



# Updated meta-analysis of survival after extrapleural pneumonectomy versus pleurectomy/decortication in mesothelioma

Dimitrios E. Magouliotis<sup>1,2</sup> · Vasiliki S. Tasiopoulou<sup>3</sup> · Kalliopi Athanassiadi<sup>4</sup>

Received: 25 August 2018 / Accepted: 24 October 2018 / Published online: 29 October 2018  
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## Abstract

**Objective** We reviewed the available literature on patients with MPM undergoing either extrapleural pneumonectomy (EPP) or pleurectomy/decortication (P/D).

**Methods** Original research studies that evaluated long-term outcomes of P/D versus EPP were identified, from January 1990 to July 2018. The 30 and 90 days mortality, along with the 1-, 2-, 3-, 5-year survival, the median overall survival and the complications were calculated according to both a fixed and a random effect model. The *Q* statistics and *I*<sup>2</sup> statistic were used to test for heterogeneity among the studies.

**Results** Fifteen studies were included, incorporating a total of 1672 patients treated with EPP and 2236 treated with P/D. The 30-day mortality was significantly higher in the EPP group [OR 3.24 (95% CI 1.70, 6.20); *p* < 0.001]. The median overall survival was significantly increased in the P/D group [WMD −4.20 (−5.66, −2.74); *p* < 0.001]. No significant differences were found regarding the 90-day mortality and the 1-, 2-, 3-, 5-year survival between the EPP and P/D groups. The incidence of postoperative atrial fibrillation, hemorrhage, empyema, bronchopleural fistula and air leak was significantly increased in the EPP group (*p* < 0.05).

**Conclusions** The present meta-analysis indicates that P/D is associated with enhanced outcomes regarding 30-day mortality, median overall survival, and complications. The P/D approach, should, therefore be preferred when technically feasible. However, the decision regarding the procedure of choice should be made on the basis of the disease status and the surgeon's experience. Well-designed, randomized studies, comparing EPP to P/D, are necessary to further assess their clinical outcomes.

**Keywords** Pleurectomy · Decortication · Extrapleural pneumonectomy · Malignant pleural mesothelioma

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s11748-018-1027-6>) contains supplementary material, which is available to authorized users.

✉ Dimitrios E. Magouliotis  
dmagouliotis@gmail.com  
Vasiliki S. Tasiopoulou  
vasilikitasiopoulou@gmail.com  
Kalliopi Athanassiadi  
k.athanassiadi@hotmail.de

<sup>1</sup> Department of Surgery, University Hospital of Larissa, Biopolis, 41110 Larissa, Greece

<sup>2</sup> Department of Pharmacology, Faculty of Medicine, University of Thessaly, Biopolis, Larissa, Greece

<sup>3</sup> Faculty of Medicine, University of Thessaly, Biopolis, Larissa, Greece

<sup>4</sup> Unit of Thoracic Surgery, Evangelismos Hospital, Athens, Greece

## Introduction

Malignant pleural mesothelioma (MPM) is a rare malignancy that is associated with poor prognosis. Despite the ban of the asbestos, which is the main etiologic factor, the incidence of MPM continues to increase worldwide. A possible explanation for this phenomenon is the great latency period between the asbestos exposure and the disease manifestation [1]. Given the aggressiveness and the poor prognosis of MPM, a multimodal treatment approach has been implemented, including neoadjuvant chemotherapy and adjuvant radiotherapy. Nonetheless, the identification of the appropriate treatment strategy is critical in the clinical setting [2]. Surgery plays an important role in the treatment strategy of MPM. Two surgical procedures are mainly performed: the extrapleural pneumonectomy (EPP) and the pleurectomy decortication (P/D). Results of individual, single-center studies have been biased in favor of either P/D

or EPP. The MARS 1 randomized controlled trial was conducted to assess the feasibility of EPP within trimodal therapy regarding the survival and complications [3]. According to its outcomes, the EPP did not offer enhanced survival in comparison with the chemotherapy alone module [3].

