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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

**Adv Respir Med. 2019; 87: 289–297**

### 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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DOI: 10.5603/ARM.2019.0051

Received: 27.05.2019

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ISSN 2451–4934

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%,  $p \leq 0.001$ ). 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.

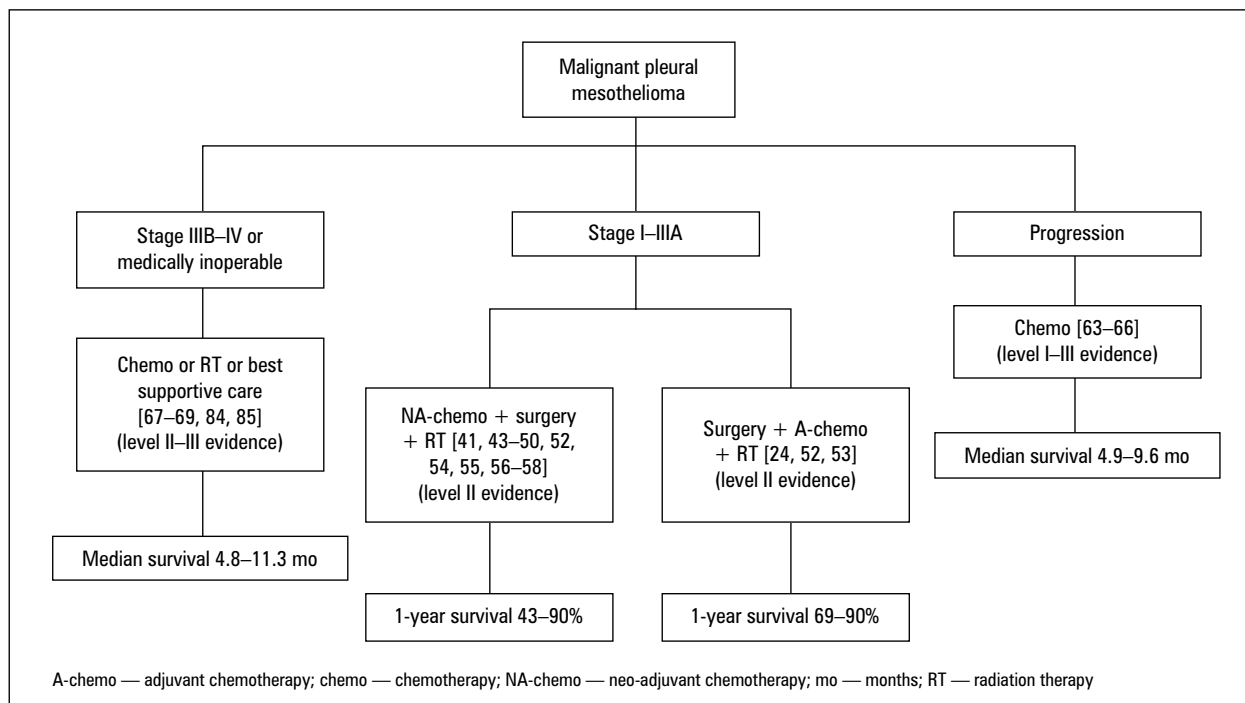


Figure 1. Treatment algorithm for malignant pleural mesothelioma

References:

- Jaurand MC, Fleury-Feith J. Pathogenesis of malignant pleural mesothelioma. *Respirology*. 2005; 10(1): 2–8, doi: 10.1111/j.1440-1843.2005.00694.x, indexed in Pubmed: 15691231.
- Mossman BT, Kamp DW, Weitzman SA. Mechanisms of carcinogenesis and clinical features of asbestos-associated cancers. *Cancer Invest*. 1996; 14(5): 466–480, doi: 10.3109/07357909609018904, indexed in Pubmed: 8816862.
- Baris I, Simonato L, Artvinli M, et al. Epidemiological and environmental evidence of the health effects of exposure to erionite fibres: a four-year study in the Cappadocian region of Turkey. *Int J Cancer*. 1987; 39(1): 10–17, doi: 10.1002/ijc.2910390104, indexed in Pubmed: 3025107.
- Emri S, Demir AU. Malignant pleural mesothelioma in Turkey, 2000–2002. *Lung Cancer*. 2004; 45 Suppl 1: S17–S20, doi: 10.1016/j.lungcan.2004.04.009, indexed in Pubmed: 15261427.
- Giordani M, Mattioli M, Ballirano P, et al. Geological occurrence, mineralogical characterization, and risk assessment of potentially carcinogenic erionite in Italy. *J Toxicol Environ Health B Crit Rev*. 2017; 20(2): 81–103, doi: 10.1080/10937404.2016.1263586, indexed in Pubmed: 28339348.
- Van Gosen BS, Blitz TA, Plumlee GS, et al. Geologic occurrences of erionite in the United States: an emerging national public health concern for respiratory disease. *Environ Geochem Health*. 2013; 35(4): 419–430, doi: 10.1007/s10653-012-9504-9, indexed in Pubmed: 23315055.
- Timblin CR, Guthrie GD, Janssen YW, et al. Patterns of c-fos and c-jun proto-oncogene expression, apoptosis, and proliferation in rat pleural mesothelial cells exposed to erionite or asbestos fibers. *Toxicol Appl Pharmacol*. 1998; 151(1): 88–97, doi: 10.1006/taap.1998.8450, indexed in Pubmed: 9705890.
