Published in final edited form as:

Curr Treat Options Oncol. 2011 June ; 12(2): 163–172. doi:10.1007/s11864-011-0146-4.

The Evolution of Multimodality Therapy for Malignant Pleural Mesothelioma

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Opinion Statement

Malignant pleural mesothelioma (MPM) is a rare neoplasm of the pleural surfaces that has been associated with asbestos exposure. MPM generally spreads locally along the ipsilateral pleura, especially at presentation, with distant metastatic disease typically seen only in the later stages of the disease course. As such, surgical resection and other local therapies have long been pursued as a primary form of treatment. Surgical options include debulking of the pleura by pleurectomy/decortication (P/D), or a more aggressive extrapleural pneumonectomy (EPP) which also involves removal of the lung, diaphragm, and involved pericardium. Even after major resection, MPM almost always recurs locally and has a poor prognosis. As such, many groups have pursued multimodality therapy, treating resectable patients with extrapleural pneumonectomy (EPP), along with hemithoracic radiation to decrease the risk of local recurrence, and chemotherapy to decrease the risk of distant metastatic disease. However, EPP is associated with significant morbidity and mortality, and many patients are not candidates for EPP due to underlying comorbid medical conditions. Additionally, many patients are unable to tolerate complete courses of adjuvant therapy after EPP. A large, multi-center retrospective analysis comparing EPP to pleurectomy/decortication (P/D) demonstrated better outcomes among those who underwent P/D. One challenge associated with P/D has been the delivery of radiation to the removed pleura with an intact lung. Yet, advances in radiation technique have allowed the exploration of high-dose radiation therapy after P/D. The ideal timing of chemotherapy relative to surgery, and the role of intracavitary chemotherapy continue to be controversial issues. Clearly, MPM requires a multi-disciplinary approach and, due to the myriad of open questions, much effort continues to focus on identifying the optimal combination of surgery, chemotherapy, and radiation.

Introduction

Malignant pleural mesothelioma (MPM) is a neoplasm derived from the mesothelial surfaces of the pleura. It typically spreads and invades locally, though distant metastases to the contralateral lung, peritoneum, bone, or liver can occur. Patients with MPM have a poor prognosis with a median survival ranging from 6 to 18 months depending on the stage of the disease at the time of diagnosis.[1] While MPM remains a rare disease, its incidence is increasing within industrialized nations [2, 3] and the annual incidence in the United States is 2000-3000.[4] In 1960, the association between MPM and asbestos was first recognized.

[5] Current patterns of MPM incidence reflect trends in asbestos exposure with a 20-40 year latency in disease development.[4, 6]

Despite the growing number of patients, MPM remains a therapeutic challenge with no universally accepted treatment approach. Perhaps the most contested issue in managing this disease is the role of surgical resection. EPP was historically considered a potentially curative surgery, however, this aggressive operation is fraught with significant morbidity, and many patients are not candidates due to poor cardiopulmonary reserve or extent of disease. P/D is less morbid, but in most cases, does not offer as complete a resection. Diffuse pleural involvement is common at presentation and therefore renders the results of surgery or radiation therapy alone sub-optimal with high local recurrence rates.[7, 8] Many have questioned the role of any surgery in this disease. However, the past decade has seen several notable advances: effective chemotherapy regimens have been developed; various surgical approaches have been explored and refined; and multiple studies with multimodality therapy have been reported. Survival is clearly more promising with multimodality treatment, but the optimal type, combination, and timing of surgery, radiation, and chemotherapy have yet to be established.

Almost all multimodality studies to date have included EPP as the surgical approach. However, a recent retrospective analysis suggested that patients who underwent an EPP had a poorer survival than patients who had P/D. The reason for this is unclear. Is this because they are better able to tolerate additional therapy? Or, rather, is this because disease that is amenable to P/D portends a better prognosis irrespective of subsequent treatment? Given the relatively small number of patients with MPM and the lack of randomized phase III clinical trials to date, some questions may never be definitively answered.

Ultimately, different multimodality approaches may be best in different clinical scenarios. Future investigations should focus on strategies to facilitate maximizing delivery of the most therapy. That is, even optimally debulked patients, however that is achieved, are at high risk for recurrence. Performing extensive surgery at the expense of delivering adjuvant therapy is not ideal. Additionally, delivering neoadjuvant chemotherapy at the expense of optimally debulking surgery is not preferred either. Currently, the combination of neoadjuvant chemotherapy, P/D, and adjuvant pleural IMRT appears to be a promising multimodality treatment paradigm, but additional investigations are needed to refine this approach.