In recent years, the use of pleurectomy/decortication (P/D) surgical approach has received attention as a less invasive lung-sparing approach in comparison with EPP. According to the consensus report of the IASLC-ISC Committee [4] the P/D is defined as parietal and visceral pleurectomy without diaphragm or pericardial resection, while the extended P/D parietal involves the resection of the diaphragm and/or pericardium. Many reports have compared the outcomes of EPP and P/D in terms of morbidity, mortality, and survival, suggesting that P/D is comparable with EPP in terms of various surgical outcomes. In fact, a meta-analysis by Taioli et al. [5] has recommended P/D as the preferred operation when possible. However, each procedure has its advantages and disadvantages, and which procedure is superior remains controversial. As the number of studies comparing the feasibility of EPP and P/D increases, while no randomized controlled trial has been published yet, it is necessary to reassess whether the results between the two techniques are at least equivalent. The purpose of this study is to summarize the existing data by comparing the surgical outcomes of EPP and P/D, to provide the best evidence that is currently available.

## Materials and methods

### Search strategy and articles selection

The present study was conducted in accordance with the protocol agreed by all authors and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [6]. A thorough literature search in PubMed (Medline), Cochrane Central Register of Controlled Studies (CENTRAL) and Scopus (ELSEVIER) were searched (last search: July 1, 2018) using the following terms in every possible combination: “mesothelioma”, “malignant pleural mesothelioma”, “mpm”, “pleurectomy”, “pleurectomy/decortication”, “p/d”, “pneumonectomy”, “pneumectomy” and “epp”. Inclusion criteria were (1) original reports with  $\geq 10$  patients, (2) written in the English language, (3) published from 1990 to 2018, (4) conducted on human subjects and (5) reporting outcomes of patients undergoing EPP and P/D for MPM. Duplicate articles were excluded. The reference lists of all included articles were also reviewed for additional studies. Two independent reviewers (DEM, VST) extracted the data from the included studies. Any discrepancies between the investigators about the inclusion or exclusion of studies were discussed with a third author (KA) to include articles

that best matched the criteria until consensus was reached. The authors had personal equipoise with regard to the best intervention.

### Data extraction

For each eligible study, data were extracted relative to demographics (number of patients, sex, mean age, histology, stage of disease), type of P/D approach according to IASLC-ISC criteria (defined or extended P/D) and perioperative parameters (median survival, 30-day survival, 90-day survival, survival at 1-, 2-, 3-, 5-years postoperatively, and complications). The outcomes related to survival were the primary endpoints and the complications were the secondary endpoints. In addition, categorical outcomes were  $2 \times 2$  tabulated, referring to patients presenting the outcome and patients free of the outcome, separately for EPP and P/D groups. Data was extracted separately for the P/D and extended P/D procedures, as defined by the IASLC-ISC criteria [4], to perform subgroup analysis. Regarding continuous outcomes, we extracted the mean, the standard deviation and the number of patients. In cases that standard deviation was not available, it was calculated using the available data. The kappa coefficient test was applied to assess the level of agreement between the reviewers.

### Statistical analysis

Regarding the categorical outcomes, the odds ratio (ORs) and 95% confidence interval (CI) were calculated, based on the extracted data, by means of random-effects or fixed-effects model (Mantel–Haenszel statistical method).  $OR < 1$  denoted outcome was more frequent in the P/D group. Continuous outcomes were evaluated by means of weighted mean difference (WMD) with its 95% CI, using fixed-effects or random-effects (inverse variance statistical method) models, appropriately to calculate pooled effect estimates. In cases where  $WMD < 0$ , values in the P/D group were higher. Inter-study heterogeneity was assessed through Cochran  $Q$  statistic and by estimating  $I^2$  [7]. High heterogeneity renders the outcome less valid. A  $p$  value of less than 0.05 was set as the threshold indicating a statistically significant result.

Where multiple studies analyzed the same population, only the larger study or the one with the longest follow-up was included in the qualitative and quantitative analysis.

