. Thus, the

Corresponding Author: Raphael Bueno, Division of Thoracic Surgery, Brigham and Women's Hospital 75 Francis Street, Boston, MA 02115, USA. Phone: (617)732-5004; Fax: (617) 566-3441; rbueno@bwh.harvard.edu.

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primary goal of current surgical options is the removal of all grossly visible, palpable, and viable tumor, i.e., complete macroscopic resection (MCR),[8] which can be achieved by extrapleural pneumonectomy (EPP) or (extended) pleurectomy/decortication (PD). Local recurrence remains a major barrier to long-term survival in surgical patients. The microscopic residual disease after surgery is often targeted with either local or systemic modalities. The multimodality approach, whether adding therapies before, during, or after surgery, leads to superior outcomes than surgery alone.[2,9,10] Other aims for surgical management are improvement of symptoms and quality of life (QoL) by the means of lung re-expansion, prevention of pleural fluid accumulation, and by relieving the painful invasive growth of the tumor.[11]

During the last decades, cytoreductive surgery in PM has largely shifted, at least in most North American centers, from EPP to PD.[11,12] This shift is based on an increasing evidence on equivalent oncologic survival between the two procedures,[13] lower short-term mortality and morbidity,[14] better quality of life,[15] and potential long-term survival associated with lung sparing operations.

The scarcity of randomized controlled trials (RCTs) due to the low incidence of PM and preconceived notions in various centers have resulted in uncertainties and controversies regarding the optimal surgery-based approach.[16] Here, we review the literature and discuss ongoing clinical trials (Table 1) regarding major unanswered questions in the surgical management of PM. Specifically, we will focus on PD-based studies and discuss I) the effects of PD, II) patient selection and prognostic markers related to surgery, and III) the multimodal therapies adjunctive of surgery.

What are the effects of pleurectomy decortication in pleural mesothelioma?

Historically, PD has been considered as a palliative procedure as opposed to more radical lung sacrificing surgery EPP. Recommendations for uniform nomenclature and surgical techniques has been previously proposed.[17,18] The agreed terminology of PD takes account the extent of resection: ePD indicates parietal and visceral pleurectomy to remove all gross tumor with resection of the diaphragm and/or pericardium, whereas PD indicates only parietal and visceral pleurectomy. Partial pleurectomy indicates only partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes.[19] For optimal staging, all procedures are usually combined with systematic mediastinal lymph node sampling or dissection.

The current evidence of survival after PD is limited to small single institutional early phase clinical studies and retrospective series (Table 2). In the datasets of over 100 PD treated patients, the median OS varies from 12 to 36 months with a median disease-free survival of 10 to 14 months.[13,20–30] Importantly, in many studies the 5-year survival has surpassed 20%.[22,25,31] Our experiences were recently published by Lapidot and colleagues.[22] We included 355 consecutive PM patients from 2007 to 2015. There were no strict restrictions on histology: in the final pathology report, most of the tumors were epithelioids (60%), compared to 33% biphasics, and 7% sarcomatoids. Out of 355 resected patients, 86% achieved MCR. The survival doubled in patients who achieved MCR (median OS 23.2

months, 95% CI 19.4 – 28.7), in contrast to non-MCR (11.6 months, 95% CI 7 – 20.2). Patients with best prognostic variables (epithelioid histology and T1 disease) experienced prolonged survival with median OS of 69.8 months and a 54.1% 5-year survival rate.

In most datasets, perioperative mortality and morbidity have been constantly lower in PD compared to EPP. Meta-analysis of survival after PD or EPP, consisted of 1,512 patients treated with PD and 1,391 with EPP, demonstrated a 30-day mortality rate of 1.7%, compared to 4.5% in EPP group.[14] Most common causes for perioperative mortality after PD are associated with cardiovascular diseases and intraoperative bleeding, especially in the setting of anticoagulation. In 2013, Cao et al.[32] published a systematic review of PD, including 34 studies and 1,916 patients. Overall, complications were reported in 20–43% of cases. Average length of hospital stay ranged from 7 to 15 days. Most common surgical complication after PD, prolonged air leak (10 – 57%), is related to lung parenchyma injury during visceral pleurectomy.[22,23,25,33] Persisted air leak can lead to prolonged hospital stay and chest tube use, and is associated with increased risk of empyema and intensive care unit re-admission.[34] Prolonged air leak is usually managed conservatively with maintenance of chest tube until full lung expansion or resolution of the air leak. If substantial lung parenchymal injury is noted, some centers install absorbable lung sealant or use intraoperative hypertonic glucose solution during surgery, but more prospective data is needed before larger adaptation of these techniques.[23,34] Other common complications related to PD are deep vein thrombosis (21 – 23%), atrial fibrillation (7 – 28%), pneumonia (7 – 28%), chyle leak (5 – 13%), and empyema (1 – 8%).[22,23,25,33]

