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## Current treatment strategies in malignant pleural mesothelioma with a treatment algorithm

### Abstract

Malignant pleural mesothelioma (MPM) is a rare disease with a poor prognosis. The main therapeutic options for MPM include surgery, chemotherapy, and radiation therapy (RT). Although multimodality therapy has been reported to improve survival, not every medically operable patient is able to undergo all recommended therapy. With improvements in surgical techniques and systemic therapies, as well as advancements in RT, there has been a potential new paradigm in the management of this disease. In this review, we discuss the current literature on MPM management and propose a functional treatment algorithm.

**Key words:** mesothelioma, surgery, chemotherapy, radiotherapy

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### Introduction

Malignant pleural mesothelioma (MPM) is an aggressive malignancy arising from the mesothelial cells lining the pleura. Asbestos exposure is the primary risk factor for MPM, causing chronic inflammation and mesothelial cell transformation by interference with mitotic spindles, release of oxygen species, and attraction of macrophages [1]. The latency period for development of MPM lasts often 20–40 years from initial exposure to asbestos [2]. Although the main risk factor is asbestos, erionite exposure can also lead to MPM [3]. Erionite is a naturally occurring fibrous mineral found in volcanic rocks

and in other hydrothermal environments, such as those occurring in the Cappadocian region of Turkey and other geological sites, including parts of northern Italy and the western United States [4–6]. While the mechanism of carcinogenesis by erionite is similar to asbestos [7, 8], experimental studies indicate that erionite is up to 800 times more carcinogenic than asbestos [9–11]. More recently it has been reported that inherited heterozygous germline mutations of the deubiquitylase BRCA-associated protein 1 (BAP1) cause a high incidence of mesothelioma in some families and that BAP1 mutations lower the threshold of asbestos required to cause mesothelioma in animal models [12].

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Although MPM is a rare malignancy (up to 30 cases per million), the incidence has been increasing in recent years likely due to the lag time in tumor development following asbestos exposure [13–16]. Diagnosis of MPM is often delayed as the disease presents with vague symptoms, including pleuritic chest pain, dyspnea, and/or weight loss. Depending on patient- and disease-related factors, treatment options may include surgery, chemotherapy, and radiation therapy (RT) and should be determined through a multidisciplinary management approach in experienced cancer centers. Despite advancements in treatment modalities, the prognosis of malignant mesothelioma remains poor with a median overall survival (OS) of 12–22 months [13,17–19]. Given the constantly evolving treatment paradigm, we herein evaluate the published data on therapeutic options for MPM and propose a functional treatment algorithm.

### Surgical resection

Surgery is an important part of MPM management and can be applied with curative or palliative intent. In general, there are two main approaches to surgery: pleurectomy/decortication (P/D) and extrapleural pneumonectomy (EPP). EPP is a complex procedure including en-bloc removal of the lung, parietal and visceral pleura, diaphragm, and pericardium [18, 19]. During P/D, complete resection of macroscopic disease is obtained with removal

of the entire pleura. If the diaphragm and/or pericardium are affected, they are also removed, and the procedure is called extended-P/D [20]. A partial resection of parietal or visceral pleura without removal of all gross tumor is a debulking operation and is termed partial pleurectomy (PP) [21].

The optimal resection technique for MPM is highly debated due to limited evidence regarding comparisons of surgical techniques. Historically, EPP was considered to be the only procedure to achieve a complete resection, and therefore, was recommended to all operable patients [19, 22, 23]. However, even with EPP, 70–100% of patients are found to have positive margins [24, 25], which has resulted in a shift towards extended-P/D as the preferred surgical approach.

Although nonrandomized controlled trials comparing surgical treatment with extended-P/D or EPP exist, retrospective series favor extended-P/D (Table 1) [26–38]. A meta-analysis published by Cao *et al.* compared EPP (n = 632) to extended-P/D (n = 513) from seven relevant studies [39]. This study demonstrated significantly lower perioperative mortality (2.9% vs 6.8%; p = 0.02) and morbidity (27.9% vs 62.0%; p < 0.0001) for patients who underwent extended-P/D compared to EPP. Additionally, Luckraz *et al.* contrasted EPP with P/D in the multi-modality management setting and found that P/D combined with postoperative adjuvant therapy was associated with better survival despite a higher proportion of patients

