Systematic Review

Systematic review of trimodality therapy for patients with malignant pleural mesothelioma

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Background: Malignant pleural mesothelioma (MPM) is an aggressive form of cancer arising from the pleural mesothelium. Trimodality therapy (TMT) involving extrapleural pneumonectomy with neoadjuvant or adjuvant chemotherapy and adjuvant radiotherapy is a recognized treatment option with a curative intent. Despite encouraging results from institutional studies, TMT in the treatment of MPM remains controversial. The present systematic review aims to assess the safety and efficacy of TMT in the current literature.

Methods: A systematic review was performed using five electronic databases from 1 January 1985 to 1 October 2012. Studies were selected independently by two reviewers according to predefined selection criteria. The primary endpoint was overall survival. Secondary endpoints included disease-free survival, disease recurrence, perioperative morbidity and length of stay.

Results: Sixteen studies were included for quantitative assessment, including one randomized controlled trial and five prospective series. Median overall survival ranged from 12.8-46.9 months. Disease-free survival ranged from 10-16.3 months. Perioperative mortality ranged from 0-12.5%. Overall perioperative morbidity ranged from 50-82.6% and the average length of stay was 9-14 days.

Conclusions: Outcomes of patients who underwent TMT in the current literature appeared to be inconsistent. Four prospective series involving a standardised treatment regimen with neoadjuvant chemotherapy indicated encouraging results based on intention-to-treat analysis. However, a small study assessing the feasibility of conducting a randomized controlled trial for TMT versus conservative treatment reported poor short- and long-term outcomes for patients who underwent pneumonectomy. Overall, results of the present systematic review suggest TMT may offer acceptable perioperative outcomes and long-term survival in selected patients treated in specialized centers.

Key Words: Systematic review; mesothelioma; trimodality therapy; extrapleural pneumonectomy

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Background

Malignant pleural mesothelioma (MPM) is an aggressive form of cancer arising from the pleural mesothelium (*Figure 1*). Although relatively rare, the incidence of MPM is expected to peak in many developed nations over the coming decade (1,2). Medical management of MPM has been limited by modest responses to modern chemotherapeutic agents and radiotherapy alone (3,4). Surgical options for patients with MPM can be divided into those with a palliative intent and those with a curative intent. In the latter group, patients who are deemed to

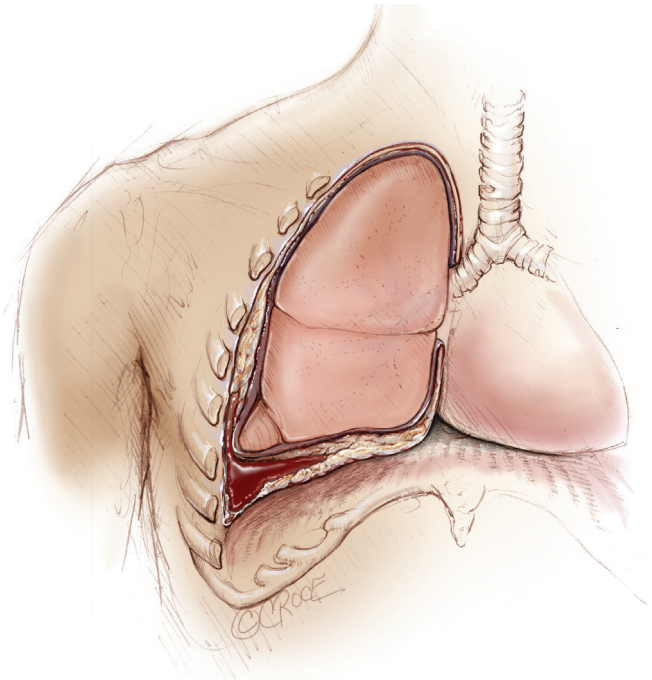

Figure 1 Malignant pleural mesothelioma is a primary neoplasm originating from the mesothelial cells that may be associated with dyspnea, pleural effusion and/or chest pain

have resectable disease can be offered surgical procedures such as extrapleural pneumonectomy (EPP) or extended pleurectomy/decortication (P/D) that aim to achieve macroscopic clearance and maximal cytoreduction.