The assessment of QoL has been infrequently reported in surgical studies. Regarding radical surgery, several studies have shown that PD is associated with better QoL than EPP.[35] Only one RCT, MesoVATS,[36], has evaluated symptomatic improvement after partial PD in patients with confirmed or suspected PM with pleural effusion. Eligible patients were randomized to partial PD (N = 87) or talc pleurodesis (N = 88). Expectedly, partial PD was associated with more complications and longer hospital stay than more conservative talc pleurodesis. However, the rate of pleural fluid reaccumulation was lower in the first 6 months after the procedure, and QoL was significantly better at 6 and 12 months in the partial PD group. Several single-center experiences without control groups have assessed QoL on PD using a standardized European Organization for Research and Treatment of Cancer core questionnaire (EORCT-QLQ-30) questionnaire. Mollberg et al.[37] used a pre- and postoperative questionnaire on 28 prospectively enrolled PD-treated PM patients. They observed no benefit nor harm on patients with low symptom rate at baseline, but symptomatic patients showed significant improvement in global QoL, fatigue, and dyspnea scores at the follow-up. Another study had 114 PM patients who underwent PD with a follow-up lasting up to 11 months from surgery[38]. The overall global health declined after 1 month from surgery but improved thereafter. Subgroup analyses showed that especially non-epithelioid histology and patients with high tumor volume had worse QoL at baseline but presented greatest improvement following PD. Burkholder et al.[39] evaluated 36 PM patients who underwent PD with lung function tests and QoL questionnaire. Similar to previous studies, they observed that patients with performance score (PS) 1 or 2 at baseline showed improvements of QoL after 4 to 5 months of surgery, while only emotional function improved in patients who had PS 0 at baseline. Also, the lung function decreased after PD in

patients with good PS status, whereas no significant changes were observed in patients who had PS 1–2 at baseline.

In summary, these operations are long and commonly complex, and associated with postoperative adverse events but carry the hope of extend 5-year survival for a minority of patients. Although selection bias may explain some of the findings, current evidence suggests that a subset of patients may benefit from PD in terms of survival and QoL. The current north American guidelines recommends maximal surgical cytoreduction as part of the multimodality approach for early-stage PM.[6] Most recent European guidelines suggests that radical surgery is performed in the context of clinical trials or registries.[7,40] An ongoing RCT, MARS2 (NCT02040272), includes 328 patients with resectable PM to standard chemotherapy with or without (e)PD.[41] In the protocol, patients receive two cycles of induction chemotherapy and thereafter are randomized to surgery or no surgery followed by four cycles of chemotherapy. The recruitment has finished, and the results are anticipated in the near future. Hopefully, the study will shed light on the fundamental question whether PD improves survival and QoL in a randomized, controlled, setting.

Who can be considered for radical surgical management?

The shift from EPP to PD has expanded the potential candidates for radical surgical management. Especially, patients with advanced age or limited cardiorespiratory reserves can be considered for PD. Comprehensive preoperative workup for surgical candidates is recommended by most recent European and North American guidelines.[6,7] We estimate that approximately one third of patients are deemed inoperative after our institutes preoperative work-up. We routinely make cardiorespiratory assessments with spirometry and diffusion capacity of the lung for carbon monoxide, ventilation perfusion scan, ECHO, and stress test. We have a low threshold of cardiology and/or pulmonology consultation for patients with abnormal findings. Preoperative imaging includes chest radiograph, contrast-enhanced computed tomography (CT) of the chest, magnetic resonance imaging (MRI) of the chest, and positron emission tomography (PET)-CT scan. To exclude mediastinal lymph node metastases, we use typically endobronchial ultrasound (EBUS), as it is less invasive and found to have comparable diagnostic accuracy to mediastinoscopy.[42] Additional imaging (e.g., brain MRI) or invasive procedures (e.g., laparoscopy or contralateral thoracoscopy) are considered in patients with symptoms or inconclusive findings. The criteria by which PM patients are evaluated as resectable or not varies from center to center, and is based on histology, tumor extent, lymph node status, and physician preferences. In general, patients are excluded from cytoreductive surgery, if they have sarcomatoid histology, positive mediastinal or other extrathoracic lymph nodes or T4-disease (i.e., multifocal, diffuse chest wall invasion or transmural pericardial, mediastinal organ, transdiaphragmatic, vertebrae or brachial plexus, or contralateral pleura invasion).[7] At our institution, patients found to have ipsilateral mediastinal lymph nodes and/or tumor extension to the chest wall on preoperative workup undergo neoadjuvant chemotherapy before re-evaluation for surgery. Candidate for surgery at our institution are patients with good function, ipsilateral disease limited to the pleura without mediastinal lymph node involvement, pain, chest contraction or chest wall extension. We forgo upfront chemotherapy in these patients, because it works at best in 40% of all comers, thus, many may experience progression and become unresectable as

discovered in the Memorial study a few years ago.[43] We routinely recommend postoperative chemotherapy immediately after surgical resection for all patients who did not receive induction chemotherapy and for all who were found to have positive lymph nodes or advanced T-stage. More recently, based on encouraging results on unresectable patients,[44] we have moved to recommend adjuvant immunotherapy for all patients with non-epithelial histology following surgery.