**Table 1. Studies of different surgical techniques for malignant pleural mesothelioma**

Authors [reference]	Study design	N	Overall survival		P
			EPP	P/D	
Bovolato <i>et al.</i> [26]	Retrospective	1365	20.9 mo	24.6 mo	0.596
Aziz <i>et al.</i> [27]	Retrospective	302	13 mo	14 mo	NS
Branscheid <i>et al.</i> [28]	Retrospective	301	284 days	315 days	SS
Flores <i>et al.</i> [29]	Retrospective	663	10 mo	13 mo	0.47
Kostron <i>et al.</i> [30]	Retrospective	167	23 mo	32 mo	0.031
Lang-Lazdunski <i>et al.</i> [31]	Prospective	86	12.8 mo	23 mo	0.004
Luckraz <i>et al.</i> [32]	Retrospective	217	10.3 mo	10.1 mo	0.09
Miyazaki <i>et al.</i> [33]	Retrospective	39	16.5 mo	22.5 mo	0.13
Okada <i>et al.</i> [34]	Retrospective	87	13 mo	17 mo	0.922
Pass <i>et al.</i> [35]	Retrospective	96	9.4 mo	14.5 mo	0.001
Rena <i>et al.</i> [36]	Retrospective	77	20 mo	25 mo	NS
Sharkey <i>et al.</i> [37]	Retrospective	362	4.7 mo	12.5 mo	0.001
Verma <i>et al.</i> [98]	Retrospective	1307	19 mo	16 mo	0.120
Kai <i>et al.</i> [38]	Retrospective	44	17 mo	34 mo	0.019

EPP — extrapleural pneumonectomy; NS — not statistically significant; mo — months; P/D — pleurectomy/decortication; SS — statistically significant

who either had advanced disease or were surgically less fit (median 26 months, range 11–40 months) [32]. Furthermore, EPP without adjuvant therapy was found to be an independent risk factor for decreased OS on multivariate analysis (hazard ratio [HR] = 9.2). In 2012, Rena *et al.* compared the long-term postoperative quality of life (QoL) in 70 patients with MPM treated with EPP or P/D [36]. While median OS was similar between surgical techniques (median 28 vs 32 months;  $p = 0.098$ ), they reported that patients who underwent EPP had a higher postoperative complication rate (62% vs 24%;  $p = 0.002$ ), a worse long-term QoL, and a shorter residual life time after recurrent disease (median 9 vs 14 months;  $p = 0.001$ ) when compared to P/D. More recently, Taioli *et al.* conducted the largest meta-analysis using 24 distinct data sets to compare EPP ( $n = 1,391$ ) to P/D ( $n = 1,512$ ) (40). There was no significant difference in OS between P/D and EPP at two years (23.8% vs 25%;  $p = 0.8$ ); however, perioperative 30-day mortality was significantly higher after EPP than after P/D (4.5% vs 1.7%;  $p < 0.05$ ), and EPP was associated with more postoperative complications than P/D (up to 68% vs 33%).

The Mesothelioma and Radical Surgery 1 (MARS 1) study was the first feasibility trial in which 50 patients with MPM were randomized to EPP and hemi-thoracic radiotherapy or no EPP, after induction chemotherapy [41]. Median OS was lower in the EPP group (14.4 months vs 19.5 months) with a HR for death of 2.75 (95% confidence interval [CI] 1.21–6.26;  $p = 0.016$ ). Furthermore, there was a trend towards worse QoL in the EPP arm. As this study did not show a survival advantage or improved QoL, the authors cautioned against the use of EPP [42].

In summary, although level I evidence favoring one surgical procedure is lacking, a number of retrospective studies and meta-analyses have demonstrated as follows: a) long-term survival after EPP is similar or lower than extended-P/D; b) higher perioperative mortality and postoperative morbidity with EPP; and c) a lower postoperative QoL in patients treated with EPP. National Comprehensive Cancer Network (NCCN) guidelines on MPM suggest P/D may be safer than EPP but do not conclude which procedure is oncologically superior because of the lack of data from randomized controlled trials.

### Systemic therapy

Chemotherapy plays an important role in the management of MPM and is recommended as part

of a multimodality regimen in medically operable patients either before or after surgery (Table 2) [24, 41, 43–58]. Trimodality therapy includes chemotherapy, surgery, and RT and has been reported to provide median OS of up to 20 to 29 months in those who are able to complete the entire course of treatment [52, 59]. Chemotherapy alone is also recommended for medically inoperable patients, for those who refuse surgery, or in the setting of progressive disease [26, 60–69].

