# Taken Together
## Effective Multimodal Approaches for Malignant Pleural Mesothelioma

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**KEYWORDS**

• Treatment for malignant pleural mesothelioma • Extrapleural pneumonectomy
• Pleurectomy/decortication • Multimodal therapy in mesothelioma

**KEY POINTS**

- Multimodal therapy is the preferred approach to patients with malignant pleural mesothelioma and is most likely available at experienced tertiary care centers.
- Although malignant pleural mesothelioma treatment has not yet been standardized, surgical debulking remains the cornerstone of treatment.
- Systemic chemotherapy and radiation therapy remain important adjuncts.
- Advances in radiation and immunotherapy may provide important new options in prolonging survival in patients with malignant pleural mesothelioma.

## INTRODUCTION

The diagnosis of malignant pleural mesothelioma (MPM) mandates prompt initiation of an aggressive multidisciplinary treatment strategy to prolong survival in this deadly disease for which median survival without treatment is approximately 7 months.[1] Multimodal therapy for MPM generally requires management at a specialized high-volume center with the resources and experience to facilitate efficient and effective treatment. Options typically include surgery, radiation, chemotherapy, and more recently immunotherapy, with the chosen strategy tailored to each patient. The use of more than 1 modality is preferred to maximize treatment efficacy.

## DISCUSSION

### *Surgery as the Cornerstone*

Although there is no defined standard treatment regimen for MPM, cancer-directed surgery is a predictor of longer survival and most studies support surgery as the cornerstone in the context of multimodality therapy.[2,3] Unfortunately, although cancer-directed surgery is offered to more than 40% of MPM patients at large tertiary centers, far fewer patients receive surgery outside of this population, including only 22% of patients with MPM in the Surveillance, Epidemiology, and End Results dataset from 1990 to 2004.[2] Surgery for MPM is centered around the principle of macroscopic resection with adjuvant therapy aimed at microscopic disease. Although the initial surgical evaluation often includes pleural biopsy via video-assisted thoracoscopic surgery, the 2 procedures that have served as the foundation of therapy are extrapleural pneumonectomy (EPP) and extended pleurectomy/decortication (PD). EPP involves en bloc resection of the lung, parietal and visceral pleura, diaphragm, and pericardium, and PD involves resection of all involved surfaces while sparing the lung parenchyma. The exact extent of resection is highly heterogeneous and

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depends on the extent of disease as well as surgeon preference. Although postoperative outcomes have improved for both of these procedures, they remain relatively morbid with a mortality rate of 2.2% to 7.0%.[4–6]

EPP as treatment for MPM was first described in 1976 by Butchart and colleagues.[7] Their early results saw a 31% perioperative mortality rate, although they acknowledged that many of these deaths might have been prevented with better patient selection, altered surgical techniques, or improved postoperative management.[7] Predictors of prolonged survival include epithelial cell type and negative resection margins,[8] an observation made even in the early work from Butchart and associates.

Although morbidity rates have improved over time, they remain relatively high. In 1 series of 183 patients undergoing EPP with adjuvant chemotherapy and radiation, mortality was 3.8% and morbidity 50% (major and minor complications) with a median survival of 19 months for those surviving the perioperative period.[8] Appropriate patient selection remains paramount and quality of life is an ongoing concern after either debulking procedure. A thorough evaluation of physiologic reserve should be performed, including a full cardiopulmonary workup. Despite the likelihood that EPP is more often performed on candidates with a lower operative risk, PD has been associated with much lower perioperative mortality and possibly increased long-term survival.[5,9] The Mesothelioma and Radical Surgery (MARS) feasibility trial aimed to compare the outcomes of EPP with no surgery, but had several limitations, including a failure to accrue adequate sample size.[10] Few meaningful conclusions can be drawn from its results.

Although universally accepted guidelines do not exist regarding a standard surgical approach to MPM, its aggressive recurrent nature is often cited as a reason to avoid EPP. The majority of recurrences after surgery tend to occur locally[5] and, given the dismal nature of this deadly disease, much of the conversation surrounding the benefits of EPP versus PD has involved the effects on patient quality of life. Impaired self-reported quality of life is prolonged after EPP, and brief improvements in fatigue, dyspnea, and chest pain are short lived, with initial improvements devolving back to baseline by 6 months.[11] There are few existing studies directly comparing quality of life after each procedure. A recent meta-analysis from our institution extracted 659 distinct patients and concluded that quality of life was diminished after either surgery for at least 6 months afterward, but was worse for EPP patients across both physical and social measures.[12] Although the negative impacts of PD seem to be less pronounced,[13–15] findings are heterogeneous and it remains unclear whether postoperative decreases in quality of life fully return to baseline. Unfortunately, most available data assessing quality of life after PD or EPP comes from small, single-center, observational studies. In consideration of these and other similar findings,[16–18] our practice has generally been to opt for PD whenever possible to preserve lung parenchyma, pericardium, and diaphragm and potentially leave patients with greater physiologic reserve to withstand adjuvant treatment and maximal quality of life.[19]