- Janssen YM, Heintz NH, Marsh JP, et al. Induction of c-fos and c-jun proto-oncogenes in target cells of the lung and pleura by carcinogenic fibers. *Am J Respir Cell Mol Biol*. 1994; 11(5): 522–530, doi: 10.1165/ajrcmb.11.5.7946382, indexed in Pubmed: 7946382.
- Fach E, Waldman WJ, Williams M, et al. Analysis of the biological and chemical reactivity of zeolite-based aluminosili-

- cate fibers and particulates. *Environ Health Perspect*. 2002; 110(11): 1087–1096, doi: 10.1289/ehp.021101087, indexed in Pubmed: 12417479.
- Carthew P, Hill RJ, Edwards RE, et al. Intrapleural administration of fibres induces mesothelioma in rats in the same relative order of hazard as occurs in man after exposure. *Hum Exp Toxicol*. 1992; 11(6): 530–534, doi: 10.1177/096032719201100615, indexed in Pubmed: 1361144.
- Wagner JC, Skidmore JW, Hill RJ, et al. Erionite exposure and mesotheliomas in rats. *Br J Cancer*. 1985; 51(5): 727–730, doi: 10.1038/bjc.1985.108, indexed in Pubmed: 2986668.
- Carbone M, Yang H. Mesothelioma: recent highlights. *Ann Transl Med*. 2017; 5(11): 238, doi: 10.21037/atm.2017.04.29, indexed in Pubmed: 28706906.
- Baas P, Fennell D, Kerr KM, et al. ESMO Guidelines Committee. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015; 26 Suppl 5: v31–v39, doi: 10.1093/annonc/mdv199, indexed in Pubmed: 26223247.
- Olsen NJ, Franklin PJ, Reid A, et al. Increasing incidence of malignant mesothelioma after exposure to asbestos during home maintenance and renovation. *Med J Aust*. 2011; 195(5): 271–274, doi: 10.5694/mja11.10125, indexed in Pubmed: 21895596.
- Frank AL, Joshi TK. The global spread of asbestos. *Ann Glob Health*. 2014; 80(4): 257–262, doi: 10.1016/j.aogh.2014.09.016, indexed in Pubmed: 25459326.
- Hashim D, Boffetta P. Occupational and environmental exposures and cancers in developing countries. *Ann Glob Health*. 2014; 80(5): 393–411, doi: 10.1016/j.aogh.2014.10.002, indexed in Pubmed: 25512155.
- Opitz I, Friess M, Kestenholz P, et al. A new prognostic score supporting treatment allocation for multimodality therapy for malignant pleural mesothelioma: a review of 12 years' experience. *J Thorac Oncol*. 2015; 10(11): 1634–1641, doi: 10.1097/JTO.0000000000000661, indexed in Pubmed: 26317916.
- Abdel-Rahman O, Elsayed Z, Mohamed H, et al. Radical multimodality therapy for malignant pleural mesothelioma. *Cochrane Database Syst Rev*. 2018; 1: CD012605, doi: 10.1002/14651858.CD012605.pub2, indexed in Pubmed: 29309720.

19. Batirel HF. Extrapleural pneumonectomy (EPP) pleurectomy decortication (P/D). *Ann Transl Med.* 2017; 5(11): 232, doi: [10.21037/atm.2017.03.82](https://doi.org/10.21037/atm.2017.03.82), indexed in Pubmed: [28706900](https://pubmed.ncbi.nlm.nih.gov/28706900/).
20. Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. *J Thorac Oncol.* 2011; 6(8): 1304–1312, doi: [10.1097/JTO.0b013e3182208e3f](https://doi.org/10.1097/JTO.0b013e3182208e3f), indexed in Pubmed: [21847060](https://pubmed.ncbi.nlm.nih.gov/21847060/).
21. Rusch VW, Chansky K, Kindler HL, et al. The IASLC mesothelioma staging project: proposals for the m descriptors and for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for mesothelioma. *J Thorac Oncol.* 2016; 11(12): 2112–2119, doi: [10.1016/j.jtho.2016.09.124](https://doi.org/10.1016/j.jtho.2016.09.124), indexed in Pubmed: [27687962](https://pubmed.ncbi.nlm.nih.gov/27687962/).
22. Opitz I, Weder W. A nuanced view of extrapleural pneumonectomy for malignant pleural mesothelioma. *Ann Transl Med.* 2017; 5(11): 237, doi: [10.21037/atm.2017.03.88](https://doi.org/10.21037/atm.2017.03.88), indexed in Pubmed: [28706905](https://pubmed.ncbi.nlm.nih.gov/28706905/).
23. Rusch VW, Giroux D, Kennedy C, et al. Initial analysis of the international association for the study of lung cancer mesothelioma database. *J Thorac Oncol.* 2012; 7(11): 1631–1639, doi: [10.1097/JTO.0b013e31826915f1](https://doi.org/10.1097/JTO.0b013e31826915f1), indexed in Pubmed: [23070243](https://pubmed.ncbi.nlm.nih.gov/23070243/).
