Meta-Analysis of Survival After Pleurectomy Decortication Versus Extrapleural Pneumonectomy in Mesothelioma

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Background. **This comprehensive meta-analysis was conducted to answer the question as to which procedure, pleurectomy decortication (P/D) or extrapleural pneumonectomy (EPP) is more beneficial to malignant pleural mesothelioma patients' outcome.**

Methods. **Original research studies that evaluated long-term outcomes of P/D versus EPP were identified, from January 1990 to January 2014. The combined percent perioperative and 2-year mortality, and median survival were calculated according to both a fixed and a random effect model. The Q statistics and I^2 statistic were used to test for heterogeneity between the studies.**

Results. **There were 24 distinct data sets, for a total of 1,512 patients treated with P/D, and 1,391 treated with EPP. There was a significantly higher proportion of short-term deaths in the EPP group versus the P/D group (percent mortality meta estimate; 4.5% vs 1.7%; $p < 0.05$). There was no statistically significant difference in 2-year mortality between the 2 groups, but there was significant heterogeneity.**

Conclusions. **The reanalysis of the large number of studies comparing P/D to EPP suggests that P/D is associated with a 2 ½ -fold lower short-term mortality (perioperatively and within 30 days) than EPP. Pleurectomy decortication should therefore be preferred when technically feasible.**

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Malignant pleural mesothelioma (MPM) is a deadly cancer, the incidence of which is increasing worldwide, despite the fact that the main etiologic factor, asbestos, has been banned from use for several decades. Opportunities for asbestos exposure continue to exist due to its history of widespread use in construction and insulation projects.

Given the aggressive nature and poor prognosis of MPM, finding the appropriate treatment option is critical in the clinical setting. The success of the 3 available options in MPM treatment (chemotherapy, radiation, surgery alone or in various combinations) have been controversial.

Surgery plays an important role in MPM management, and is carried out according to 2 main procedures; radical pleurectomy decortication (P/D) and extrapleural pneumonectomy (EPP). Results of individual, single-center studies have been biased in favor of either P/D or EPP.

A randomized controlled trial was conducted in the UK to assess the feasibility of randomizing patients to evaluate the effectiveness of EPP in terms of survival, complications, and quality of life [1]. The investigators concluded that EPP did not offer any survival advantage in comparison with chemotherapy alone [1]. However, this feasibility trial was not designed to answer the question as to which surgical procedure, P/D or EPP, is better.

There has been 1 recent meta-analysis comparing the 2 surgical procedures that suggested significantly lower perioperative mortality and a trend toward longer survival for P/D in comparison with EPP [2]. The analysis, however, included only a small fraction of the published literature comparing the 2 surgical procedures. We have conducted a comprehensive meta-analysis to answer the question as to which procedure, P/D or EPP, is more beneficial to MPM patients' outcome.

Material and Methods

Original research studies that evaluated long-term outcomes of P/D versus EPP were identified by searching the National Library of Medicine and National Institutes of Health PubMed database and Embase. The search strategy included the following keyword search terms: "mesothelioma", "pleurectomy", "pneumonectomy", "pneumectomy", and "malignant pleural mesothelioma", and spanned from January 1990 to January 2014. In addition, references included in 2 previously published reviews [2, 3] were reviewed. Reference lists from all retrieved articles were also reviewed in search of additional eligible articles.

Eligibility

Studies were considered eligible based on four a priori criteria. First, the studies must be written in English. Second, the studies must be observational. Third, a

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Table 1. Studies Included in the Meta-Analysis