An international consensus report recently concluded that more surgeons believed EPP could provide adequate cytoreduction compared to extended P/D (90% *vs*. 68%) (5). In most specialised centres, EPP is now routinely performed as part of a trimodality treatment (TMT) regimen involving neoadjuvant or adjuvant chemotherapy, surgery and adjuvant radiotherapy. Despite encouraging results from institutional reports, a number of studies comparing EPP to less invasive procedures have questioned the merit of this surgical technique, and the evidence for TMT remains controversial according to current guidelines (6-8). The primary aim of the present systematic review was to assess the safety and efficacy of TMT involving EPP, and to identify its role in the surgical management of patients with MPM.

Methods

Literature search strategy

Electronic searches were performed using Ovid Medline, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, and Database of Abstracts of Review of Effectiveness (DARE) from January 1985 to October 2012. To achieve the maximum sensitivity of the search strategy and identify all studies, we combined the terms "mesothelioma" and "pneumonectomy" as either key words or MeSH terms. The reference lists of all retrieved articles were reviewed for further identification of potentially relevant studies. All identified articles were systematically assessed using the inclusion and exclusion criteria.

Selection criteria

Eligible studies for the present systematic review included those in which patients with histologically proven MPM were treated by EPP, neoadjuvant or adjuvant chemotherapy, and adjuvant radiotherapy. All forms of systemic chemotherapy and radiotherapy were included. For studies that included patients who underwent TMT as a subset of patients who had other treatment regimens, results for patients who underwent TMT were extracted when possible. When centres have published duplicate trials with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for qualitative appraisal at each time interval. It is acknowledged that patient selection for TMT varied amongst institutions and sometimes within an institution at different time periods. All publications were limited to human subjects and in English language. Abstracts, case reports, conference presentations, editorials and expert opinions were excluded. Review articles were omitted due to potential publication bias and possible duplication of results. Studies that included fewer than twenty patients intended for treatment in prospective studies or who underwent EPP in retrospective studies were also excluded.

Data extraction and critical appraisal

All data were extracted from article texts, tables and figures. Two investigators (D.T. and P.M.) independently reviewed each retrieved article. Discrepancies between the two reviewers were resolved by discussion and consensus. The final results were reviewed by the senior investigators (C.C. and T.D.Y.).

Results

Quantity and quality of trials

A total of 502 references were identified through the five

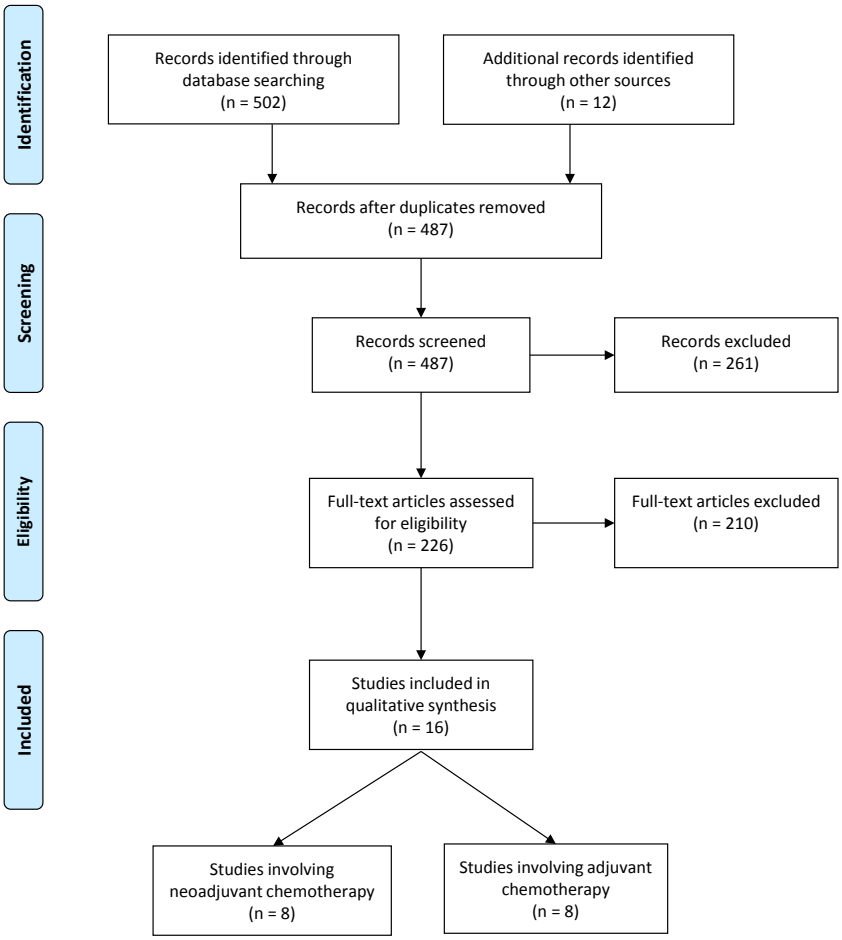

Figure 2 Search strategy of systematic review on trimodality therapy involving extrapleural pneumonectomy, chemotherapy and radiotherapy for patients with malignant pleural mesothelioma