24. Hasani A, Alvarez JM, Wyatt JMa, et al. Outcome for patients with malignant pleural mesothelioma referred for Trimodality therapy in Western Australia. *J Thorac Oncol.* 2009; 4(8): 1010–1016, doi: [10.1097/JTO.0b013e318a255bf](https://doi.org/10.1097/JTO.0b013e318a255bf), indexed in Pubmed: [19546819](https://pubmed.ncbi.nlm.nih.gov/19546819/).
25. Sugarbaker D, Flores R, Jaklitsch M, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: Results in 183 patients. *J Thorac Cardiovasc Surg.* 1999; 117(1): 54–65, doi: [10.1016/s0022-5223\(99\)70469-1](https://doi.org/10.1016/s0022-5223(99)70469-1).
26. Bovolato P, Casadio C, Billè A, et al. Does surgery improve survival of patients with malignant pleural mesothelioma? A multicenter retrospective analysis of 1365 consecutive patients. *J Thorac Oncol.* 2014; 9(3): 390–396, doi: [10.1097/JTO.000000000000064](https://doi.org/10.1097/JTO.000000000000064), indexed in Pubmed: [24518090](https://pubmed.ncbi.nlm.nih.gov/24518090/).
27. Aziz T, Jilaihawi A, Prakash D. The management of malignant pleural mesothelioma; single centre experience in 10 years. *Eur J Cardiothorac Surg.* 2002; 22(2): 298–305, doi: [10.1016/s1010-7940\(02\)00273-7](https://doi.org/10.1016/s1010-7940(02)00273-7), indexed in Pubmed: [12142203](https://pubmed.ncbi.nlm.nih.gov/12142203/).
28. Branscheid D, Krysa S, Bauer E, et al. Diagnostic and therapeutic strategy in malignant pleural mesothelioma. *Eur J Cardiothorac Surg.* 1991; 5(9): 466–72; discussion 473, doi: [10.1016/1010-7940\(91\)90142-7](https://doi.org/10.1016/1010-7940(91)90142-7), indexed in Pubmed: [1931091](https://pubmed.ncbi.nlm.nih.gov/1931091/).
29. Flores RM, Pass HI, Seshan VE, et al. Extrapleural pneumonectomy versus pleurectomy/decortication in the surgical management of malignant pleural mesothelioma: results in 626 patients. *J Thorac Cardiovasc Surg.* 2008; 135(3): 620–6, doi: [10.1016/j.jtcvs.2007.10.054](https://doi.org/10.1016/j.jtcvs.2007.10.054), indexed in Pubmed: [18329481](https://pubmed.ncbi.nlm.nih.gov/18329481/).
30. Kostron A, Friess M, Inci I, et al. Propensity matched comparison of extrapleural pneumonectomy and pleurectomy/decortication for mesothelioma patients. *Interact Cardiovasc Thorac Surg.* 2017; 24(5): 740–746, doi: [10.1093/icvts/ivw422](https://doi.org/10.1093/icvts/ivw422), indexed in Pubmed: [28453802](https://pubmed.ncbi.nlm.nih.gov/28453802/).
31. Lang-Lazdunski L, Bille A, Lal R, et al. Pleurectomy/decortication is superior to extrapleural pneumonectomy in the multimodality management of patients with malignant pleural mesothelioma. *J Thorac Oncol.* 2012; 7(4): 737–743, doi: [10.1097/JTO.0b013e31824ab6c5](https://doi.org/10.1097/JTO.0b013e31824ab6c5), indexed in Pubmed: [22425923](https://pubmed.ncbi.nlm.nih.gov/22425923/).
32. Luckraz H, Rahman M, Patel N, et al. Three decades of experience in the surgical multi-modality management of pleural mesothelioma. *Eur J Cardiothorac Surg.* 2010; 37(3): 552–556, doi: [10.1016/j.ejcts.2009.07.032](https://doi.org/10.1016/j.ejcts.2009.07.032), indexed in Pubmed: [19717307](https://pubmed.ncbi.nlm.nih.gov/19717307/).
33. Miyazaki T, Yamasaki N, Tsuchiya T, et al. Is pleurectomy/decortication superior to extrapleural pneumonectomy for patients with malignant pleural mesothelioma? A single-institutional experience. *Ann Thorac Cardiovasc Surg.* 2018; 24(2): 81–88, doi: [10.5761/atcs.0a.17-00192](https://doi.org/10.5761/atcs.0a.17-00192), indexed in Pubmed: [29367501](https://pubmed.ncbi.nlm.nih.gov/29367501/).
34. Okada M, Mimura T, Ohbayashi C, et al. Radical surgery for malignant pleural mesothelioma: results and prognosis. *Interact Cardiovasc Thorac Surg.* 2008; 7(1): 102–106, doi: [10.1510/icvts.2007.166322](https://doi.org/10.1510/icvts.2007.166322), indexed in Pubmed: [18048410](https://pubmed.ncbi.nlm.nih.gov/18048410/).
35. Pass HI, Kranda K, Temeck BK, et al. Surgically debulked malignant pleural mesothelioma: results and prognostic factors. *Ann Surg Oncol.* 1997; 4(3): 215–222, indexed in Pubmed: [9142382](https://pubmed.ncbi.nlm.nih.gov/9142382/).