### Quality and publication bias assessment

The Newcastle–Ottawa Quality Assessment Scale (NOS) [8] was used as an assessment tool to evaluate non-RCTs. The scale’s range varies from zero to nine stars, and studies with a score equal to or higher than five were considered to have the adequate methodological quality to be included. There

were no RCTs in the literature to be included. Two reviewers (DEM, VST) rated the studies independently and a final decision was reached by consensus. Visual inspection of funnel plot asymmetry was performed to address for possible small-study effect.

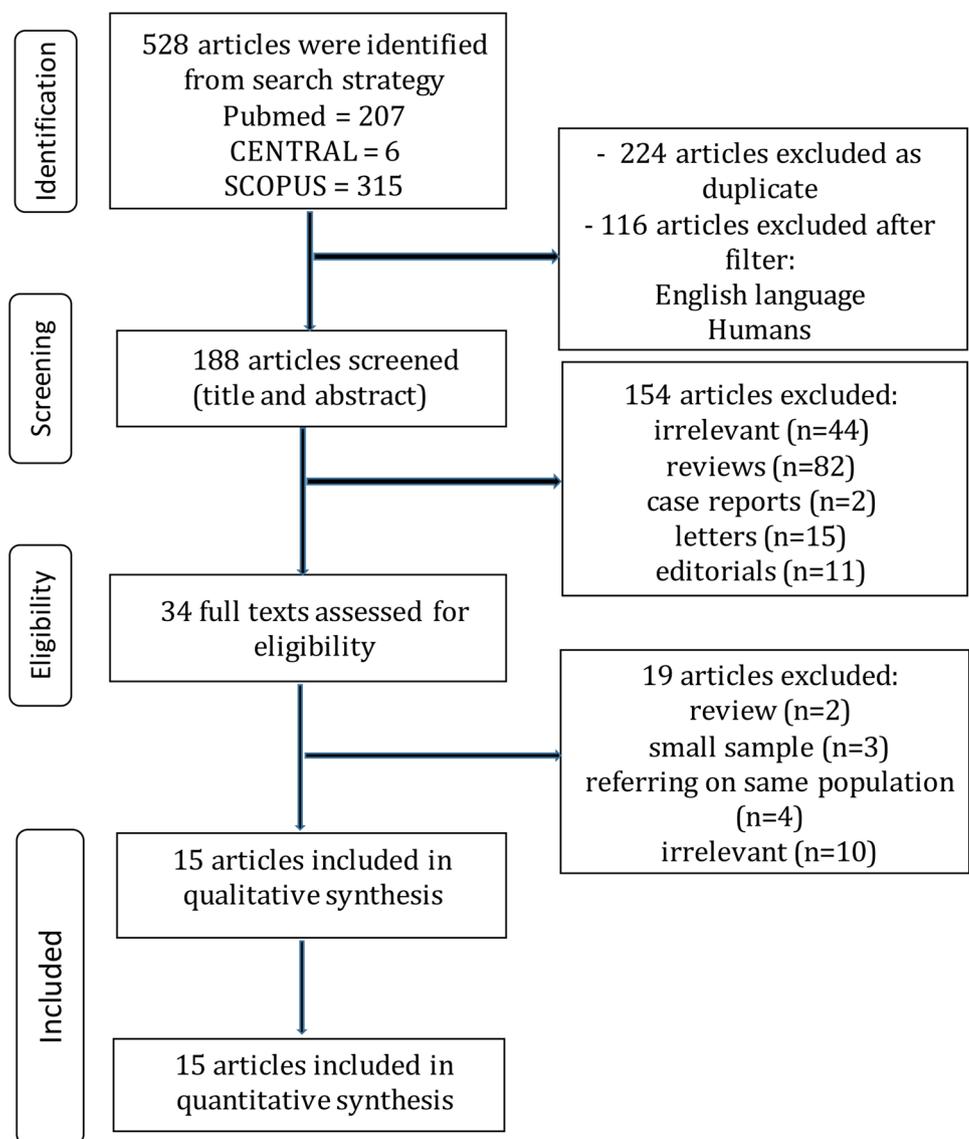
## Results

### Article selection and patient demographics

The flow diagram of the search of the literature is shown in Fig. 1 and the Prisma Checklist (Table S1). The characteristics of the included studies are summarized in Table 1. Among the 528 articles in PubMed, Scopus, and CENTRAL that were retrieved, 15 studies were included in the qualitative and quantitative synthesis [9–23]. The level of