### *Multimodal Therapy for Malignant Pleural Mesothelioma: Chemotherapy*

Systemic chemotherapy in the form of combined pemetrexed and cisplatin remains first-line medical treatment since the results of the Evaluation of Mesothelioma in a Phase III Trial of Pemetrexed with Cisplatin (EMPHACIS), a landmark study comparing results from cisplatin versus cisplatin/pemetrexed in patients with unresectable MPM. The response rate, progression-free survival rate, and overall survival rate were all increased in the combination cisplatin/pemetrexed group.[20] For patients unable to tolerate cisplatin, the use of carboplatin/pemetrexed is a viable option.[21,22] For those unable to receive pemetrexed, the alternative combination of cisplatin with gemcitabine has been supported.[23,24]

For patients presenting with resectable disease, chemotherapy can be given either before or after surgery. A number of studies have established the effectiveness of neoadjuvant chemotherapy in the setting of trimodal treatment. EPP followed by radiation and cisplatin/pemetrexed or carboplatin/gemcitabine have reported median survival rates of 25.5 to 39.4 months.[25,26] The previously mentioned MARS feasibility trial, which aimed to compare outcomes after EPP or chemotherapy alone, suggested no benefit of surgery but had limitations including its small cohort and high perioperative mortality rate.[10]

Current recommendations are limited by the lack of quality data from randomized controlled trials, including any comparing neoadjuvant to adjuvant chemotherapy. A systematic review of 45 studies of multimodal treatment approaches found overall survival after adjuvant chemotherapy ranging from 11.0 to 56.4 months, and disease-free survival ranging from 8.0 to 27.1 months. Overall survival after induction chemotherapy ranged from 8.8 to 35.5 months, although the

authors cited limitations owing to limited data regarding completion rates of induction therapy. In 4 prospective studies with predominantly completed trimodal therapy, the median survival was 16.8 to 25.5 months with disease-free survival ranging from 7.6 to 44.0 months.[27]

Included in this analysis was data from several studies involving hyperthermic intraoperative chemotherapy, an immediate form of adjuvant treatment involving the instillation of intrapleural chemotherapy, usually cisplatin, to deliver high doses locally. Early data on hyperthermic intraoperative chemotherapy have been conflicting. Although Sugarbaker and colleagues[28] found evidence of a benefit for select populations, other data indicate more frequent complications and worse survival rates after hyperthermic intraoperative chemotherapy in a trimodality setting involving EPP.[29] A recent study of hyperthermic intraoperative chemotherapy with cisplatin/doxorubicin after PD found a median overall survival of 16.1 months, with a survival of 17.9 months for the epithelioid subtype and 28.2 months for those with a macroscopically complete resection. In this cohort of 71 patients, the 30-day mortality was 1.4% and the 90-day mortality was 2.8%.[30] At this point, stronger evidence is needed to either support or disprove the role of hyperthermic intraoperative chemotherapy in current treatment algorithms.

As surgical treatment trends toward a less radical approach, there is ongoing investigation into the effectiveness of multimodal therapy involving PD rather than EPP. MARS 2 is an ongoing clinical trial (NCT 02040272) currently recruiting to investigate outcomes of PD with platinum-based chemotherapy versus chemotherapy alone. Another ongoing study by the European Organization for Research and Treatment of Cancer (NCT 02436733) aims to compare results from initial PD with adjuvant pemetrexed/cisplatin versus neoadjuvant chemotherapy followed by delayed PD.

### *Improving Treatment Efficacy with Immunotherapy*

Immunotherapy for MPM has made recent advances as a potential means of increasing existing treatment efficacy. Cytotoxic T lymphocyte-associated protein 4 and programmed cell death protein-1 with its associated ligand are checkpoint inhibitors that have shown increasing promise as immunotherapy targets. A recent phase IB study has demonstrated that the programmed cell death protein-1 inhibitor pembrolizumab is reasonably safe and effective in this setting, with fatigue and nausea being the most common adverse effects. In this cohort of 25 patients who had failed or were unable to receive standard therapy, therapy was given every 2 weeks in an ongoing fashion; 20% had a partial response and 52% had stable disease, with a median duration of stable disease of 5.6 months.[31] Further phase II trials are now underway.

The anti-cytotoxic T lymphocyte-associated protein 4 monoclonal antibody tremelimumab, although initially showing promise in earlier single-center studies,[32,33] was subsequently the subject of the multicenter randomized controlled DETERMINE trial, administered to patients with unresectable pleural or peritoneal mesothelioma who had progressed on systemic treatment. The investigators found no difference in survival between treatment and placebo groups.[34] More recently, a phase II study of tremelimumab with durvalumab, an anti–programmed cell death ligand-1 monoclonal antibody, showed promising results with 63% of patients having disease control.[35]

Interest has also grown with regard to the addition of the vascular endothelial growth factor inhibitor bevacizumab to standard first line treatments. In a large phase III study, Zalcman and colleagues[36] reported improved progression-free and overall survival when bevacizumab was added to pemetrexed/cisplatin, although there were increases in the rate of side effects such as hypertension and thrombotic events. Importantly, a benefit was seen regardless of epithelioid, sarcomatoid, or mixed histology. Currently, bevacizumab is an option for first line therapy according to National Comprehensive Cancer Network guidelines.