36. Rena O, Casadio C. Extrapleural pneumonectomy for early stage malignant pleural mesothelioma: a harmful procedure. *Lung Cancer.* 2012; 77(1): 151–155, doi: [10.1016/j.lungcan.2011.12.009](https://doi.org/10.1016/j.lungcan.2011.12.009), indexed in Pubmed: [22244608](https://pubmed.ncbi.nlm.nih.gov/22244608/).
37. Sharkey AJ, Tenconi S, Nakas A, et al. The effects of an intentional transition from extrapleural pneumonectomy to extended pleurectomy/decortication. *Eur J Cardiothorac Surg.* 2016; 49(6): 1632–1641, doi: [10.1093/ejcts/ezv403](https://doi.org/10.1093/ejcts/ezv403), indexed in Pubmed: [26637211](https://pubmed.ncbi.nlm.nih.gov/26637211/).
38. Kai Y, Tsutani Y, Tsubokawa N, et al. Prolonged post-recurrence survival following pleurectomy/decortication for malignant pleural mesothelioma. *Oncol Lett.* 2019; 17(3): 3607–3614, doi: [10.3892/ol.2019.9979](https://doi.org/10.3892/ol.2019.9979), indexed in Pubmed: [30867804](https://pubmed.ncbi.nlm.nih.gov/30867804/).
39. Cao C, Akhunjy Z, Fu B, et al. Systematic review of pleurectomy in the treatment of malignant pleural mesothelioma. *Lung Cancer.* 2013; 81(3): 319–327, doi: [10.1016/j.lungcan.2013.04.024](https://doi.org/10.1016/j.lungcan.2013.04.024), indexed in Pubmed: [23769317](https://pubmed.ncbi.nlm.nih.gov/23769317/).
40. Taioli E, Wolf AS, Flores RM. Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. *Ann Thorac Surg.* 2015; 99(2): 472–480, doi: [10.1016/j.athoracsur.2014.09.056](https://doi.org/10.1016/j.athoracsur.2014.09.056), indexed in Pubmed: [25534527](https://pubmed.ncbi.nlm.nih.gov/25534527/).
41. Treasure T, Lang-Lazdunski L, Waller D, et al. MARS trials. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. *Lancet Oncol.* 2011; 12(8): 763–772, doi: [10.1016/S1470-2045\(11\)70149-8](https://doi.org/10.1016/S1470-2045(11)70149-8), indexed in Pubmed: [21723781](https://pubmed.ncbi.nlm.nih.gov/21723781/).
42. Domen A, De Laet C, Vanderbruggen W, et al. Malignant pleural mesothelioma: single-institution experience of 101 patients over a 15-year period. *Acta Chir Belg.* 2017; 117(3): 157–163, doi: [10.1080/00015458.2016.1272253](https://doi.org/10.1080/00015458.2016.1272253), indexed in Pubmed: [28399779](https://pubmed.ncbi.nlm.nih.gov/28399779/).
43. Rosenzweig KE, Zauderer MG, Laser B, et al. Pleural intensity-modulated radiotherapy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys.* 2012; 83(4): 1278–1283, doi: [10.1016/j.ijrobp.2011.09.027](https://doi.org/10.1016/j.ijrobp.2011.09.027), indexed in Pubmed: [22607910](https://pubmed.ncbi.nlm.nih.gov/22607910/).
44. Bille A, Belcher E, Raubenheimer H, et al. Induction chemotherapy, extrapleural pneumonectomy, and adjuvant radiotherapy for malignant pleural mesothelioma: experience of Guy's and St Thomas' hospitals. *Gen Thorac Cardiovasc Surg.* 2012; 60(5): 289–296, doi: [10.1007/s11748-011-0915-9](https://doi.org/10.1007/s11748-011-0915-9), indexed in Pubmed: [22453539](https://pubmed.ncbi.nlm.nih.gov/22453539/).
45. Stahel RA, Riesterer O, Xyrafas A, et al. Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomised, international, multicentre phase 2 trial. *Lancet Oncol.* 2015; 16(16): 1651–1658, doi: [10.1016/S1470-2045\(15\)00208-9](https://doi.org/10.1016/S1470-2045(15)00208-9), indexed in Pubmed: [26538423](https://pubmed.ncbi.nlm.nih.gov/26538423/).
46. Hasegawa S, Okada M, Tanaka F, et al. Trimodality strategy for treating malignant pleural mesothelioma: results of a feasibility study of induction pemetrexed plus cisplatin followed by extrapleural pneumonectomy and postoperative hemithoracic radiation (Japan Mesothelioma Interest Group 0601 Trial). *Int J Clin Oncol.* 2016; 21(3): 523–530, doi: [10.1007/s10147-015-0925-1](https://doi.org/10.1007/s10147-015-0925-1), indexed in Pubmed: [26577445](https://pubmed.ncbi.nlm.nih.gov/26577445/).
47. Van Schil PE, Baas P, Gaafar R, et al. Trimodality therapy for malignant pleural mesothelioma: results from an EORTC phase II multicentre trial. *Eur Respir J.* 2010; 36(6): 1362–1369, doi: [10.1183/09031936.00039510](https://doi.org/10.1183/09031936.00039510), indexed in Pubmed: [20525721](https://pubmed.ncbi.nlm.nih.gov/20525721/).