electronic database searches. A summary of the study selection process is summarized in *Figure 2*. After inclusion of 12 studies from other sources and exclusion of duplicate references, 487 potentially relevant articles were retrieved for more detailed evaluation. After applying the selection criteria, 226 studies remained for assessment. Manual search of the reference lists did not identify any additional relevant studies. Full articles were obtained and further evaluated. Of the 16 studies included for final analysis in the present systematic review, one study was a feasibility-testing randomized controlled trial, 5 were prospective series, and the remainder were from retrospective observational studies, as summarized in *Table 1A*,*1B* (7-22).

In these 16 studies, 744 patients with MPM who underwent EPP were included, and 612 patients underwent TMT. Studies that only included patients who underwent neoadjuvant chemotherapy, EPP and adjuvant radiotherapy are presented separately to patients who had adjuvant chemotherapy, as summarized in *Table 1A* and *1B* respectively. Baseline characteristics, patient selection and follow-up periods varied between institutions.

Assessment of overall survival

A summary of median overall survival outcomes is presented in *Table 2*. In studies involving neoadjuvant chemotherapy, the definition of overall survival differed between institutions, with some centres calculating survival from the date of diagnosis (7,11), randomization (8), registration (9) or commencement of chemotherapy (10,12-14). In this group, four prospective studies reported a median overall survival of 16.8-25.5 months on intention-to-treat analysis (9,10,13,14). A randomized controlled trial reported a median survival of 14.4 months from 24 patients who were randomized

Table 1A Summary of study characteristics on trimodality therapy involving neoadjuvant chemotherapy, extrapleural pneumonectomy and adjuvant radiotherapy for patients with malignant pleural mesothelioma

Author	Treatment center	Year	Study period	Study type	Number of patients undergone treatment (% ITT)			Follow-up (months)
					Neoadjuvant chemotherapy	EPP	Radiotherapy	
Lang-Lazdunski (7)	Guy's & St Thomas' Hospital, UK	2012	2004-2011	Retrospective OS	25	22	17	12.9
Treasure (8)	12 UK Hospitals	2011	2005-2008	RCT	24	19	8	24.7
van Schil (9)	11 European Hospitals	2010	2005-2007	Prospective OS	58 (100%)	42 (72%)	38 (66%)	19.3
Krug (10)	Memorial Sloan-Kettering Cancer Center, NY, USA	2009	2003-2006	Prospective OS	77 (100%)	57 (74%)	44 (57%)	NR
Buduhan (11)	Swedish Cancer Institute, Seattle, USA	2009	1997-2008	Retrospective OS	55	46	38	20.6[MV]
de Perrot (12)	Toronto General Hospital, Canada	2009	2001-2007	Retrospective OS	60	45	30	NR
Rea (13)	Istituto Oncologico Veneto, Padua, Italy	2007	2000-2003	Prospective OS	21 (100%)	17 (81%)	15 (71%)	69
Weder (14)	University Hospital, Zurich, Switzerland	2007	2000-2003	Prospective OS	61 (100%)	45 (74%)	36 (59%)	46

Table 1B Summary of study characteristics on trimodality therapy involving extrapleural pneumonectomy, adjuvant chemotherapy and adjuvant radiotherapy for patients with malignant pleural mesothelioma

Author	Treatment center	Year	Study period	Study type	Number of patients undergone treatment (% ITT)			Follow-up (months)
					EPP	Adjuvant chemotherapy	Radiotherapy	
Ambrogi (15)	Tor Vergata University, Rome, Italy	2012	1997-2007	Retrospective OS	29	21	19	16
Patel (16)	Duke University Medical Center, NC, USA	2012	2004-2010	Retrospective OS	30	21	30	15
Rena (17)	Azienda Ospedaliero-Universitaria, Novara, Italy	2012	1998-2009	Retrospective OS	40	40*	40	NR
Tonoli (18)	Brescia, Annunziata and Modena Hospitals, Italy	2011	2005-2010	Retrospective OS	56	48*	56	20
Luckraz (19)	University Hospital, Cardiff, UK	2010	NR	Retrospective OS	49	29	23; TMT = 15	10
Batirel (20)	Marmara University Hospital, Istanbul, Turkey	2008	2003-2007	Prospective OS	20 (100%)	16 (80%)	12 (60%)	16