The current staging system is the eighth edition of the AJCC tumor, node, and metastasis (TNM) system. The pathologic staging is based on surgically resected samples.[45] A key clinical barrier is that clinical staging tends to underestimate the true extension of the disease. The T-status, which accounts for the location and invasiveness of the tumor, can be especially difficult to measure from imaging. In a review of IASLC staging project,[46] initial T categories were upstaged in 56% for T1 cases, 54% of T2 cases, and 39% of T3 cases during surgery. Only 4% of all cases were assigned to lower pathological than clinical T-stage category. Thus, several additional methods to quantify tumor burden, such as CT-assessed tumor volume (TV), have been proposed but not yet implemented in the official staging system.[47–49] Our group proposed a novel quantitative clinical staging method, including TV and maximal fissural thickness from preoperative CT scans.[47] A total of 472 patients were evaluated, and quantitative staging was compared to clinical TNM. We found that quantitative clinical staging performed statistically (c-index = 0.64, 95% CI 0.60–0.67) better as a prognostic classifier compared to clinical TNM stage (c = 0.56, 95% CI 0.53–0.60).

Prognostic variables in surgical patients have been extensively studied in patients who underwent EPP, and findings from PD series largely reflects similar associations.[10,28,50–52] In 2015, multivariable analyses from 102 PD patients demonstrated that MCR and epithelioid histology were associated with best prognosis.[25] In 2017, Shaikh et al.[24] analyzed 209 patients who underwent PD and adjuvant RT between 1974 and 2015. They observed that, after adjustments, higher Karnofsky PS status, epithelioid histology, MCR, and the use of adjuvant chemotherapy and/or intensity-modulated pleural RT were significant factors for longer survival. However, the association with MCR and survival was challenged in a study by Batirel and colleagues.[53] They analyzed 154 patients who underwent PD (N = 90), EPP (N = 42), or exploratory procedures (N = 22). MCR was achieved in half of the patients, and although survival was increased, it did not reach statistical significance (median OS 21.4 vs 16.3 months, P = 0.60). The study from Friedberg et al.[23] included 73 epithelioid PMs. They demonstrated that, similar to previous EPP series,[54] advanced nodal status (N1-2) and male sex were associated with worse prognosis. The largest dataset on PD studied factors associated with survival in a cohort of 304 patients who achieved MCR.[22] Independent predictors of prolonged survival were short hospital stay, epithelioid histology, low TV, early T-stage, intraoperative heated chemotherapy (IOHC), and adjuvant chemotherapy.

Interestingly, in contrast to many EPP series, age has not been a major prognostic factor among PD-treated patients. Along those findings, Williams et al.[26] compared outcomes after ePD in patients over 70 (N = 54) and under 70 years (N = 63). Even if comorbidities were, expectedly, higher in elder patients, the rate of postoperative mortality (3.7% vs 3.2%) or

major complications (5.5% vs 11.1%) did not significantly differ between study groups. Survival was also similar in both groups (median OS 15.6 months in elder vs 14.0 months in younger). Sharkey and colleagues[27] presented their experiences from an intentional shift from EPP to ePD during 1999 to 2014. Albeit they observed no survival differences between the two groups, patients over 65 years had significantly longer OS in patients undergoing ePD (12.5 vs 4.7 months, P = 0.001).

Histology remains one of the most important prognostic factors and sarcomatoid histology is used as an exclusion criteria in most clinical trials.[10,55] In a review of 1,183 patients in the SEER database, the medial OS in surgically treated patients with epithelial, biphasic, and sarcomatoid disease was 19, 12, and 4 months, respectively.[56] However, histologic subtype is not always reliably diagnosed from core-needle or surgical biopsies. Our group examined 759 consecutive patients treated by PD or EPP and compared the pre- and postsurgical histologies.[57] Of note, preoperative biopsies were mostly (96%) thoracoscopic. The overall concordance for histologic subtyping between initial biopsies and surgical resections was 81.6%. The discordant diagnoses included 112 of 575 patients with initial epithelioid PM who were subsequently diagnosed as biphasic. Similarly, 19 of 140 who were initially diagnosed as biphasic were subsequently diagnosed as epithelioid (N = 15) or sarcomatoid (N = 4). In addition, 7 of the 36 (19%) sarcomatoid PM were reclassified as biphasic in the surgical resection. Recently, we analyzed the outcomes of all patients with biphasic histology with intended PD.[58] Similar to the larger group with all histology, MCR was achieved in 86% of cases. The median OS was 16.7 months in those with MCR and 24 months in those patients younger than 70 years. In univariate analysis, age and preoperative lung function were associated with survival. We did not measure the extent of sarcomatoid histology in tumor specimens, which has been demonstrated as an important prognostic factor in previous studies.[59,60]