Current first-line chemotherapy for MPM consists of a doublet regimen of pemetrexed and cisplatin. The evidence for this regimen comes from a large phase III trial by Vogelzang *et al.*, in which 448 medically inoperable chemotherapy-naïve patients with MPM were randomly assigned to receive either cisplatin as monotherapy or a combination of cisplatin-pemetrexed [70]. Patients treated with cisplatin-pemetrexed had significantly longer median OS (12.1 months vs 9.3 months;  $p = 0.020$ ), progression-free survival (5.7 vs 3.9 months;  $p = 0.001$ ), and higher treatment response rates (41% vs 16%,  $p < 0.001$ ). In 2016, Zalcman *et al.* randomized 448 medically inoperable chemotherapy-naïve MPM patients with no bleeding or thrombosis to cisplatin-pemetrexed alone or bevacizumab-cisplatin-pemetrexed followed by maintenance bevacizumab [71]. OS was significantly increased with addition of bevacizumab (18.8 months vs 16.1 months;  $p = 0.0167$ ); however, 71% of patients receiving bevacizumab and 62% receiving cisplatin-pemetrexed alone had grade 3–4 adverse events. Thromboembolic events (6% vs 1%) and serious hypertension (23% vs 0%) were more frequent in the subjects who received bevacizumab. Based on this trial, NCCN guidelines recommend this regimen for bevacizumab-eligible patients with unresectable MPM.

Alternative first-line combination chemotherapy options include pemetrexed-carboplatin and gemcitabine-cisplatin [72–77]. In a phase II study, Ceresoli *et al.* treated 102 chemotherapy-naïve MPM patients who were not eligible for curative surgery with pemetrexed and carboplatin [73]. Median time to progression was 6.5 months and median OS was 12.7 months. More recently, Kartizoglou *et al.* treated 62 chemotherapy-naïve MPM patients with pemetrexed and carboplatin in a phase II study [72]. Median OS was 14 months (range, 11.8–16.2 months) and median time to progression was 7 months (range, 5.8–8.2 months). A combination of gemcitabine and cisplatin was used in 39 MPM patients in a phase II study with a reported median OS of 20.7 months (10.7–30.8 months) [75]. Based on these studies,

**Table 2. Studies of trimodality therapy for malignant pleural mesothelioma**

Authors [reference]	Study design	N	Treatment	Overall survival
Rosenzweig <i>et al.</i> [43]	Prospective	36	NA-chemo + P/D + RT	1 yr 75% 2 yr 53%
Treasure <i>et al.</i> [41]	Prospective	112	NA-chemo + EPP + RT	1 yr 52%
Bille <i>et al.</i> [44]	Prospective	25	NA-chemo + EPP + RT	1 yr 75% 2 yr 53%
Stahel <i>et al.</i> [45]	Prospective	151	NA-chemo + EPP + RT	1 yr 70% 2 yr 23%
Hasegawa <i>et al.</i> [46]	Prospective	42	NA-chemo + EPP + RT	2 yr 50%
Van Schil <i>et al.</i> [47]	Prospective	59	NA-chemo + EPP + RT	1 yr 70.2%
Federico <i>et al.</i> [48]	Prospective	54	NA-chemo + EPP + RT	1 yr 59.2%
de Perrot <i>et al.</i> [49]	Retrospective	60	NA-chemo + EPP + RT	5 yr 10%
Rimner <i>et al.</i> [50]	Prospective	45	NA-chemo + P/D + RT	1 yr 80% 2 yr 59%
Minatel <i>et al.</i> [51]	Prospective	69	P/D + A-chemo + RT	1 yr 90% 2 yr 65%
Krug <i>et al.</i> [52]	Prospective	77	NA-chemo + EPP + RT	1 yr 90% 2 yr 61.2%
Bolukbas <i>et al.</i> [53]	Prospective	102	P/D + A-chemo + RT	1 yr 69% 2 yr 50%
Buduhan <i>et al.</i> [54]	Retrospective	46	NA-chemo + EPP + RT	Median 25 mo
Fahrner <i>et al.</i> [55]	Retrospective	41	NA-chemo + EPP + RT	1 yr 71% 2 yr 28%
Hasani <i>et al.</i> [24]	Retrospective	36	EPP + A-chemo + RT	1 yr 76%
Kimura <i>et al.</i> [56]	Prospective	15	NA-chemo + EPP + RT	1 yr 43.1%
Thieke <i>et al.</i> [57]	Prospective	62	NA-chemo + EPP + RT	1 yr 63% 2 yr 42%
Trousse <i>et al.</i> [58]	Prospective	83	NA-chemo + EPP + RT	1 yr 62.4% 2 yr 32.2%

A-chemo — adjuvant chemotherapy; EPP — extrapleural pneumonectomy; NA-chemo — neo-adjuvant chemotherapy; mo — months; P/D — pleurectomy/decortication; RT — radiation therapy; yr — year

pemetrexed-carboplatin and gemcitabine-cisplatin are now considered to be acceptable first-line options.