agreement between the two reviewers was “very good” ( $\kappa = 0.906$ ; 95% CI 0.801, 1.000). The study design was prospective in one study [19], retrospective in 14 studies [9–18, 20–23]. The included studies were conducted in UK [9, 15, 16, 22], Italy [10, 20], Germany [11], South Africa [12], the USA [13, 19, 21, 23], Switzerland [14], Japan [17, 18], and were published between 1991 and 2018. The EPP and P/D sample size ranged from 15 to 385 and from 9 to 1036 patients, respectively. The total sample size was 3908 patients, 1672 patients treated with EPP and 2236 patients treated with either P/D or extended P/D. The baseline characteristics of studies comparing the outcomes between patients treated with either EPP, P/D or extended P/D are provided in Table 1 and the pooled estimates in Table 2. The Newcastle–Ottawa rating scale assessment for all studies is shown in Table 1.

**Fig. 1** EPP versus P/D for MPM flow diagram



**Table 1** Characteristics of the studies that were finally included in the meta-analysis

Study ID, year	Country	Study design	P/D approach	Patients, <i>n</i>		Female, <i>n</i> (%)		Mean age ± SD		Stage	Nos.
				EPP	P/D	EPP	P/D	EPP	P/D		
Aziz et al., 2002 [9]	UK	R	N/A	64	47	–	–	–	–	I–III	5
Bovolato et al., 2014 [10]	Italy	R	P/D	301	202	76 (25.3)	53 (26.2)	58.7 (33–78)	62.5 (30–87)	I: 9.5%; II: 27.6%; ≥ III: 19%; ND: 43.7%	6
Branscheid et al., 1991 [11]	Germany	R	P/D	76	82	–	–	–	–	I: 2%; II: 11%; III: 56%; IV: 15%	5
de Vries et al., 2003 [12]	South Africa	R	P/D	17	29	–	–	–	–	I–III	5
Flores et al., 2008 [13]	USA	R	Extended P/D	385	278	69 (18)	58 (21)	60	63	I: 2%; II: 95%; III: 24%; IV: 16%; ND: 48%	7
Kostron et al., 2017 [14]	Switzerland	R	P/D and extended P/D	141	26	16 (11)	1 (4)	61 (36–73)	66 (34–77)	I–IV	7
Lang-Lazdunski et al., 2012 [15]	UK	P	P/D and extended P/D	22	54	2 (8.1)	7 (13)	62 (52–68)	62.5 (45–74)	I–IV	6
Lueckraz et al., 2009 [16]	UK	R	P/D	49	90	0 (0)	4 (12)	57.8 (12.6)	63.5 (9.1)	I–III	5
Miyazaki et al., 2018 [17]	Japan	R	P/D	30	9	6 (20)	0 (0)	63 (47–78)	69 (55–77)	I–III	5
Okada et al., 2008 [18]	Japan	R	Extended P/D	31	34	4 (13)	3 (9)	60 (35–72)	60 (37–78)	I–IV	6
Pass et al., 1997 [19]	USA	R	P/D	39	39	6 (15)	8 (21)	57 (30–72)	59 (34–77)	–	5
Rena et al., 2012 [20]	Italy	R	P/D	40	37	29 (27)	6 (32)	56 ± 11	58.5 ± 9.5	I, II	6
Schipper et al., 2008 [21]	USA	R	P/D and extended P/D	73	44	–	–	–	–	IA: 20; IB: 82; II: 24; III: 75; IV: 60; ND: 24	5
Sharkey et al., 2016 [22]	UK, Italy	R	Extended P/D	133	229	19 (14)	33 (14)	57 (14–70)	65 (42–81)	I: 4%; II: 14%; III: 57%; IV: 25%	6
Verma et al., 2017 [23]	USA	R	Extended P/D	271	1036	60 (22)	217 (21)	65 (58–71)	69 (62–76)	I–IV	7