Several previously described PM prognostic scores are based on patients undergoing chemotherapy,[61,62] while surgical-based models have been limited.[63–65] Multimodality prognostic score (MMPS), presented by Opitz et al.,[63] was based on 128 patients undergoing induction chemotherapy followed by EPP. Each of the items were counted as a single point: pre-treatment TV greater than 500ml, non-epithelioid histology, serum C-reactive protein value over 30mg/L, and progression after induction chemotherapy assessed by modified RECIST criteria. MMPS sorted patients into different survival groups: Patients with a score of 0 had a median survival of 34 months compared to 17 months in score 1, 12 months in score 2, and 4 months in score 3–4 (P<0.0005). The authors stated that patients with MMPS score over three don’t benefit from multimodal approach. Recently, the authors validated MMPS with 88 patients treated by EPP (16%) or PD (84%).[66] They also investigated whether pre-treatment circulating biomarkers (erythrocytes, neutrophils, monocytes, albumin, gamma-glutamyl transferase, and alkaline phosphatase) would increase its discriminative ability. They observed that serum albumin had the largest influence on OS and incorporated it into a new MMPS score. Harris et al.[65] applied a previously derived classification and regression tree (CART) model to 289 surgically treated cases from Australia and Japan. The variables used to define the four risk groups were weight loss, hemoglobin (Hb), albumin, histology, and ECOG PS. The survival across the four risk groups was significantly different (P<0.0001): The median OS in group 1 (no weight loss,

Hb > 153 g/L, albumin > 43g/L) was 82.5 months (IQR 28.1 – 152.4) in contrast to 42.3 months (IQR 24.6 – 73.9) in group 2, 35.2 months (IQR 18.1 – 54.8) in group 3, and 22 months (IQR 10.1–41.9) in group 4. More recently, we investigated if genetic transcriptional expression profiles can add value to commonly used clinicopathological factors. Our final model, mesothelioma risk score (MRiS),[64] includes ECOG PS, pre-treatment TV, serum albumin, and serum neutrophil/lymphocyte ratio as clinical parameters. We also included previously described and validated Mesothelioma Prognostic Test (MPT)[67,68], which calculates geometric mean for several gene ratios along with claudin/vimentin ratio[69] that distinguish epithelioid from non-epithelioid subtypes. Although the original MPT was discovered and validated on EPP patients, the MRiS score could divide PD treated patients into three distinct survival groups (c = 0.64, 95% CI 0.53 – 6.22). MRiS achieved higher accuracy than previously published models (c = 0.57 – 0.58) and pathologic staging (c = 0.55 – 0.57). We have created an online tool that can be used for preoperative variables to calculate MRiS score and expected median survival associated with each type of surgery (https://mris.brighamandwomens.org/). Importantly, all presented predictive models use variables that can be achieved before surgery.

The intraoperative adjunctive therapies in pleural mesothelioma

Several intracavitary therapies have been proposed to target microscopic residual disease and to improve loco-regional effects of surgery. The rationale for intracavitary therapies is to spread cytotoxic agents on the microscopic tumor surface, limiting the systemic toxicity and adverse effects.[70] However, the lack of comparative trials, the heterogeneity in inclusion criteria, and differences among treatment regimen in previous studies prevent from making strict recommendations among different local treatments. Current guidelines consider even the most studied intracavitary therapies, IOHC, photodynamic therapy (PDT), and hyperthermic povidone-iodine (PI), as investigational agents preferably performed in the context of clinical trials.[6,40]