48. Federico R, Adolfo F, Giuseppe M, et al. Phase II trial of neoadjuvant pemetrexed plus cisplatin followed by surgery and radiation in the treatment of pleural mesothelioma. *BMC Cancer.* 2013; 13: 22, doi: [10.1186/1471-2407-13-22](https://doi.org/10.1186/1471-2407-13-22), indexed in Pubmed: [23324131](https://pubmed.ncbi.nlm.nih.gov/23324131/).

49. de Perrot M, Feld R, Cho BC, et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Clin Oncol.* 2009; 27(9): 1413–1418, doi: [10.1200/JCO.2008.17.5604](https://doi.org/10.1200/JCO.2008.17.5604), indexed in Pubmed: [19224855](https://pubmed.ncbi.nlm.nih.gov/19224855/).
50. Rimmer A, Zauderer MG, Gomez DR, et al. Phase II Study of Hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) As Part of Lung-Sparing Multimodality Therapy in Patients With Malignant Pleural Mesothelioma. *J Clin Oncol.* 2016; 34(23): 2761–2768, doi: [10.1200/JCO.2016.67.2675](https://doi.org/10.1200/JCO.2016.67.2675), indexed in Pubmed: [27325859](https://pubmed.ncbi.nlm.nih.gov/27325859/).
51. Minatel E, Trovo M, Bearz A, et al. Radical radiation therapy after lung-sparing surgery for malignant pleural mesothelioma: survival, pattern of failure, and prognostic factors. *Int J Radiat Oncol Biol Phys.* 2015; 93(3): 606–613, doi: [10.1016/j.ijrobp.2015.06.029](https://doi.org/10.1016/j.ijrobp.2015.06.029), indexed in Pubmed: [26281826](https://pubmed.ncbi.nlm.nih.gov/26281826/).
52. Krug LM, Pass HI, Rusch VW, et al. Multicenter phase II trial of neoadjuvant pemetrexed plus cisplatin followed by extrapleural pneumonectomy and radiation for malignant pleural mesothelioma. *J Clin Oncol.* 2009; 27(18): 3007–3013, doi: [10.1200/JCO.2008.20.3943](https://doi.org/10.1200/JCO.2008.20.3943), indexed in Pubmed: [19364962](https://pubmed.ncbi.nlm.nih.gov/19364962/).
53. Bölükbas S, Manegold C, Eberlein M, et al. Survival after trimodality therapy for malignant pleural mesothelioma: Radical Pleurectomy, chemotherapy with Cisplatin/Pemetrexed and radiotherapy. *Lung Cancer.* 2011; 71(1): 75–81, doi: [10.1016/j.lungcan.2009.08.019](https://doi.org/10.1016/j.lungcan.2009.08.019), indexed in Pubmed: [19765853](https://pubmed.ncbi.nlm.nih.gov/19765853/).
54. Buduhan G, Menon S, Aye R, et al. Trimodality therapy for malignant pleural mesothelioma. *Ann Thorac Surg.* 2009; 88(3): 870–5; discussion 876, doi: [10.1016/j.athoracsur.2009.05.036](https://doi.org/10.1016/j.athoracsur.2009.05.036), indexed in Pubmed: [19699914](https://pubmed.ncbi.nlm.nih.gov/19699914/).
55. Fahrner R, Ochslein A, Schmid RA, et al. Long term survival after trimodal therapy in malignant pleural mesothelioma. *Swiss Med Wkly.* 2012; 142: w13686, doi: [10.4414/smw.2012.13686](https://doi.org/10.4414/smw.2012.13686), indexed in Pubmed: [23135895](https://pubmed.ncbi.nlm.nih.gov/23135895/).
56. Kimura T, Doi Y, Nakashima T, et al. Clinical experience of volumetric modulated arc therapy for malignant pleural mesothelioma after extrapleural pneumonectomy. *J Radiat Res.* 2015; 56(2): 315–324, doi: [10.1093/jrr/rru102](https://doi.org/10.1093/jrr/rru102), indexed in Pubmed: [25599996](https://pubmed.ncbi.nlm.nih.gov/25599996/).
57. Thieke C, Nicolay NH, Sterzing F, et al. Long-term results in malignant pleural mesothelioma treated with neoadjuvant chemotherapy, extrapleural pneumonectomy and intensity-modulated radiotherapy. *Radiat Oncol.* 2015; 10: 267, doi: [10.1186/s13014-015-0575-5](https://doi.org/10.1186/s13014-015-0575-5), indexed in Pubmed: [26715491](https://pubmed.ncbi.nlm.nih.gov/26715491/).
58. Trousse DS, Avaro JP, D'Journo XB, et al. Is malignant pleural mesothelioma a surgical disease? A review of 83 consecutive extra-pleural pneumonectomies. *Eur J Cardiothorac Surg.* 2009; 36(4): 759–763, doi: [10.1016/j.ejcts.2009.04.044](https://doi.org/10.1016/j.ejcts.2009.04.044), indexed in Pubmed: [19523843](https://pubmed.ncbi.nlm.nih.gov/19523843/).
59. Lang-Lazdunski L, Bille A, Papa S, et al. Pleurectomy/decortication, hyperthermic pleural lavage with povidone-iodine followed by adjuvant chemotherapy in patients with malignant pleural mesothelioma. *J Thorac Oncol.* 2011; 6(10): 1746–1752, doi: [10.1097/JTO.0b013e3182288af9](https://doi.org/10.1097/JTO.0b013e3182288af9), indexed in Pubmed: [21876457](https://pubmed.ncbi.nlm.nih.gov/21876457/).