Table 1B *(continued)*

Table 1B *(continued)*

Author	Treatment center	Year	Study period	Study type	Number of patients undergone treatment (% ITT)			Follow-up (months)
					EPP	Adjuvant chemotherapy	Radiotherapy	
Pagan (21)	Umberto I General Hospital, Venezia-Mestre, Italy	2006	1997-2004	Retrospective OS	44	32	33; TMT = 31	NR
Sugarbaker (22)	Brigham and Women's Hospital, Boston, USA	1999	1980-1997	Retrospective OS	183	183	183	13

ITT, intention-to-treat; NR, not reported; *Studies involving patients who received neoadjuvant or adjuvant chemotherapy; TMT, trimodality therapy; OS, observational study; RCT, randomized controlled trial; MV, mean value

Table 2 Summary of survival and perioperative outcomes of patients with malignant pleural mesothelioma who underwent trimodality therapy involving neoadjuvant or adjuvant chemotherapy, extrapleural pneumonectomy and adjuvant radiotherapy

Author	Median survival (months)			Disease free survival (months)	Perioperative mortality	Perioperative morbidity		Length of stay
						Overall	Major	
Lang-Lazdunski (7)	12.8[DD]			NR	4.5%	68%	NR	14
Treasure (8)	14.4[DR]			7.6	12.5%	69%	42%	NR
van Schil (9)	ITT: 18.4[RE]	NC+EPP: NR	TMT: 33	13.9	6.5%	82.6%	NR	NR
Krug (10)	ITT: 16.8[CC]	NC+EPP: 21.9	TMT: 29.1	10.1	3.7%	NR	NR	NR
Buduhan (11)	25[DD]			NR	4.3%	80%	54%	9.2[MV]
de Perrot (12)	14[CC]			NR	6.7%	NR	33%	NR
Rea (13)	ITT: 25.5[CC]	NC+EPP: 27.5	TMT: NR	16.3	0%	52.4%	23.8%	NR
Weder (14)	ITT: 19.8[CC]	NC+EPP: 23	TMT: NR	13.5	2.2%	NR	35%	NR
Ambrogi (15)	19.5[DS]			NR	3.4%	NR	41%	NR
Patel (16)	23.2[DS]			15	NR	NR	NR	NR
Rena (17)	20			14	5%	62%	NR	9
Tonoli (18)	46.9[DS]			NR	NR	NR	NR	NR
Luckraz (19)	19.5[DS]			NR	8.2%	53%[TMT]	NR	10
Batirel (20)	ITT: 17.2	EPP+AC: 19.6	TMT: 23.9	10	5%	55%	NR	NR
Pagan (21)	20[DS]			NR	4.5%	50%	36.3%	11.5[MV]
Sugarbaker (22)	19[DS]			NR	3.8%	50%	24.5%	9

ITT, intention-to-treat; DD, survival calculated from the date of diagnosis; DR, date of randomization; RE, date of registration; CC, date of chemotherapy; DS, date of surgery; TMT, trimodality therapy; NR, not reported; EPP, extrapleural pneumonectomy; NC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; MV, mean value

to undergo EPP (8). Ten patients in this trial were also included in a retrospective institutional report, which presented a median overall survival of 12.8 months from the date of diagnosis (7). In studies involving adjuvant chemotherapy, the majority of studies reported survival from the date of EPP (15,16,18,19,21,22). but not specified in others (17,20). In this group, apart from one multi-centre retrospective study reporting a median survival of 46.9 months, the remaining studies reported median survival periods of 19-24 months (15-17,19-22).