Subsequent systemic therapy options for MPM may include immune checkpoint inhibitors such as pembrolizumab or nivolumab with (or without) ipilimumab [78–83]. In 2019, Scherpereel *et al.* reported the result of the IFCT-1501 MAPS2 trial in which 125 MPM patients pre-treated with one or two lines of chemotherapy were randomized to a combination of ipilimumab plus nivolumab or nivolumab alone [78]. One-year survival estimates were 49.2% [36.9–61.6] in the nivolumab group and 58.1% (45.8–70.3) in the nivolumab plus ipilimumab group. Nine (14%) patients in the nivolumab group and 16 (26%) in the combination group had grade 3–4 toxicities. A recently published phase II trial (INITIATE) also assessed the combination

of ipilimumab and nivolumab in MPM patients who had progressed after at least one line of chemotherapy [79]. This study found that 68% of persons had disease control at 12 weeks, 29% had a partial response, and 38% had stable disease. The KEYNOTE-028 trial assessed the use of pembrolizumab as subsequent therapy in PD-L1 positive MPM patients and recently reported that the median OS was 18 months with 20% grade 3–4 toxicity [80]. These latest studies indicate that immunotherapy represents one of the most recent advances in management of MPM.

### Radiation therapy

In patients with MPM, RT has been used as part of multimodality therapy with curative intent (Table 2) or administered alone as palliative therapy for pain relief [84, 85]. The RT dose

should be based on the purpose of treatment as delivery of RT to the entire hemithorax, which is challenging given the complex shape of the pleura and the proximity of critical organs such as the lungs and heart [86].

RT is commonly delivered after surgical intervention with or without chemotherapy and has been shown to decrease the local recurrence rate following EPP [87–90]. In a phase II study, Rusch *et al.* have assessed the feasibility of hemithoracic radiation (54 Gy) in 88 patients after surgical resection (70% underwent EPP) [87]. Patients with stage I–II disease had a median OS of 22.8 months and those with stage III–IV disease had a median OS of 10 months. Only two patients treated with EPP had a local recurrence and five individuals had locoregional and distant recurrence. Krug *et al.* prospectively treated 77 subjects with neoadjuvant pemetrexed plus cisplatin, EPP, and adjuvant hemithoracic RT (54 Gy) [52]. Forty patients (52%) were able to complete all therapies with a median OS of 29.1 months. In the JMIG 0601 trial, Hasegawa *et al.* enrolled 42 MPM patients to neoadjuvant pemetrexed plus cisplatin, EPP, and adjuvant hemithoracic RT (54 Gy) [46]. Significantly longer OS was observed for patients who received trimodality therapy (40%) in comparison with patients who completed EPP but not RT (39.4 vs 11.4 months;  $p = 0.0243$ ). As has been previously reported in multiple prospective studies, RT improves local control (LC) and OS as part of trimodality therapy with EPP; however, only about 50% of the patients are able to undergo all therapy.

High-dose RT to the entire hemithorax was traditionally not recommended in patients with an intact lung as it was found to not improve survival and was associated with significant toxicity [91–93]. With the recent trend in surgical management towards lung-sparing surgical techniques (P/D or extended-P/D), a new method using intensity modulated RT (IMRT) has been reported in the IMPRINT trial to adequately treat the peripheral pleural space that carries the highest risk of local recurrence while sparing critical structures [50]. In this phase II trial, Rimmer *et al.* enrolled 45 MPM patients to a trimodality regimen consisting of induction chemotherapy, P/D, and adjuvant hemithoracic RT using IMRT (50.4 Gy) [50]. When possible, the total mean lung dose was limited to 21 Gy, ipsilateral lung V20Gy to  $\leq 37\%$  to  $40\%$ , and contralateral lung V20Gy to  $\leq 7\%$ . Twenty-seven patients (60%) were able to start radiation therapy. The one- and two-year OS rates for patients with resectable disease were 80% and 59%, respectively.

Grade 2–3 radiation pneumonitis was reported in 30%. Based on this trial, the NCCN guidelines currently recommend consideration of hemithoracic IMRT following induction chemotherapy and P/D in centers with expertise.