60. Blomberg C, Nilsson J, Holgersson G, et al. Randomized trials of systemic medically-treated malignant mesothelioma: a systematic review. *Anticancer Res.* 2015; 35(5): 2493–2501, indexed in Pubmed: [25964522](https://pubmed.ncbi.nlm.nih.gov/25964522/).
61. Kelly RJ, Sharon E, Hassan R. Chemotherapy and targeted therapies for unresectable malignant mesothelioma. *Lung Cancer.* 2011; 73(3): 256–263, doi: [10.1016/j.lungcan.2011.04.014](https://doi.org/10.1016/j.lungcan.2011.04.014), indexed in Pubmed: [21620512](https://pubmed.ncbi.nlm.nih.gov/21620512/).
62. Ellis P, Davies AM, Evans WK, et al. The use of chemotherapy in patients with advanced malignant pleural mesothelioma: a systematic review and practice guideline. *J Thorac Oncol.* 2006; 1(6): 591–601, indexed in Pubmed: [17409924](https://pubmed.ncbi.nlm.nih.gov/17409924/).
63. Zauderer MG, Kass SL, Woo K, et al. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. *Lung Cancer.* 2014; 84(3): 271–274, doi: [10.1016/j.lungcan.2014.03.006](https://doi.org/10.1016/j.lungcan.2014.03.006), indexed in Pubmed: [24690410](https://pubmed.ncbi.nlm.nih.gov/24690410/).
64. Jänne P, Wozniak A, Belani C, et al. Pemetrexed alone or in combination with cisplatin in previously treated malignant pleural mesothelioma: outcomes from a phase IIIB expanded access program. *J Thorac Oncol.* 2006; 1(6): 506–512, doi: [10.1016/s1556-0864\(15\)30351-8](https://doi.org/10.1016/s1556-0864(15)30351-8).
65. Jassem J, Ramlaoui R, Santoro A, et al. Phase III trial of pemetrexed plus best supportive care compared with best supportive care in previously treated patients with advanced malignant pleural mesothelioma. *J Clin Oncol.* 2008; 26(10): 1698–1704, doi: [10.1200/JCO.2006.09.9887](https://doi.org/10.1200/JCO.2006.09.9887), indexed in Pubmed: [18375898](https://pubmed.ncbi.nlm.nih.gov/18375898/).
66. Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung Cancer.* 2009; 63(1): 94–97, doi: [10.1016/j.lungcan.2008.04.001](https://doi.org/10.1016/j.lungcan.2008.04.001), indexed in Pubmed: [18486273](https://pubmed.ncbi.nlm.nih.gov/18486273/).
67. Verma V, Wegner RE, Brooks ED, et al. Chemotherapy versus supportive care for unresected malignant pleural mesothelioma. *Clin Lung Cancer.* 2019; 20(4): 263–269, doi: [10.1016/j.clcl.2019.03.003](https://doi.org/10.1016/j.clcl.2019.03.003), indexed in Pubmed: [30992187](https://pubmed.ncbi.nlm.nih.gov/30992187/).
68. Metintas M, Ak G, Erginel S, et al. A retrospective analysis of malignant pleural mesothelioma patients treated either with chemotherapy or best supportive care between 1990 and 2005 A single institution experience. *Lung Cancer.* 2007; 55(3): 379–387, doi: [10.1016/j.lungcan.2006.11.005](https://doi.org/10.1016/j.lungcan.2006.11.005), indexed in Pubmed: [17174436](https://pubmed.ncbi.nlm.nih.gov/17174436/).
69. Wu TH, Lee LJH, Yuan CT, et al. Prognostic factors and treatment outcomes of malignant pleural mesothelioma in Eastern Asian patients. A Taiwanese study. *J Formos Med Assoc.* 2019; 118(1 Pt 2): 230–236, doi: [10.1016/j.jfma.2018.04.001](https://doi.org/10.1016/j.jfma.2018.04.001), indexed in Pubmed: [29709339](https://pubmed.ncbi.nlm.nih.gov/29709339/).
70. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol.* 2003; 21(14): 2636–2644, doi: [10.1200/JCO.2003.11.136](https://doi.org/10.1200/JCO.2003.11.136), indexed in Pubmed: [12860938](https://pubmed.ncbi.nlm.nih.gov/12860938/).
71. Zalcman G, Mazieres J, Margery J, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase III trial. *Lancet.* 2016; 387(10026): 1405–1414, doi: [10.1016/S0140-6736\(15\)01238-6](https://doi.org/10.1016/S0140-6736(15)01238-6), indexed in Pubmed: [26719230](https://pubmed.ncbi.nlm.nih.gov/26719230/).
72. Katirtzoglou N, Gkiozos I, Makrilia N, et al. Carboplatin plus pemetrexed as first-line treatment of patients with malignant pleural mesothelioma: a phase II study. *Clin Lung Cancer.* 2010; 11(1): 30–35, doi: [10.3816/CLC.2010.n.005](https://doi.org/10.3816/CLC.2010.n.005), indexed in Pubmed: [20085865](https://pubmed.ncbi.nlm.nih.gov/20085865/).