Treatment

- MPM usually requires multiple therapeutic modalities including surgery, chemotherapy, and radiation therapy but the optimal combination of therapies remains unidentified.
- In all settings, clinical trials should be considered as cure rates are still low.

Surgery

Extrapleural Pneumonectomy (EPP)

- EPP involves the en bloc resection of lung, pleura, pericardium, and diaphragm. This aggressive surgery is associated with significant morbidity and mortality (22-37% and 4-15% respectively)[9, 10], even at experienced centers, but has long been considered potentially curative surgery.
- Local recurrence after EPP occurs in up to 80% of patients.[10, 11] Hemithoracic radiation to the chest cavity after EPP appears to decrease this risk. In a phase II trial administering 54Gy to the chest cavity after EPP, the local recurrence rate was reduced to 13%.[12]

- While the combination of EPP with adjuvant radiation dramatically reduced the rate of local recurrence, distant recurrence remained a problem in up to 55% of patients.[12] This, along with the advent of reasonably effective chemotherapy regimens, prompted the inclusion of chemotherapy into the multimodality approach.
- Multiple groups have now reported their results using trimodality therapy (that is, EPP, radiation, and chemotherapy) with fairly similar outcomes across the studies. Over the past six years, twelve trimodality studies of EPP, chemotherapy, and radiation, have been reported. Four of the twelve were retrospective, and four utilized adjuvant as opposed to neoadjuvant chemotherapy. Typically, about 80% of patients are able to have a resection. The median overall survival ranges from 14 to 28 months.[13-24]
- Unfortunately, a high proportion of patients are unable to complete all three treatment modalities (Tables 1A and 1B). In the largest prospective study of adjuvant chemotherapy and radiation after EPP, only 57% of patients who underwent EPP were able to complete chemotherapy.[20] Many patients are also unable to complete adjuvant radiation. In six prospective trials that used neoadjuvant chemotherapy (Table 1B), only 32-63% of post-EPP patients were able to complete courses of radiation therapy.[16, 18, 21-24]
- The outcomes after EPP, as opposed to pleurectomy/decortication (P/D), were examined in a retrospective analysis of 667 patients.[25] In a multivariate analysis controlling for histology, stage, gender, and multimodality therapy, patients who underwent EPP had a poorer survival with a hazard ratio of 1.4 compared to P/D. As this was a retrospective analysis, selection bias may have played a role in the observed difference. Nonetheless, this report has had a dramatic impact on the practice patterns of many thoracic surgeons, with many fewer EPPs being performed since its publication.
- Furthermore, no randomized trial has ever demonstrated the benefit of any surgery in treating MPM. To that end, as discussed in more detail below, an ongoing trial, Mesothelioma and Radical Surgery Randomized Controlled Trial (MARS), will attempt to address this question.

Pleurectomy/Decortication (P/D)

- P/D involves resection of the parietal and visceral pleurae, pericardium, and diaphragm (if needed) while leaving the lung intact and, historically, was reserved for patients who were unable to undergo EPP. The mortality associated with this procedure is less than that with EPP and ranges from 3-7%.[26-28]
- Since, as described above, radiation and chemotherapy along with EPP improve local and distant recurrence rates, and P/D was recently shown to have improved outcomes relative to EPP[25], P/D is now being considered in a multimodality paradigm. However, to date, only one prospective multimodality series has utilized P/D as the surgical approach. Median overall survival in this small trial of 35 patients was 30 months.[26]
- The complete delivery of trimodality therapy appears more feasible with P/D as compared to EPP. After P/D, only 6-16% of patients, as opposed to 19-61% with EPP, were unable to complete adjuvant chemotherapy and radiation.[26, 29]
- If P/D, as opposed to EPP, allows the complete delivery of adjuvant treatment modalities, overall survival may be improved with less radical surgery. Further

trials incorporating P/D into the trimodality paradigm are needed to corroborate these early but intriguing results.

Chemotherapy

Agents

- In 2003, a phase III trial demonstrated an approximate 3 month survival benefit with the combination of cisplatin and pemetrexed versus cisplatin alone.[30] Since then, cisplatin and pemetrexed has been adopted as the standard front-line regimen.