If no contraindication exists, our approach is to use the lavage of cisplatin at a dose of 175 mg/m^2 with or without gemcitabine at 1000 to 1200mg/m^2 that is circulated up to 60 minutes at 42°C. Hypertermia increases the penetration of chemotherapy at the pleural surface and enhances cytotoxicity to tumor cells.[71] For cytoprotection, we routinely use intravenous sodium thiosulfate of 12g/m^2 and amifostine at a dose of 910mg/m^2.[72] The vast majority of previous studies have used single agent cisplatin, while some have used combinations of agents.[73] Several early phase studies have demonstrated the feasibility and safety of cytoreductive surgery combined with IOHC.[72,74–76] In 2013, Sugarbaker and colleagues[77] compared the outcomes of patients treated with EPP or PD with or without IOHC. They focused on patients with favorable prognostic factors with minimal differences between the study groups. They observed that both OS (35 vs 23 months, P = 0.026) and disease-free interval (DFI) (27 vs 13 months, P = 0.0084) were longer in patients who received IOHC. More recently, two systematic reviews have evaluated the efficacy and safety of IOHC.[78,79] Dawson et al.[79] included 15 studies that report OS and/or DFI in PM patients undergoing cytoreductive surgery with IOHC. They observed no difference in 30-day mortality (4.7% vs 3.8%) or morbidity (40% vs 39%) rate among those who had

IOHC against those who did not, respectively. IOHC was associated with longer OS (range 11–75 vs 5–36 months) and DFI (range 7.2–57 vs 12.1–21 months).

The distinction between intracavitary lavage from surgery-related toxicities is difficult from non-randomized series. Atrial fibrillation (20.4%) and renal complications (16.8%) are the most frequently reported complications associated with cytoreductive surgery and IOHC.[79] Kidney injury is especially linked to systemic absorption rate of intracavitary cisplatin.[75] Hod et al.[80] evaluated 503 patients who underwent cytoreductive surgery and IOHC at our institution. The incidence of acute kidney injury (AKI) was 48.3%. Severe AKI, requiring renal replacement, was observed in 16 (3.2%) patients and was associated with EPP and higher dose (over 175mg/m^2) of cisplatin. The most frequent risk factors for AKI were male sex, intraoperative cisplatin usage, prior systemic cisplatin exposure, hypertension, elevated baseline eGFR, and prolonged surgery time. Other studies have investigated strategies to decrease postoperative complications associated with IOHC. In a phase I-II study, Richards and colleagues[74] studied the maximum-tolerated dose of intracavitary cisplatin in 44 patients undergoing PD. The dose of cisplatin was associated with survival and adverse effects: dose-limiting renal toxicity occurred at 250mg/m^2 and four of the fifth deaths were in patients treated with a cisplatin dose of 225 to 250mg/m^2. In another study, a nonsignificant reduction of renal toxicity was observed in patients treated with intravenous sodium thiosulfate and amifostine (1 in 27 vs 7 in 65).[72] In addition, preclinical models as well as a small phase I study have demonstrated that cisplatin loaded to fibrin gel can increase local drug concentration and reduce systemic toxicity.[75]

PDT is another widely studied modality that can complement surgery. It relies on non-ionizing visible light that is generated by a laser device. PDT uses a systemic light-absorbing photosensitizing agent (i.e., photosensitizer) that can accumulate in tumor cells and is activated by wavelength-specific light to produce reactive oxygen leading to cell death.[81] The benefit, compared to IOHC, is that PDT can be administered repeatedly without cumulative toxicity with minimal adverse effects. Indeed, several early phase studies have demonstrated that PDT is feasible and a safe option with cytoreductive surgery.[82] Also, the rate of complications did not differ among two clinical trials that compared cytoreductive surgery with or without PDT.[83,84] In 1997, a phase III RCT (N = 63) compared a protocol of cytoreductive surgery and postoperative cisplatin, interferon α−2b, and tamoxifen with or without first-generation PDT.[83] They observed no differences between the study groups in terms of OS (14.4 vs 14.1 months) or progression free survival (8.5 vs 7.7 months). In 2004, study by Matzi et al.[84] investigated effects of hyperbaric oxygenation with PD and intraoperative PDT. They included 34 patients, out of which 65% underwent PD plus PDT regimen and the rest PD alone. At 6 months, the recurrence rate was higher in the non-PDT group (83%) than the PDT group (41%). They also observed a survival advantage related to PDT (15 versus 10 months, P = 0.0179). In 2017, Friedberg and colleagues[23] published a retrospective series, including 73 epithelioid PMs who underwent PD and PDT. Most of the patients (93%) also received adjuvant chemotherapy. The median OS was 36 months with a DFI of 14 months. The role of PDT is now under investigation in an ongoing randomized trial (NCT02153229), where investigators aim to randomize 102 participants with epithelioid PM into PD plus adjuvant chemotherapy with or without intraoperative PDT.

Povidone-iodine has been widely used an antiseptic and intrapleural pleurodesis agent over past decades without signs of major adverse effects.[85] Preclinical studies in PM, and other malignancies, have demonstrated direct, dose-dependent, cytotoxic effect on tumor cells.[86,87] Lang-lazdunski and colleagues[25] have adopted intraoperative hyperthermic PI lavage into their PD protocol followed by prophylactic chest wall RT and systemic chemotherapy. In a report of 102 patients, they demonstrated it as a safe and well-tolerated multimodality regimen. The perioperative mortality rate was zero with few postoperative complications. The median OS was 32 months with a median DFI of 12 months.