Table 3A Summary of treatment regimens and disease recurrence patterns for patients with malignant pleural mesothelioma who underwent trimodality therapy involving neoadjuvant chemotherapy, extrapleural pneumonectomy and adjuvant radiotherapy

Author	Neoadjuvant chemotherapy regimen	Radiotherapy regimen	Disease recurrence			
			Local	Distant	Local and distant	Overall
Lang-Lazdunski (7)	Cisplatin (80 mg/m^2) + gemcitabine (1,000 mg/m^2) ×3 (n=11) or cisplatin (80 mg/m^2) + pemetrexed (500 mg/m^2) ×3 (n=14)	54 Gy in 30 once-daily 1.8 Gy fractions (n=17)	NR	16%	NR	81%
Treasure (8)	Cisplatin + gemcitabine (n=10) or cisplatin + pemetrexed (n=8) or mitomycin + vinblastine + cisplatin (n=6) ×3	54 Gy in 30 once-daily 1.8 Gy fractions (n=8)	NR	NR	NR	79%
van Schil (9)	Pemetrexed (500 mg/m^2) + cisplatin (75 mg/m^2) d 1, 21-d cycle×3 (n=58)	54 Gy in 30 once-daily 1.8 Gy fractions (n=38)	16%	27%	NR	NR
Krug (10)	Cisplatin (75 mg/m^2) d 1 + pemetrexed (500 mg/m^2) d 1, 21-d cycle ×4 (n=77)	54 Gy in 30 once-daily 1.8 Gy fractions (n=44)	14%	21%	5%	40%
Buduhan (11)	Cisplatin/carboplatin + pemetrexed (n=24) or cisplatin + methotrexate + vinblastine (n=23) or cisplatin + gemcitabine (n=5) or other (n=3)	30 Gy in 1.8–2 Gy fractions (n=24), boost 9-18Gy; or IMRT 50 Gy (n=14), boost 24 Gy	18%	21%	NR	63%
de Perrot (12)	Cisplatin + vinorelbine (n=26) or pemetrexed (n=24) or raltitrexed (n=6) or gemcitabine (n=4) ×2-6	50 Gy in 2 Gy fractions, boost 10 Gy; or IMRT 54 Gy in 1.8 Gy fractions (n=30)	17%	37%	7%	53%
Rea (13)	Gemcitabine (1,000 mg/m^2) d 1, 8, 15 + carboplatin (AUC 5) d 1, 28-d cycle ×3 (n=21)	45 Gy in 1.8 Gy fractions (n=15), boost 10-14 Gy in 2 Gy fractions	35%	65%	NR	77%
Weder (14)	Gemcitabine (1,000 mg/m^2) d 1, 8, 15 + cisplatin (80 mg/m^2) d 1, 28-d cycle ×3 (n=61)	50-60 Gy in 2 Gy daily fractions (n=36)	NR	NR	NR	84%

Table 3B Summary of treatment regimens and disease recurrence patterns for patients with malignant pleural mesothelioma who underwent trimodality therapy involving extrapleural pneumonectomy, adjuvant chemotherapy and adjuvant radiotherapy

Author	Adjuvant chemotherapy regimen	Radiotherapy regimen	Disease recurrence			
			Local	Distant	Local and distant	Overall
Ambrogi (15)	Cisplatin (100 mg/m^2) d 15 + gemcitabine (1 g/m^2) d 1, 8, 15, 28-d cycle ×4-6 (n=21)	30-40 Gy in 1.5 Gy fraction (n=19), boost 14 Gy in 2-Gy fractions	41%	21%	NR	NR
Patel (16)	Pemetrexed (500 mg/m^2) + cisplatin (75 mg/m^2), 21-d cycle (n=17) or carboplatin (n=2); gemcitabine + cisplatin (n=2)	IMRT 45 Gy (n=30); boost 11.8 Gy (n=10)	13%	40%	20%	NR
Rena (17)	Pre-2000 (n=7): adjuvant platinum-based chemotherapy; post-2000 (n=33): neoadjuvant platinum-based chemotherapy	45-60 Gy (n=40)	21%	53%	26%	NR