The first author of every study along with the year of publication, the country of origin, the study design, the type of P/D according to IASLC-ISC criteria, the number of participants, the number of female patients, along with the mean age and the number of stars according to the Newcastle–Ottawa Quality Assessment Scale (NOS)

The Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomized studies. Every study is judged on three perspectives: the selection, the comparability and the ascertainment of the exposure of the study groups. The highest quality studies are awarded up to nine stars

The P/D and extended P/D approaches were defined according to the IASLC-ISC criteria

R retrospective, P prospective, ND non-defined, EPP extrapleural pneumonectomy, P/D pleurectomy/decortication, NOS Newcastle–Ottawa Scale

**Table 2** Summary of the analysis of the categorical and continuous outcomes

Categorical outcomes	<i>n</i>	OR (95% CI)	<i>p</i>	Heterogeneity	
				<i>I</i> <sup>2</sup> (%)	<i>p</i>
<b>EPP versus P/D</b>					
30-day mortality	11	3.24 (1.70, 6.20)	<0.001	0	0.92
90-day mortality	2	1.51 (0.47, 4.82)	0.49	19	0.27
OS survival 1 year	5	0.99 (0.47, 2.06)	0.97	63	0.03
OS survival 2 years	9	0.80 (0.58, 1.10)	0.17	0	0.55
OS survival 3 years	5	1.16 (0.68, 2.00)	0.58	13	0.3
OS survival 5 years	5	1.04 (0.53, 2.04)	0.90	0	0.93
Atrial fibrillation	8	4.41 (2.94, 6.62)	<0.001	7	0.37
Hemorrhage	5	4.02 (1.94, 8.35)	<0.001	0	0.67
Empyema	2	8.99 (1.55, 52.02)	0.01	0	0.71
Bronchopleural fistula	5	10.01 (2.63, 38.08)	<0.001	0	0.86
Pulmonary embolism	4	3.59 (0.74, 17.47)	0.11	0	0.91
ARDS	4	1.55 (0.35, 6.94)	0.57	0	0.82
Air leak	4	0.04 (0.01, 0.18)	<0.001	0	0.65
<b>EPP versus extended P/D</b>					
30-day mortality	5	1.34 (0.89, 2.01)	0.16	0	0.82
90-day mortality	1	1.55 (0.79, 3.03)	0.20	N/A	–
OS survival 1 year	2	0.81 (0.20, 3.22)	0.76	68	0.08
OS survival 2 years	2	1.17 (0.88, 1.55)	0.28	0	0.69
OS survival 3 years	3	1.36 (1.01, 1.82)	0.04	0	0.37
OS survival 5 years	2	0.55 (0.13, 2.24)	0.40	58	0.12
Atrial fibrillation	3	2.01 (0.83, 4.89)	0.12	39	0.20
Hemorrhage	4	5.86 (1.86, 18.51)	0.003	0	0.88
Empyema	1	23.30 (1.39, 391.11)	0.03	N/A	–
Bronchopleural fistula	1	16.26 (2.04, 129.83)	0.009	N/A	–
Pulmonary embolism	2	1.46 (0.25, 8.52)	0.67	51	0.15
ARDS	2	2.45 (0.51, 11.72)	0.26	38	0.21
Air leak	1	0.03 (0.00, 0.57)	0.02	N/A	–
<b>Continuous outcomes</b>					
	<i>n</i>	WMD (95% CI)		<i>I</i> <sup>2</sup>	<i>p</i>
<b>EPP versus P/D</b>					
Median survival	13	–4.20 (–5.66, –2.74)	<0.001	53	0.01
<b>EPP versus extended P/D</b>					
Median survival	3	1.22 (–0.55, 2.99)	0.18	8	0.34