Diagnosis of MPM is often made by pleural biopsy *via* CT-guided needle biopsy, thoracoscopy, video-assisted thoracic surgery, or thoracotomy, which can all lead to tumor cell seeding and chest wall metastasis. Prophylactic RT is often used to prevent instrument-tract recurrence; however, this has been controversial as older randomized trials demonstrated conflicting results [94–96]. A recent phase III trial (SMART) randomized 203 MPM patients with a chest wall intervention to prophylactic RT (21 Gy in 3 fractions) or deferred RT [97]. No significant difference in procedure-tract recurrence was observed between the groups (9% vs 16%;  $p = 0.14$ ). Based on the SMART trial, routine prophylactic RT to prevent instrument-tract recurrence after pleural intervention is no longer recommended.

## Conclusions

MPM is a rare disease with a poor prognosis but improvements in surgical techniques and systemic therapies as well as advancements in RT have led to a potential new paradigm in MPM management. Surgery for MPM is indicated mainly as a part of trimodality therapy. Whether EPP or extended-P/D is the superior approach remains a highly debated topic, with a shift towards extended-P/D in recent years. Chemotherapy plays an important role and is recommended as part of multimodality therapy as well as alone in locally advanced or progressive disease. The current first-line regimen consists of a combination of pemetrexed and cisplatin with alternatives, including pemetrexed-carboplatin and gemcitabine-cisplatin. Recent advancements in immunotherapy suggest the potential use of pembrolizumab or nivolumab with (or without) ipilimumab as subsequent systemic therapy. Although the use of RT was historically limited to palliation, recent advances in treatment planning and delivery techniques allow RT to improve LC and OS as a part of trimodality therapy. We critically reviewed the literature and devised an evidence-based treatment algorithm for patients with MPM (Figure 1). Nevertheless, the best treatment approach for MPM is determined through a multidisciplinary approach in experienced cancer centers.

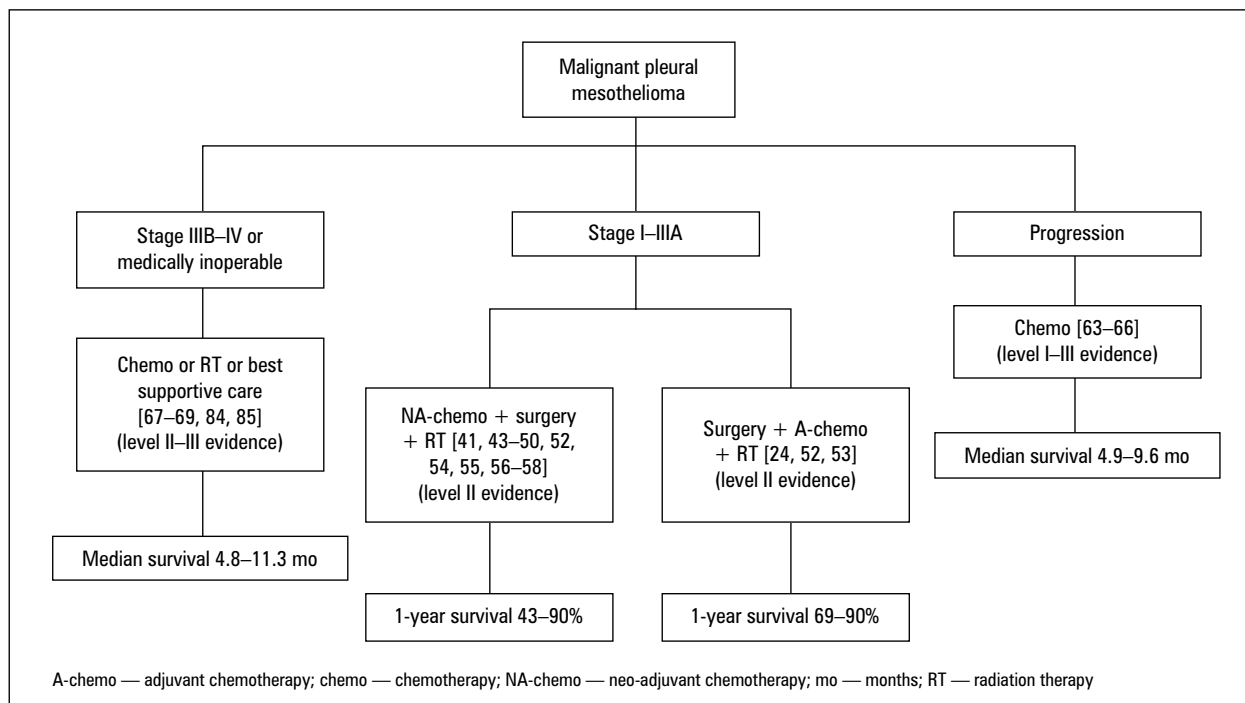


Figure 1. Treatment algorithm for malignant pleural mesothelioma

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