Antimesothelin antibodies target the mesothelin cell surface glycoprotein, which is present in a variety of solid tumors, though its expression in sarcomatoid mesotheliomas is limited.[37] A phase II trial of 89 patients receiving the antimesothelin antibody amatuximab for up to 6 cycles in combination with pemetrexed/cisplatin showed a 40% partial response rate with another 51% of patients having stable disease.[38]

### *Radiation for Malignant Pleural Mesothelioma: Targeting Microscopic Disease in a Large Field*

Radiation therapy is a critical adjunct in many cancers to decrease local recurrence, and rates of local recurrence in the ipsilateral hemithorax remain high in MPM.[39] Radiation of the pleura involves the entire ipsilateral hemithorax and although removal of the lung via EPP can facilitate radiation, patients with 1 lung have an associated

diminished postoperative physiologic reserve. Common complications of adjuvant radiation include pneumonitis and pericarditis, and although less toxic than previous techniques, intensity modulated radiation therapy (IMRT) can still lead to excess radiation to the contralateral lung.[40]

Currently, no consensus exists regarding standard use of radiation in MPM treatment. Adjuvant low-dose hemithoracic radiation and photodynamic therapy have failed to effectively prolong survival or provide adequate local control.[39,41] Although multimodal therapy improves overall survival over surgery alone,[5] a Surveillance, Epidemiology, and End Results data analysis found no survival difference when surgery with radiation was compared with surgery alone and found an increased adjusted hazard ratio for patients undergoing treatment with just radiation.[42] An analysis of data from the National Cancer Database has suggested improved survival rates with adjuvant radiation,[43] although the information from both databases is inherently heterogeneous.

In a review of 86 patients treated at MD Anderson Cancer Center, Gomez and colleagues[44] reported a 6% rate of fatal lung toxicity in patients receiving IMRT after EPP, with another 6% developing severe radiation pneumonitis. The same group published a follow-up study comparing survival after IMRT after EPP or PD and found no differences in grade 4 to 5 toxicity or time to local or distant recurrence, although the survival rates favored a combination of PD and IMRT.[45]

The use of pleural IMRT alongside the growing surgical trend toward PD has been shown to be safe and effective for the ipsilateral lung, although there remains a significant portion of patients who develop chronic radiation pneumonitis.[46] More recent findings have indicated that treatment with PD and adjuvant hemithoracic pleural IMRT results in longer intervals to both local and distant recurrence compared with those receiving partial pleurectomy or definitive IMRT.[47] A phase II study of patients receiving hemithoracic pleural IMRT after chemotherapy and PD reported no grade 4 or 5 toxicities out of 27 patients who completed intended treatment.[48] The median progression-free survival was 12.4 months and the median overall survival was 23.7 months, with a 2-year overall survival of 59% in patients with resectable disease. When assessed in conjunction with chemotherapy and PD, adjuvant hemithoracic pleural IMRT has been identified as a significant factor for increased overall survival.[49]

Few data are available regarding the effectiveness of induction radiation, with the majority of data and experience centered around radiation after EPP or PD. A feasibility study of the Surgery for Mesothelioma After Radiation Therapy (SMART) approach out of Princess Margaret Cancer Center in Toronto described results from a technique of administering 25 Gy neoadjuvant IMRT over 1 week (with a 5-Gy boost to high-risk areas) followed by EPP within 1 week of completed radiotherapy. Patients with pathologically involved N2 nodes also received adjuvant cisplatin-based chemotherapy within 24 weeks of surgery. They reported promising results, with no 30-day or in-hospital mortalities, no bronchopleural fistulae, and only 1 death from empyema during follow-up.[50]

Their follow-up data, encompassing 62 patients over approximately 6 years, reported a 1.6% perioperative mortality, a 4.8% treatment-related mortality, and a median survival on an intention-to-treat basis of 36 months.[51] The median overall survival in the epithelioid subtypes was 51 months compared with 10 months in biphasic subtypes, suggesting a reevaluation of the role for EPP in certain patients at specialized centers.

## SUMMARY

Although much remains to be discovered about the ideal approach to MPM, it is clear that effective treatment is not encompassed by 1 approach, and therapy for disease progression can involve any of these modalities. Whatever treatment approach is decided, it is critical to prioritize quality of life given the deadly nature of this disease.

## CLINICS CARE POINTS

- Multimodal discussion and therapy is the preferred approach to patients with MPM, and is most likely available at experienced tertiary referral centers.
- Systemic chemotherapy treatments, most commonly in the form of cisplatin/pemetrexed, can be given in a neoadjuvant or adjuvant setting, and emerging immunotherapy targets can increase their efficacy.
- No standard approach exists regarding radiation therapy for MPM, although ongoing investigations may point to a new role for induction radiation.
- Surgery via en bloc resection remains a critical aspect of treatment, and debulking via PD is growing in favor over EPP.

## DISCLOSURE

The authors have nothing to disclose.

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