Table 3B *(continued)*

Table 3B *(continued)*

Author	Adjuvant chemotherapy regimen	Radiotherapy regimen	Disease recurrence			
			Local	Distant	Local and distant	Overall
Tonoli (18)	Neoadjuvant CDDP + pemetrexed, 2-7 cycle (n=20) or adjuvant CDDP + pemetrexed, 2-3 cycles (n=25), or both (n=3)	45 Gy in 24 fractions (n=4); IMRT 50 Gy in 25 fractions (n=52 inc 2 HT); boost 60 Gy in 25 fractions (n=20)	4%	29%	NR	32%
Luckraz (19)	Cisplatin + pemetrexed + vinorelbine (n=29)	50-55 Gy (n=23)	NR	NR	NR	NR
Batirel (20)	Gemcitabine (1,250 mg/m^2) d 1, 8 + cisplatin (75 mg/m^2) d 1, 21-d cycle ×3; or pemetrexed (500 mg/m^2) d 1 + cisplatin (75 mg/m^2) d 1, 21-d cycle×3	54 Gy in 1.8 Gy fractions, boost 9 Gy (n=12)	NR	NR	NR	56%
Pagan (21)	Carboplatinum (AUC 5) + taxol (175 mg) ×4 and taxol (60 mg/m^2) ×5 (n=32)	50 Gy in 2 Gy fractions (n=33)	5%	5%	18%	27%
Sugarbaker (22)	Pre-1985 (n=9): doxorubicin (50-60 mg/m^2) + cyclophosphamide (600 mg/m^2) ×4-6; 1985-1994 (n=80): additional cisplatin (70 mg/m^2); 1995-1997 (n=94): carboplatin (AUC 6) + paclitaxel (200 mg/m^2)	30-40 Gy in 1.5 Gy fractions (n=183), boost 14 Gy in 2 Gy fractions	NR	NR	NR	NR

Gy, Gray; IMRT, intensity modulated radiotherapy; HT, helical tomotherapy; NR, not reported

Reporting of disease-free survival (DFS) was variable between centres, and differences in the form and frequency of follow-up made interpretation difficult. In studies involving neoadjuvant chemotherapy, four prospective series reported DFS of 10.1-16.3 months (9,10,13,14), whilst the randomized controlled trial reported 7.6 months (8). Three studies involving adjuvant chemotherapy reported DFS of 10-15 months (16,17,20).

Assessment of perioperative outcomes

A summary of perioperative outcomes, including perioperative mortality, morbidity and length of stay, is presented in *Table 2*. Perioperative mortality ranged from 0-12.5%. Perioperative morbidity was measured according to different grading systems in various institutions, with an overall rate of 50-83%. Major perioperative complications ranged between 24-54%. The average length of stay was reported to be 9-14 days.

Adjuvant therapy and treatment failure

In studies involving neoadjuvant chemotherapy, four prospective series had standardized regimens (9,10,13,14), whilst the remaining retrospective reports (7,11,12) and the randomized controlled trial (8) had variable treatment combinations. Studies on TMT involving adjuvant chemotherapy also reported inconsistent therapeutic regimens. The form of adjuvant radiotherapy also differed between institutions, with the introduction of intensity modulated radiotherapy (IMRT) in some centres in recent years (11,12,16,18). The reporting of local disease recurrence ranged from 4-41%, distant recurrence ranged from 5-65%, and overall disease recurrence ranged from 27-84%. However, duration and methodology of follow-up varied between institutions. A summary of chemotherapy and radiotherapy regimens and patterns of disease recurrence are presented in *Table 3A,3B*.

Conclusions

The necessity of adjuvant therapy with EPP was identified by Eric Butchart in the 1970s, when he stated in a personal communication that "we have recently analysed our experience with both pleuropneumonectomy and pleurectomy/decortication for mesothelioma. The very strong message from this analysis is that adjuvant therapy is

essential in order to achieve any degree of long term survival with either surgical procedure" (23). In his original report of 29 patients who underwent EPP, there was a perioperative mortality rate of 31%, a perioperative morbidity rate of 45%, and a median survival of merely 10 months (24). Since then, improvements in surgical techniques and perioperative care, as well as advances in medical and radiation oncology, have resulted in significantly superior outcomes in patients treated by TMT (10,12). In addition, an improved understanding of the important prognostic factors and a refinement of the patient selection process have helped to identify patients who may benefit most from aggressive therapy and avoid futile treatment in patients who are unsuitable surgical candidates (25).

Although TMT involving EPP, adjuvant chemotherapy and radiotherapy has been utilized since the introduction of EPP for selected patients with MPM, the first prospective study assessing the safety and efficacy of a standardized TMT program involving neoadjuvant chemotherapy, EPP and adjuvant radiotherapy was not published until 2004 (26). In their pilot study, Weder and colleagues treated 19 patients with neoadjuvant gemcitabine and cisplatin, followed by EPP in 16 patients and adjuvant radiotherapy in 13 patients. The authors stated that the neoadjuvant chemotherapeutic approach offered both logistical and biological advantages compared to the adjuvant chemotherapy regimen. This was reflected by a reported median survival of 23 months by an intention-to-treat analysis, which was far superior to a median survival of 10 months during their previous treatment protocol involving EPP followed by adjuvant chemotherapy and radiotherapy. Subsequently, a larger cohort of patients from the same investigators replicated these early encouraging outcomes (14).