Induction or adjuvant systemic therapies in multimodality protocols?

In a review of prognostic variables of 2,141 resected patients, either induction or adjuvant chemotherapy, were associated with prolonged survival in multivariable analysis (HR 1.56, $P < 0.001$).[10] The generally accepted chemotherapeutic agents in both settings have been platinum plus pemetrexed, based on its superiority to cisplatin in unresectable PM.[88] In 2012, a non-randomized prospective trial compared two multimodal protocols: induction chemotherapy followed by EPP and adjuvant RT (N = 22) compared to PD with intraoperative PI-lavage followed by adjuvant chemotherapy (N = 54).[89] The primary difference was that the majority of patients (96.3%) completed all treatments in the PD group, in contrast to 68% in the EPP group. This was also associated with superior OS in the PD group (median 23 months, 95% CI 14.1–31.9 vs 12.8 months, 95% CI 7.8–17.7, P = 0.004).

In 2012, Cao et al.[90] performed a systematic review of trimodality therapy involving EPP in PM. They found four prospective studies with induction chemotherapy with median OS of 16.8–25.5 months on intention-to-treat analysis. In comparison, on eight studies with adjuvant chemotherapy regimen, median survival ranged from 19 to 46.9 months. More recently, a retrospective analysis by Sharkey et al.[91] explored whether the timing of chemotherapy affects outcomes in a cohort of EPP (N = 81) or ePD (N = 197) treated patients. Interestingly, they included also patients who received chemotherapy only after progression or recurrence. Overall, they observed no association with the timing of chemotherapy and OS (P = 0.39) or DFI (P = 0.33) in chemotherapy patients. Voight and colleagues[92] performed an intention-to-treat analysis to identify if induction chemotherapy impacts survival using data from a single institution (N = 257) and the National Cancer Database (NCDB; N = 1949). Neither dataset demonstrated an association of induction chemotherapy and OS. Importantly, postresection mortality was higher in both cohorts in patients who underwent induction chemotherapy (HR 1.85, 95% CI 1.21–2.83 and HR 1.19, 95% CI 1.02–1.39). Similarly, another analysis of NCDB using a more restricted dataset (N = 361) compared survival in patients who underwent induction or adjuvant chemotherapy along with cytoreductive surgery.[93] They reported no survival differences on the whole cohort (20.9 vs 21.7 months, P = 0.500) or propensity-matched patients (20.8 vs 22.0 months, P = 0.270). However, induction chemotherapy was associated with longer hospitalization (median of 7 vs 6 days, P = 0.001) and higher 30-day mortality (3.3% vs 0%, P = 0.020). Another potential drawback of induction chemotherapy is the rate of patients who experience severe toxicities or progress during treatment. Indeed, in prospective phase II trials, the rate of patients progressing to “unsuitable for surgery” has been 10–40%.[43,94,95]

On the other hand, induction chemotherapy can be used for downstaging and is usually better tolerated than postoperative therapy as many patients experience extended recovery or significant morbidities from surgery. Further, response to induction chemotherapy is often prognostic and can help for patient selection.[62]

No definite answers can be given from the present data whether chemotherapy should be delivered before or after surgery. As discussed earlier, we tend to adjust individually the timing of chemotherapy based on pre- and postoperative findings. One prospective randomized phase II trial, EORTC 1205 (NCT02436733), is investigating this question.[96] Eligible patients will be randomized between PD preceded or followed by 3 cycles of platinum-pemetrexed chemotherapy. Moreover, as the immune checkpoint inhibitors have emerged into management of unresectable PM,[44] several trials are exploring their role either as induction or adjuvant setting (Table 1).

Role of radiotherapy in surgical patients

Similar to systemic therapies, RT can either precede or follow surgery to improve locoregional control. Traditionally, PM has been considered to be resistant to RT. The evolvement of RT techniques, especially intensity modulated radiation therapy (IMRT), has optimized the delivery of high-dose RT to target areas.[97] The early experiences of IMRT after EPP demonstrated high risk of fatal pneumonitis.[98] Subsequently, with improved technique and greater experience, the reports have shown that IMRT can be delivered safely after EPP or PD.[97]