Timing

- Given the successful experience with surgery after neoadjuvant chemotherapy in locally advanced non-small cell lung cancer, the neoadjuvant paradigm was applied to mesothelioma.
- Neoadjuvant chemotherapy poses several potential advantages: more chemotherapy is able to be delivered in the pre-operative setting, especially given the significant morbidity associated with EPP, and response to chemotherapy can be assessed on imaging.
- The risk of neoadjuvant chemotherapy is that for the fraction of patients who progress during chemotherapy or experience severe toxicity, surgery may become more challenging or even impossible. However, in several studies of neoadjuvant chemotherapy in combination with EPP, these concerns have not been realized. [14-16, 18, 21-24]
- More patients complete both chemotherapy and EPP when chemotherapy is given pre-operatively than post-operatively.[13-23, 31] In the largest prospective trial of neoadjuvant chemotherapy followed by EPP and radiation, 81% of patients completed all four planned cycles of chemotherapy.[18] A small percentage of patients had disease progression during chemotherapy and did not proceed on to surgery. This response assessment also allows the selection for aggressive therapy of those with a more favorable biology. In that trial, response to chemotherapy was the best predictor for improved survival. The median survival for responders to chemotherapy was 26 months, as compared to 14 months in patients with stable disease or progression. Perhaps patients with refractory disease, as evidenced by rapid progression during chemotherapy, should be spared an aggressive surgery from which they may not derive benefit.
- With neoadjuvant chemotherapy, however, significant fractions of patients do not complete adjuvant radiation after EPP (Table 1B). In fact, the completion of all three therapeutic modalities (chemotherapy, surgery, and radiation) is similar for both the adjuvant and neoadjuvant chemotherapy groups. Yet, since more patients do complete at least two of the three therapeutic modalities with the neoadjuvant approach, most ongoing studies involve neoadjuvant chemotherapy with attempts to improve the delivery of adjuvant radiation therapy.

Intracavitary Chemotherapy

- As MPM is a disease in which local recurrence is a significant problem, intracavitary chemotherapy delivery has been explored in order to deliver higher doses of chemotherapy locally with less toxicity than systemic therapy. Hyperthermia has also been utilized to improve drug absorption and the cytotoxic effect of the drugs. Several phase I and phase II trials have demonstrated this approach to be feasible and safe.[9, 32-36]

- In one of the largest studies to date, 92 patients received hyperthermic intraoperative chemotherapy at the time of EPP and 48.9% experienced morbidity. [35] Median overall survival was 13 months and 16.9 months for cancer-specific mortality. Renal toxicity, however, is a significant dose-limiting concern but the use of renal cytoprotectants such as sodium thiosulfate and amifostine have ameliorated this risk.[37]
- Further study is needed to help identify the ideal population to benefit from this intervention.

Radiation

Hemithoracic

- There was a long-standing belief that cytotoxic doses of radiation could not be safely delivered to the entire hemithorax. However, a phase II trial of adjuvant high-dose hemithoracic radiation after EPP, demonstrated the safety and efficacy of this technique.[12] In this trial, the local recurrence rate was 13% which is much lower than historical controls.[10, 11]. Hemithoracic radiation, therefore, gained routine acceptance in this setting.[7, 12, 38]
- Until recently, all but one of the prospective and retrospective multi-modality studies has used adjuvant hemithoracic radiation (Tables 1 and 2).[13, 15-23, 26, 29, 31, 39] Completion rates of adjuvant hemithoracic radiation after chemotherapy and surgery in these trials range from 38 to 94%.[13, 15-23, 26, 29, 31, 39]
- Fewer data are available regarding hemithoracic radiation in combination with P/D. In one retrospective analysis of 123 patients who underwent P/D and hemithoracic radiation, 56% experienced local failure.[38] These discouraging results prompted the investigation of novel radiation delivery techniques, such as IMRT, to improve local control.

Intensity Modulated Radiation Therapy (IMRT)