Over the last decade, a number of improvements have been developed in adjuvant therapy for MPM in combination with EPP. A randomized controlled trial by Vogelzang *et al*. has established pemetrexed and cisplatin as the accepted first-line chemotherapy regimen for MPM in many centres (3,27). More recently, the emergence of biological and immunotherapy agents have gained intense interest, with a number of Phase I trials currently under investigation (28,29). Advances in radiation oncology in the form of IMRT have resulted in further improvements in overall survival (11,16,27,30). Compared to other surgical options, EPP allows higher doses of radiotherapy to the hemithorax by avoiding pulmonary toxicity, and this approach has demonstrated a significant reduction in loco-regional relapses (30). Modern techniques such as helical tomography allow the delivery of superior dose homogeneity in the target volume whilst minimizing radiation to the normal critical structures such as the spinal cord, heart, oesophagus and liver. The improved outcomes of patients who underwent TMT involving modern radiation oncology treatment was presented by Tonoli and colleagues, who reported a median survival of 46.9 months for patients who underwent IMRT with a median dose of 52 Gy (18).

Overall, the present systematic review identified 16 studies on TMT involving neoadjuvant or adjuvant chemotherapy, EPP and adjuvant radiotherapy according to predefined criteria, including one randomized controlled trial and five prospective series. Studies on TMT involving EPP, adjuvant chemotherapy and radiotherapy were mostly retrospective reports with non-standardized chemotherapy regimens. In comparison, studies involving neoadjuvant chemotherapy, EPP and adjuvant radiotherapy were relatively more recent, mostly including patients treated after year 2000. Four prospective studies involving patients treated by a standardized neoadjuvant chemotherapy regimen, EPP and adjuvant radiotherapy reported a median survival of 16.8-25.5 months, with a perioperative mortality of 0-5% (9,10,13,14). In these four studies, the majority of patients (57-71%) were able to complete the trimodality therapy on an intention-to-treat analysis. In contradistinction, the Mesothelioma and Radical Surgery (MARS) trial reported a median survival of 14.4 months for the 24 patients randomized to undergo EPP, of whom 10 were reported in another study by Lang-Lazdunski *et al*. (7,8) Investigators of the MARS trial pointed out that survival outcomes were calculated from the later timepoint of randomization, with a median period of 3.6 months after the registration process. The primary intent of this trial was to assess the feasibility of conducting a randomized controlled trial for EPP in the management of MPM. However, the study design and subsequent data analysis have met significant criticism (31,32). Major points of contention include the speculative conclusions drawn from a feasibility-testing study, the non-standardized chemotherapy agents and timing of chemoradiation, limited numbers of recruited patients and significant protocol violations between the two treatment arms. Indeed, with a mortality rate of 18% for the 17 patients who underwent EPP per protocol, it represents one of the highest mortality rates for EPP in the current literature (27,31). Despite this, investigators from the MARS trial are considered to have the unique opportunity to perform a definitive therapeutic trial that could assess the efficacy of EPP compared to

medical management (32). Of the remaining studies within the present systematic review, the perioperative mortality ranged from 0-8.2%, with a wide range of perioperative morbidity and disease recurrence outcomes, partly due to non-standardized reporting.

In conclusion, the present systematic review has shown that EPP for patients with MPM can be performed with an acceptable perioperative mortality rate in specialized centres. However, the evidence for long-term survival in patients treated by TMT in the current literature is inconsistent. A number of prospective studies with standardized therapeutic regimens have reported relatively favourable outcomes on intention-to-treat analysis. These encouraging results demonstrate the potential benefit TMT can offer for patients treated by a multi-disciplinary approach in well-integrated programs. Conversely, one randomized controlled trial reported relatively poor perioperative and long-term outcomes for patients randomized to EPP (8). Investigators of the MARS trial should be commended for their efforts in demonstrating the feasibility of conducting a randomized study on EPP versus conservative treatment. However, further evidence is required before definitive conclusions can be drawn about the efficacy of this surgical procedure. The present study is limited by potential publication bias, and it should be acknowledged that the majority of data presented have been obtained from tertiary centres with a special interest in the surgical management of MPM. Hence, these results should be interpreted with caution and may not be applicable to non-specialized institutions.

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