A prospective single-arm phase II trial showed that multimodality regimen of induction chemotherapy followed by PD and adjuvant IMRT was safe and feasible.[43] Out of 45 enrolled patients, 27 patients were able to start IMRT. Eight patients experienced grade 2–3 radiation pneumonitis, while no severe toxicities were noted. The median DFI was 12.4 months with a local progression within the radiation field observed in 59% of cases, with an association of gross residual disease at surgery. The median OS was 23.7 months with a 2-year OS of 59%. Subsequently, several retrospective studies have demonstrated that RT improves local control.[99,100] However, reducing the rate of local recurrences haven't always translated into better outcomes.[100] This is in line with the only randomized phase II trial that explored the role of postoperative RT after induction chemotherapy and EPP.[95] The study included two parts: first all patients were given induction chemotherapy followed by EPP (N = 113), and those who achieved MCR (and were still eligible for RT) were randomly assigned to either RT (N = 27) or surveillance (N = 27). There was no difference on the primary end point of locoregional relapse-free survival: 7.6 months (95% CI 4.5 – 10.7) in surveillance group compared to 9.4 months (95% CI 6.5 – 11.9) in the RT group. The survival was also similar in both groups: 20.8 months (95% CI 14.4 – 27.8) in surveillance group and 19.3 (95% CI 11.5 – 21.8) in the RT group. In addition, one patient died of RT-related pneumonitis. Although the trial suffered poor statistical power, the authors concluded that the addition of hemithoracic RT after EPP provides additional treatment burden without significant benefits. A phase III RCT (NCT04158141) is currently investigating the effects of IMRT with PD. They aim to randomize 150 participants to PD plus chemotherapy with or without IMRT.

The possibility of delivering RT in the induction setting has been investigated in a phase II study.[101] A total of 96 patients underwent accelerated course of IMRT followed by EPP. IMRT was well tolerated, and all of the RT-treated patients completed the protocol. Although, the perioperative mortality rate was only 1%, the reported 30-day grade 3–4 complication rate of 49% was significantly higher than previous surgery-based studies. The median OS for the intention-to-treat group was 24.4 months (95% CI 18.5 – 31.1) and DFI 18 months (95% CI 12.6 – 21.7). The local recurrence rate was 20%, and the most common recurrence sites were contralateral chest (46%) and peritoneal cavity (44%).

In conclusion, RT, whether given before or after surgery, is associated with increased toxicities when compared to surgery alone. However, the data suggests that it is effective for reducing local recurrences, but, whether it affects main surgical outcomes needs to be further investigated. Some of the challenges identified during these studies are currently being addressed in subsequent trials with modified protocols (Table 1).

Conclusion

The paucity of randomized trials in PM, particularly in surgery, has led to heterogeneity in management across the mesothelioma centers and differences in the current treatment guidelines.[6,7,40] However, recent advancements gives reasons for optimism. First, the shift of cytoreductive surgery from EPP to PD has already led to better outcomes in most recent surgical series. Second, the progress of systemic therapies has translated into several innovative ongoing trials in surgically fit patients. Finally, we anticipate that ongoing landmark trials will shed light on the most relevant unanswered questions in the surgical management of PM.

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Synopsis for Table of Contents:

We highlight the most important questions of current surgical management in pleural mesothelioma. We focus on cytoreductive surgery, specifically, pleural decortication as it has shifted into most common form of radical surgery.

Table 1.

Summary of ongoing surgical clinical trials on pleural mesothelioma.

Identifier	Phase	Design	Investigational treatment/ intervention	Control group/ treatment regimen	Estimated enrollment	Primary outcomes
Efficacy						
MARS2 (NCT02040272)	NA	Multicenter, open-label RCT[1]	CHT[2]+ePD[3]	CHT	328	1.Survival
Intraoperative treatment						
NCT03678350	I	Single-arm	PDT[4]	Surgery (nonspecified)	12	1. Safety 2. Effective therapy guide
MPM-PDT (NCT02153229)	II	Open-label RCT	PDT+ePD+CHT	ePD+CHT	102	1. Survival
Induction						
NCT04162015	I	Single-arm	ICI[5]+CHT	ePD	35	1.Feasibility 2. Safety
NCT02707666	I	Single-arm	ICI	ePD+CHT	15	1.Response rate (Gamma-Interferon Gene Expression Profile) 2. Safety
NCT03760575	I	Single-arm	ICI	ePD/EPP+CHT	20	1. Safety
NCT03918252	I-II	Single-arm	A) ICI alone B) ICI combination	ePD	30	1. Safety 2. Feasibility
NCT03228537	I	Single-arm	ICI+CHT	EPP[6]/ePD± RT[7]	24	1. Progression free survival 2. Survival 3. Response rate
SMARTER (NCT04028570)	NA	Single-arm	RT	EPP/ePD	18	1. Maximum tolerated dose for background radiation
SMARTEST (NCT05380713)	II	Open-label RCT	RT+CHT vs RT	EPP/ePD+ICI	30	1. CD8 TILs density/ gross tumor volume
NCT00652574	I	Single-arm	DAS[8]	EPP/ePD	60	1. p-Src Tyr419 expression modulation
NCT04162015	I	Single-arm	CHT+DCT[9]	EPP/ePD+DCT	16	1. Feasibility
MESODEC (NCT03228537)	I-II	Single-arm	CHT+DCV[10]	±ePD	20	1. Feasibility 2. Safety
NCT04525859	I	Single-arm	Poly-ICLC[11]	EPP/ePD	19	1. Safety
Adjuvant						
EORCT-1205 (NCT02436733)	II	Multicenter, open-label RCT	ePD+CHT	Induction CHT+ePD	64	1. Rate of success to complete the full treatment
NCT04177953	II	Multicenter, open-label RCT	ePD+CHT	ePD+CHT+ICI	92	1.Time to next treatment 2. Safety
NCT04996017	III	Multicenter, double-blind, RCT	ePD+ICI	ePD+PLC[12]	162	1. Disease free survival