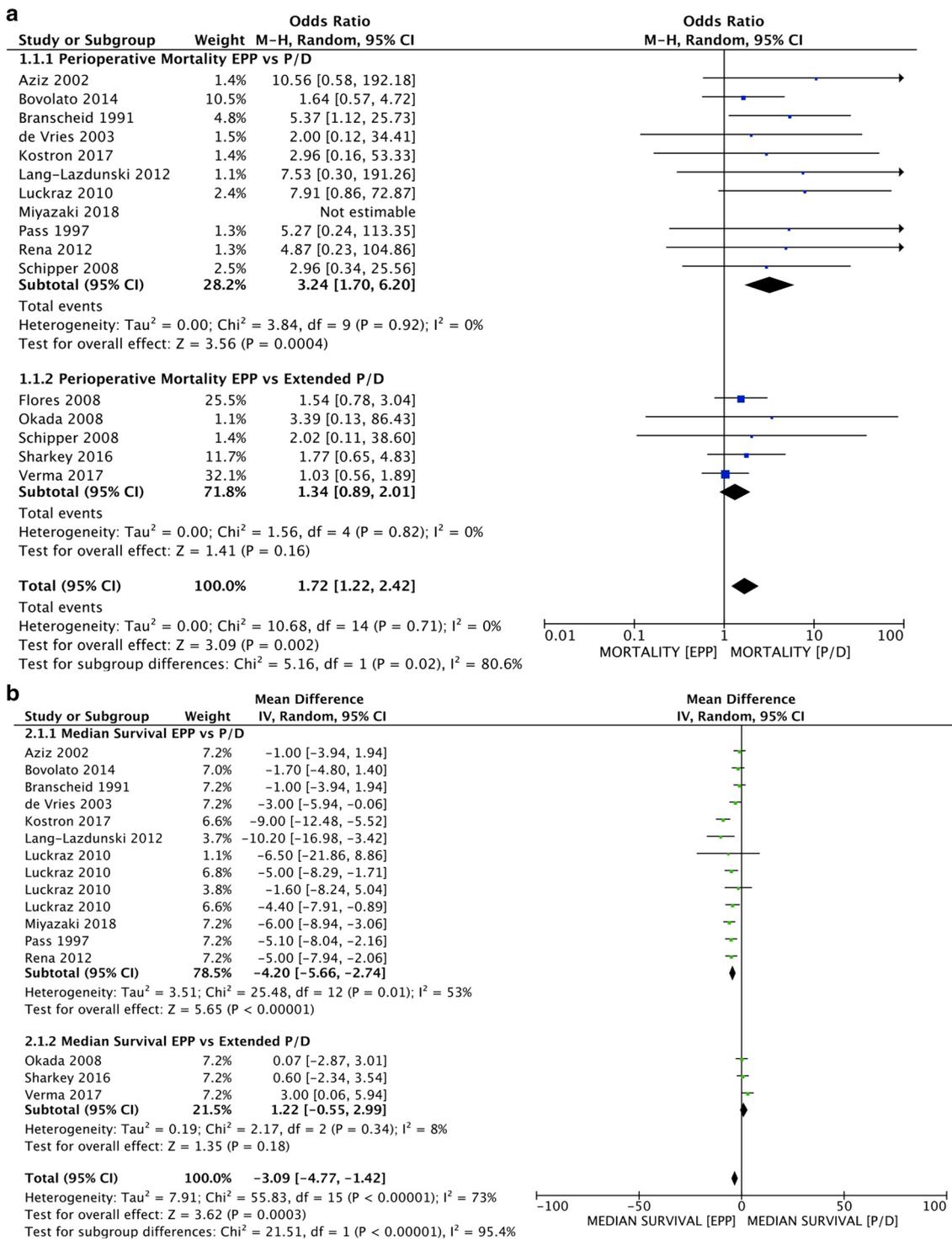
OR odds ratio, WMD weighted mean difference, CI confidence intervals

### Short-term mortality

The pooled estimates regarding the 30-day and 90-day perioperative mortality are presented in Table 2. The 30-day mortality (Fig. 2a) was significantly increased in patients treated with EPP [OR 1.72 (95% CI 1.22, 2.42);  $p=0.002$ ] according to the total analysis. The 30-day mortality was also increased in the EPP group compared to the P/D subgroup [OR 3.24 (95% CI 1.70, 6.20);  $p=0.0004$ ] but similar to the extended P/D subgroup [OR 1.34 (95% CI 0.89, 2.01);  $p=0.16$ ]. No significant difference was found regarding the 90-day mortality (Table 2).