73. Ceresoli GL, Zucali PA, Mencoboni M, et al. Phase II study of pemetrexed plus carboplatin in malignant pleural mesothelioma. *J Clin Oncol.* 2006; 24(9): 1443–1448, doi: [10.1200/JCO.2005.04.3190](https://doi.org/10.1200/JCO.2005.04.3190), indexed in Pubmed: [16549838](https://pubmed.ncbi.nlm.nih.gov/16549838/).
74. Castagneto B, Botta M, Aitini E, et al. Phase II study of pemetrexed in combination with carboplatin in patients with malignant pleural mesothelioma (MPM). *Ann Oncol.* 2008; 19(2): 370–373, doi: [10.1093/annonc/mdm501](https://doi.org/10.1093/annonc/mdm501), indexed in Pubmed: [18156144](https://pubmed.ncbi.nlm.nih.gov/18156144/).
75. Arrieta O, López-Macías D, Mendoza-García VO, et al. A phase II trial of prolonged, continuous infusion of low-dose gemcitabine plus cisplatin in patients with advanced malignant pleural mesothelioma. *Cancer Chemother Pharmacol.* 2014; 73(5): 975–982, doi: [10.1007/s00280-014-2429-5](https://doi.org/10.1007/s00280-014-2429-5), indexed in Pubmed: [24687408](https://pubmed.ncbi.nlm.nih.gov/24687408/).
76. van Haarst JMW, Baas P, Manegold Ch, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer.* 2002; 86(3): 342–345, doi: [10.1038/sj.bjc.6600118](https://doi.org/10.1038/sj.bjc.6600118), indexed in Pubmed: [11875695](https://pubmed.ncbi.nlm.nih.gov/11875695/).
77. Nowak AK, Byrne MJ, Williamson R, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer.* 2002; 87(5): 491–496, doi: [10.1038/sj.bjc.6600505](https://doi.org/10.1038/sj.bjc.6600505), indexed in Pubmed: [12189542](https://pubmed.ncbi.nlm.nih.gov/12189542/).
78. Scherpereel A, Mazieres J, Greillier L, et al. Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial. *Lancet Oncol.* 2019; 20(2): 239–253, doi: [10.1016/S1470-2045\(18\)30765-4](https://doi.org/10.1016/S1470-2045(18)30765-4), indexed in Pubmed: [30660609](https://pubmed.ncbi.nlm.nih.gov/30660609/).
79. Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of a prospective, sin-



- gle-arm, phase 2 trial. *Lancet Respir Med.* 2019; 7(3): 260–270, doi: [10.1016/S2213-2600\(18\)30420-X](https://doi.org/10.1016/S2213-2600(18)30420-X), indexed in Pubmed: [30660511](https://pubmed.ncbi.nlm.nih.gov/30660511/).
80. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol.* 2017; 18(5): 623–630, doi: [10.1016/S1470-2045\(17\)30169-9](https://doi.org/10.1016/S1470-2045(17)30169-9), indexed in Pubmed: [28291584](https://pubmed.ncbi.nlm.nih.gov/28291584/).
  81. Quispel-Janssen J, van der Noort V, de Vries JF, et al. Programmed death 1 blockade with nivolumab in patients with recurrent malignant pleural mesothelioma. *J Thorac Oncol.* 2018; 13(10): 1569–1576, doi: [10.1016/j.jtho.2018.05.038](https://doi.org/10.1016/j.jtho.2018.05.038), indexed in Pubmed: [29908324](https://pubmed.ncbi.nlm.nih.gov/29908324/).
  82. Metaxas Y, Rivalland G, Mauti LA, et al. Pembrolizumab as palliative immunotherapy in malignant pleural mesothelioma. *J Thorac Oncol.* 2018; 13(11): 1784–1791, doi: [10.1016/j.jtho.2018.08.007](https://doi.org/10.1016/j.jtho.2018.08.007), indexed in Pubmed: [30142389](https://pubmed.ncbi.nlm.nih.gov/30142389/).
  83. Kindler HL, Ismaila N, Armato SG, et al. Treatment of malignant pleural mesothelioma: american society of clinical oncology clinical practice guideline. *J Clin Oncol.* 2018; 36(13): 1343–1373, doi: [10.1200/JCO.2017.76.6394](https://doi.org/10.1200/JCO.2017.76.6394), indexed in Pubmed: [29346042](https://pubmed.ncbi.nlm.nih.gov/29346042/).
  84. Foroudi F, Smith JG, Putt F, et al. High-dose palliative radiotherapy for malignant pleural mesothelioma. *J Med Imaging Radiat Oncol.* 2017; 61(6): 797–803, doi: [10.1111/1754-9485.12636](https://doi.org/10.1111/1754-9485.12636), indexed in Pubmed: [28727277](https://pubmed.ncbi.nlm.nih.gov/28727277/).
  85. Graaf-Strukowska Lde, Zee Jv, Putten Wv, et al. Factors influencing the outcome of radiotherapy in malignant mesothelioma of the pleura — a single-institution experience with 189 patients. *Int J Radiat Oncol Biol Phys.* 1999; 43(3): 511–516, doi: [10.1016/s0360-3016\(98\)00409-x](https://doi.org/10.1016/s0360-3016(98)00409-x).