- IMRT involves modifying the intensity of radiation in multiple small volumes using highly sophisticated 3-dimensional treatment planning techniques. This allows more radiation delivery to the tumor while sparing the normal surrounding tissue. Because of the successful incorporation of IMRT into the treatment of cancers in anatomically challenging regions such as the prostate and head and neck, IMRT techniques were extrapolated to treat the thorax for MPM.[40]
- Unfortunately, when used to treat the thorax after EPP, IMRT was associated with severe pulmonary toxicity, including a 46% incidence of fatal pneumonitis in one series.[41] Consequently, there has been great concern regarding the use of IMRT to treat MPM.[42]
- Further retrospective analyses, however, have demonstrated that IMRT pulmonary complications are associated with the dose of radiation delivered to the contralateral lung.[41, 43] When normal tissue constraints such as the mean lung dose and V20 (the percent volume of the lung receiving more than 20Gy of radiation) are more rigorously applied, IMRT use is associated with acceptable toxicity in patients with and without intact lungs. [40]
- In one retrospective series, patients received either adjuvant external beam radiation therapy (EBRT) or IMRT after EPP based on the preference of the treating radiation oncologist.[14] Those who received IMRT had significantly less local recurrence without increased complications compared to those who received EBRT, 14% versus 42%.[14]

- IMRT to the pleura is now being explored in patients who have not had an EPP, that is, patients with two intact lungs. In a retrospective cohort, 36 patients were treated with pleural IMRT.[44] Twenty patients had a prior P/D, and 16 patients were unresectable. Twenty percent of patients experienced grade 3 or worse pneumonitis, though all but one patient recovered. The median survival for patients treated with P/D and pleural IMRT was 26 months (measured from the beginning of radiation therapy). The 1-year and 2-year overall survival rates were 80% and 55% respectively. For patients who did not have surgery, the median survival was 17 months, with a 1-year survival of 75% and a 2-year survival of 21%.

Ongoing Studies

- Despite the best multimodality therapy, MPM is still a highly fatal disease. Efforts to better understand and characterize the biology of MPM may lead to the identification of new treatment strategies or therapeutic targets.

IMRT in multi-modality paradigm

- Given the promising advances in local control with pleural IMRT in patients with two intact lungs, but concerns regarding its risk of pneumonitis, there is an ongoing single-center phase II trial of neoadjuvant chemotherapy followed by P/D, if feasible, and IMRT to the pleura. The primary end-point of this study is the safety of the IMRT.

MARS (Mesothelioma and Radical Surgery Randomized Controlled Trial)

- As discussed earlier, EPP has historically been considered the standard surgical approach for MPM. However, there are no randomized data to support this approach. In fact, there are no randomized data to support the benefit of any surgery in the treatment of MPM. The MARS trial is designed to address this question by randomizing patients after three cycles of chemotherapy to EPP and hemithoracic radiation versus best oncological care.[45] An initial report indicated the feasibility of accruing patients to this study, and most recently there has been reports of an interim analysis that there was a trend towards improved survival in the no EPP arm (<http://the3ccancernet.org.uk/downloads/David%20Waller%20The%20MARS%20trial.pdf>). While the MARS trial initially included EPP as the only surgical option, given the changing surgical landscape, P/D will also be offered as a surgical option going forward.

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Table 1

A. EPP, adjuvant chemotherapy, and adjuvant radiation							
Author	Year	N	Study Design	EPP	Chemo	XRT	OS median (mos.)
Pagan[20]	2006	54	Prospective	44/54	31/42	31/42	20
Hasani[17]	2009	36	Retrospective	18/22	15/16	14/16	19
Batirel[13]	2008	20	Prospective	16/20	12/12	12/16	17.2
Okubo[19]	2009	16	Retrospective	16/16	14/16	13/14	28.1
complete all							
							57%
							39%
							60%
							81%
B. Neoadjuvant chemotherapy, EPP, and adjuvant radiation							
Author	Year	N	Study Design	Chemo	EPP	XRT	OS (mos.)
Krug[18]	2009	77	Prospective	64/77	57/64	40/44	16.8
dePerrot[15]	2009	67	Retrospective	56/60	45/60	30/45	14
Weder[24]	2007	61	Prospective	58/61	45/61	24/36	19.8
Van Schil[22]	2010	59	Prospective	55/58	42/58	37/38	18.4
Buduhari[14]	2009	55	Retrospective	55/55	46/55	38/46	24
Flores[16]	2006	21	Prospective	10/21	9/10	7/8	19
Rea[21]	2007	21	Prospective	20/21	17/21	13/15	25.5
Weder[23]	2004	19	Prospective	18/19	16/19	6/13	23
							32%

Table 2

P/D, adjuvant chemotherapy, and adjuvant radiation								
Author	Year	N	Study Design	P/D	Chemo	XRT	OS median (mos.)	completing all
Bolukbas[26]	2009	35	Prospective	35/35	35/35	33/35	30	94%
Maggi[29]	2001	32	Retrospective	32/32	32/32	27/30	not reported	84%