Identifier	Phase	Design	Investigational treatment/ intervention	Control group/ treatment regimen	Estimated enrollment	Primary outcomes
NCT04158141	III	Multicenter, open-label RCT	ePD+CHT+RT	ePD+CHT	150	1. Survival

1. RCT, randomized controlled trial;

2. CHT, chemotherapy;

3. ePD, Extended pleurectomy decortication;

4. PDT, photodynamic therapy;

5. ICI, immune checkpoint inhibitor;

6. EPP, extrapleural pneumonectomy;

7. RT, radiotherapy;

8. DAS, dasatinib;

9. DCT, dendritic cell therapy;

10. DCV, dendritic cell vaccination;

11. Poly-ICLC, Polyinosinic-polycytidylic acid stabilized with polylysine and carboxymethylcellulose;

12. PLC, placebo

Table 2.

The outcomes and complications from largest pleurectomy decortication series.

Author (year)	Study design	No. ePD treated patients	Treatment regimen	30-day mortality*	Major complications (>grade 3)*	Overall survival (Median, mo)*
Lapidot[22] (2020)	Single-center, observational	355	IOHC[1] (80%) Induction CHT[2] (24%) Adjuvant CHT (67%)	3.0%	47%	20.7 (ITT[3]) 23.2 (MCR[4])
Klotz[33] (2019)	Single-center, observational	71	IOHC (100%) Induction CHT (11%)	1.4%	NS	16.1
Verma[20] (2017)	National cancer registry	1036	NS[5]	5%	NA	16
Friedberg[23] (2017)	Single-center, observational	73	IOPDT[6] (100%) Induction CHT (23%) Adjuvant CHT (84%)	3%	NS	36
Shaikh[24] (2017)	Single-center, observational	209	Adjuvant RT[7] (100%), CHT (41%)	NS	NS	20.2 (IMPRINT) 12.3 (CONV)
Lang-Lazdunski[25] (2015)	Single-center, observational	102	IOHPI[8] (100%) Induction CHT (14%) Adjuvant RT (100%), CHT (81%)	0	NS	32
Williams[26] (2015)	Single-center, observational	117	Induction CHT (18%) Adjuvant CHT (62%)	3.4%	9%	14.4
Sharkey[27] (2015)	Single-center, observational	229	Induction CHT (17%) Adjuvant CHT (32%)	3.5%	NS	12.3
Nakas[28] (2014)	Single-center, observational	140	Induction CHT (NS) Adjuvant CHT (NS)	NS	NS	16.2
Bovolato[29] (2014)	Multicenter, observational	202	Adjuvant CHT (79%), RT (6%)	2.6%	NS	20.5
Burt[21] (2014)	Multicenter database	130	NS	3.1%	3.8%	NS
Flores[13] (2008)	Multi-center, observational	278	Adjuvant CHT (NS) Adjuvant RT (NS)	4%	8%	16
Lucchi[31] (2007)	Phase II single-arm	49	Induction IIL2[9] (100%) Adjuvant IE[10] (100%), IIL2 (100%) RT (100%), CHT (100%)	0	NS	26
Richards[74] (2006)	Phase I-II single-arm	44	IOHC (100%)	11%	25%	13
Gupta[30] (2005)	Single-center, observational	123	IOBT[11] (44%) Induction CHT (5%) Adjuvant CHT (7%), RT (100%)	3.3%	37%	13.5

1. IOHC, intraoperative heated chemotherapy;

2. CHT, chemotherapy;

3. ITT, intention-to-treat;

4. MCR, macroscopic complete resection;

[5] NS, not specified;

[6] IOPDT, intraoperative photodynamic therapy;

[7] RT, radiotherapy;

[8] IOHPI, intraoperative heated povidone-iodine;

[9] IIL2, intrapleural interleukin-2;

[10] IE, intrapleural epidoxorubicin;

[11] IOBT, intraoperative brachytherapy;

* Refers to the outcomes of ePD group.