### Median survival

There were 13 studies [9–12, 14–20, 22, 23] that reported the postoperative median survival. The difference regarding the median survival after EPP and P/D was plotted (Fig. 2b). The median survival was significantly higher in the P/D group [WMD –4.20 (95% CI –5.66, –2.74);  $p<0.001$ ]. Nonetheless, there was no significant difference between the EPP and extended P/D groups [WMD 1.22 (95% CI –0.55, 2.99);  $p=0.18$ ].



**Fig. 2** Forest plots describing the differences in **a** 30-day mortality, **b** median survival. **a** 30-day mortality was lower in the P/D group. **b** Median survival was increased in the P/D group. *M–H* Mantel–Haen-

szel statistical method, *IV* inverse variance statistical method, 95% *CI* 95% confidence intervals

## Long-term survival

Eight studies [10, 14–18, 21, 23] report survival at various times during the follow-up; 5 studies reported 1-year survival for 461 patients who underwent EPP and 285 patients who underwent either P/D or extended P/D. No significant difference was reported regarding the 1-year survival [OR 1.03 (95% CI 0.64, 1.64);  $p=0.76$ ], as shown in Table 2. The 2-year survival (Table 2) was also similar between the two groups [OR 1.17 (95% CI 0.88, 1.55);  $p=0.28$ ]. The 3-year survival was similar between the two groups according to the overall analysis [OR 1.26 (95% CI 0.98, 1.64);  $p=0.08$ ]. The 3-year survival was also similar between the EPP and P/D groups [OR 1.16 (95% CI 0.68, 2.00);  $p=0.58$ ]. However, the 3-year survival was greater in the EPP group compared to the extended P/D group [OR 1.36 (95% CI 1.01, 1.82);  $p=0.04$ ]. The 5-year survival was similar between the two groups (Table 2).

## Complications

The incidence of postoperative hemorrhage, empyema and bronchopleural fistula was significantly greater in the EPP group (Table 2). The incidence of atrial fibrillation was increased in the EPP compared to the P/D group [OR 4.41 (95% CI 2.94, 6.62);  $p<0.001$ ], but similar between the EPP and extended P/D groups (OR 2.01 (95% CI 0.83, 4.89);  $p=0.12$ ). No significant difference between the two groups was reported regarding the postoperative rate of pulmonary embolism, ARDS and tracheotomy (Table 2).

## Publication bias

Heterogeneity was low regarding the outcomes except from the overall survival at 1 year postoperatively. The funnel plots that were produced to assess publication bias are shown in Figure S2. The asymmetries that were found are mainly attributed to the small number of the included studies and the bias regarding the selection of the patients, thus proposing that more are necessary to eliminate publication bias.

## Discussion

The current evidence regarding the benefits of EPP over P/D for MPM is limited, while there is no RCT available. In this context, the present study represents the highest level of evidence. Although, a previous meta-analysis [5] compared EPP and P/D, the IASLC-ISC criteria regarding the employed procedures were not implemented by the authors, thus posing a certain limitation. This meta-analysis included 15 articles describing EPP and P/D (defined P/D and extended P/D) as alternative procedures for patients with

MPM, measuring patients' outcomes on survival and published between 1991 and 2018. In fact, in the present study, a subgroup analysis was performed to compare EPP with P/D and extended P/D, as defined by the IASLC-ISC consensus [4]. Given the great technical complexity and higher physiologic strain of the EPP approach as compared with P/D, an increased survival rate should be reported to counterbalance the perioperative risk.