  86. Ashton M, O'Rourke N, Currie S, et al. The role of radical radiotherapy in the management of malignant pleural mesothelioma: A systematic review. *Radiother Oncol.* 2017; 125(1): 1–12, doi: [10.1016/j.radonc.2017.08.003](https://doi.org/10.1016/j.radonc.2017.08.003), indexed in Pubmed: [28859932](https://pubmed.ncbi.nlm.nih.gov/28859932/).
  87. Flores RM, Krug LM, Rosenzweig KE, et al. A phase II trial of surgical resection and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg.* 2001; 122(4): 788–795, doi: [10.1067/mtc.2001.116560](https://doi.org/10.1067/mtc.2001.116560), indexed in Pubmed: [11581615](https://pubmed.ncbi.nlm.nih.gov/11581615/).
  88. Gomez DR, Hong DS, Allen PK, et al. Patterns of failure, toxicity, and survival after extrapleural pneumonectomy and hemithoracic intensity-modulated radiation therapy for malignant pleural mesothelioma. *J Thorac Oncol.* 2013; 8(2): 238–245, doi: [10.1097/JTO.0b013e31827740f0](https://doi.org/10.1097/JTO.0b013e31827740f0), indexed in Pubmed: [23247629](https://pubmed.ncbi.nlm.nih.gov/23247629/).
  89. Yajnik S, Rosenzweig KE, Mychalczak B, et al. Hemithoracic radiation after extrapleural pneumonectomy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys.* 2003; 56(5): 1319–1326, doi: [10.1016/s0360-3016\(03\)00287-6](https://doi.org/10.1016/s0360-3016(03)00287-6), indexed in Pubmed: [12873676](https://pubmed.ncbi.nlm.nih.gov/12873676/).
  90. Rice DC, Stevens CW, Correa AM, et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. *Ann Thorac Surg.* 2007; 84(5): 1685–92; discussion 1692, doi: [10.1016/j.athoracsur.2007.04.076](https://doi.org/10.1016/j.athoracsur.2007.04.076), indexed in Pubmed: [17954086](https://pubmed.ncbi.nlm.nih.gov/17954086/).
  91. Baldini EH, Jänne PA, Baldini EH. Patterns of failure following surgical resection for malignant pleural mesothelioma. *Thorac Surg Clin.* 2004; 14(4): 567–573, doi: [10.1016/j.thor-surg.2004.06.006](https://doi.org/10.1016/j.thor-surg.2004.06.006), indexed in Pubmed: [15559064](https://pubmed.ncbi.nlm.nih.gov/15559064/).
  92. van Thiel ERE, Surmont VF, van Meerbeeck JP. Malignant pleural mesothelioma: when is radiation therapy indicated? *Expert Rev Anticancer Ther.* 2011; 11(4): 551–560, doi: [10.1586/era.10.169](https://doi.org/10.1586/era.10.169), indexed in Pubmed: [21504322](https://pubmed.ncbi.nlm.nih.gov/21504322/).
  93. Gupta V, Mychalczak B, Krug L, et al. Hemithoracic radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys.* 2005; 63(4): 1045–1052, doi: [10.1016/j.ijrobp.2005.03.041](https://doi.org/10.1016/j.ijrobp.2005.03.041), indexed in Pubmed: [16054774](https://pubmed.ncbi.nlm.nih.gov/16054774/).
  94. Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. *Chest.* 1995; 108(3): 754–758, doi: [10.1378/chest.108.3.754](https://doi.org/10.1378/chest.108.3.754), indexed in Pubmed: [7656629](https://pubmed.ncbi.nlm.nih.gov/7656629/).
  95. O'Rourke N, Garcia JC, Paul J, et al. A randomised controlled trial of intervention site radiotherapy in malignant pleural mesothelioma. *Radiother Oncol.* 2007; 84(1): 18–22, doi: [10.1016/j.radonc.2007.05.022](https://doi.org/10.1016/j.radonc.2007.05.022), indexed in Pubmed: [17588698](https://pubmed.ncbi.nlm.nih.gov/17588698/).
  96. Bydder S, Phillips M, Joseph DJ, et al. A randomised trial of single-dose radiotherapy to prevent procedure tract metastasis by malignant mesothelioma. *Br J Cancer.* 2004; 91(1): 9–10, doi: [10.1038/sj.bjc.6601957](https://doi.org/10.1038/sj.bjc.6601957), indexed in Pubmed: [15199394](https://pubmed.ncbi.nlm.nih.gov/15199394/).
  97. Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled trial. *Lancet Oncol.* 2016; 17(8): 1094–1104, doi: [10.1016/S1470-2045\(16\)30095-X](https://doi.org/10.1016/S1470-2045(16)30095-X), indexed in Pubmed: [27345639](https://pubmed.ncbi.nlm.nih.gov/27345639/).
  98. Verma V, Ahern CA, Berlind CG, et al. National cancer database report on pneumonectomy versus lung-sparing surgery for malignant pleural mesothelioma. *J Thorac Oncol.* 2017; 12(11): 1704–1714, doi: [10.1016/j.jtho.2017.08.012](https://doi.org/10.1016/j.jtho.2017.08.012), indexed in Pubmed: [28843362](https://pubmed.ncbi.nlm.nih.gov/28843362/).