Currently, no consensus has been reached regarding the superiority of either procedure, while the MARS 1 trial [3] doubted the usefulness of EPP for the treatment of MPM. In a previous meta-analysis, the short-term mortality rate (within 30 days) was significantly increased in the EPP group [5]. The present study demonstrated that the perioperative 30-day survival was significantly greater after P/D as compared with EPP, but similar between EPP and extended P/D. However, the 90-day survival was similar between the two groups. The median overall survival was also significantly increased in patients treated with P/D, but similar between the EPP and extended P/D groups. Since neither the pericardium nor the diaphragm was implicated in the operation, the P/D approach was associated with lower complication rates. Nonetheless, the overall survival at 1, 2, 3 and 5 years postoperatively was similar between the EPP and P/D groups. In the same context, the overall survival at 1, 2 and 5 years postoperatively was similar regarding the EPP and extended P/D approaches. Although, the extended P/D technique was associated with increased overall survival at 3 years, this outcome should be treated with caution due to the small number of studies included in this subgroup analysis. Given that there is greater variability in the operative approach of a defined or extended P/D than an EPP, it is possible that a higher proportion of lung-sparing cases included in this analysis were more palliative than definitive in intent, thus decreasing the survival of P/D relative to EPP.

Given the lack of randomized clinical trials comparing the feasibility of EPP and P/D for MPM, the current work is the largest up-to-date comparative study, implementing the IASLC-ISC criteria, incorporating 2236 patients treated with P/D and 1672 treated with EPP. Two meta-analyses [5, 24] have been previously published, but both were subject to certain limitations. The most recent meta-analysis [5] suggested that P/D is associated with a lower short-term mortality than EPP. However, that study did not distinguish the P/D from extended P/D approach, did not report the 90-day mortality, while the most distant follow-up was limited to two years postoperatively and was associated with high heterogeneity. Furthermore, the other meta-analysis [24] included only 7 studies, thus limiting the value of the study. The present analysis supports the outcomes of the previous while providing greater clarity regarding significant long-term survival endpoints. Since no certain advantage has been identified in terms of greater survival after EPP, the present

study reconfirms the P/D approach is associated with lower complication rates and should be preferred when possible. However, the decision regarding the cytoreductive procedure should be made on the basis of disease status along with institutional and surgeon experience, as described during the IMIG Congress [25].

This meta-analysis demonstrates the need for additional studies comparing intraoperative P/D with the EPP. Ideally, these would be multi-institutional randomized controlled studies, with a prospective design, well-specified inclusion and exclusion criteria, clinical matching of the P/D and EPP samples, along with longer follow-up.

The limitations of this meta-analysis reflect the limitations of the studies included. The majority of the studies were retrospective, one study was prospective and there were no randomized controlled studies amongst the comparative studies included, thus posing a certain limitation in this study. Moreover, the inter-institutional differences in the selection criteria for either procedure, along with the perioperative management pose a certain limitation. In fact, the selection criteria were not homogenous and may have been based on the patients' clinical attributes and status, thus posing a selection bias that could not be adjusted in the present study. In the same context, it is possible that chemotherapy was less commonly administered to patients with poorer performance status, thus affecting the overall survival. Finally, the suboptimal coding regarding several variables, such as histology, may have affected the integrity of propensity matching, along with the survival outcomes.

The pooled estimate of the median survival is highly heterogeneous, thus indicating that certain factors associated with the basic surgical approach, the surgeon's level of specialization or the standardization of data definition across the different institutions, may have implicated. Finally, another limitation is the differences amongst institutions regarding the multimodal treatment protocols that have been applied to the included patients.

On the other hand, the strengths of this study include (1) the clear data-extraction protocol, (2) the well-specified inclusion–exclusion criteria, (3) search performed in three different databases, (4) the quality assessment of the included studies and (5) the detailed presentation of the results of data extraction and analysis.

## Conclusion

This meta-analysis identified 15 unique peer-reviewed studies comparing P/D, extended P/D and EPP as alternative surgical options for patients with MPM. These studies suggest that P/D is associated with lower mortality at 30 days postoperatively and with increased median survival. Since no certain advantage has been identified in terms of greater

survival after EPP, the present study reconfirms the P/D approach should be preferred when possible. Nonetheless, the decision regarding the procedure of choice should be made on the basis of disease status along with the institutional and surgeon experience. These results should be interpreted with caution due to the lack of randomized controlled trials. Future RCTs with greater clarity in significant outcomes, such as the survival and complications, are necessary to demonstrate the differences in efficacy between EPP and P/D.

## Compliance with ethical standards

**Conflict of interest** The authors declare no conflicts of interest.

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