Author, Year	Study Design	Country	Sex M/F	Age (Years), Range, Mean ± SD	Histology	Stage	Number of Patients Pleurectomy Decortication (P/D) n = 1,512	Number of Patients Extrapleural Pneumonectomy (EPP) n = 1,391
Branscheid D, 1991	Retro (1978-89)	Germany	235/66	22–87, mdn = 59	Epithelial (50%); mixed (25%); sarcomatous (12%); unclassified (13%)	I (2%); II (11%); III (56%); V (15%)	82	76
Allen KB, 1994	Retro (1958-93)	USA	79/17	μ = 55.2 ± 1.5 (EPP); 63.5 ± 9.6(P)	Epithelial (56%), mixed (29%), sarcomatous (15%)	I (51%); II (38%); III (8%); IV (3%)	56	40
Pass HI, Kranda K, 1997; Pass HI, Temeck BK, 1997	Reanalysis of clinical trial (1990-95)	USA	78/17	30-77	Epithelial, 60; sarcomatoid, 6, biphasic, 12		39	39
Moskal TL, 1998	Retro (1991-96)	USA	31/9	21-77; μ = 60;	Epithelial (62.5%); biphasic (25%); sarcomatous (12.5%)	I, I I = 13; III, IV = 24	28	7
Lampl L, 1999	Retro (1986-98)	Germany	45/8	n/a	sarcomatous	II & III (P/D)	23	22
Rusch VW, 1999[a]	Retro (1983-98)	USA	192/39	24-80; mdn = 62	Epithelial = 164 (71%), fibrosarcomatous = 14 (6%). Mixed = 51 (22%), desmoplastic = 1, unk = 1	I = 21; II = 40; III = 102; IV = 68	59	115
Aziz T, 2002	Retro (1989-99)	UK	244/61	34-77; mdn = 57	Epithelial & sarcomatous	I, II, III	47	64
Yom SS, 2003	Phase I trial on PDT	UK	8/1	39-75	Epithelioid = 7, biphasic = 2		8	1
de Vries WJ, 2003	Retro (1976-2001)	South Africa	33/13	35-80	Epithelial, sarcomatoid, mixed	I, II, III	29	17
Rosenzweig KE, 2005	Phase II trial (1994-96)	USA				T2 - T3, N0-N2	6	7
Flores RM, 2007[a]	Retro (1990-2005)	USA	755/190	26-93,mdn = 66	Epithelioid = 319 (34%), mixed = 99 (10%), sarcomatoid = 44 (5%), unclassified = 483 (51%)	I (2%); II (95); III (24%); IV (16%), unk (48%)	176	208
Okada M, 2008	Retro (1986-2006)	Japan	58/7	35-78; mdn = 60 yrs	Epithelial (74%), mixed (17%), sarcomatous (9%)	I (12%), II (20%), III (62%), IV (6%)	34	31
Schipper PH, 2008	Retro (1985-2003)	USA	236/49	26-91, mdn = 66	Epithelial = 134, nonepithelial = 108, unclassified = 43	IA = 20, IB = 82, II = 24, III = 75, IV = 60, unknown = 24	44	73

(*Continued*)

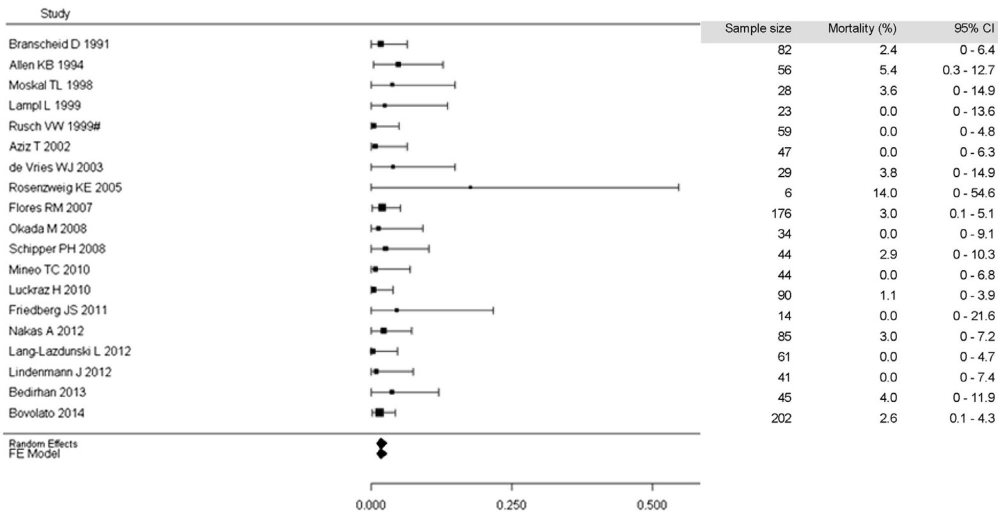
Table 1. Continued

Author, Year	Study Design	Country	Sex M/F	Age (Years), Range, Mean ± SD	Histology	Stage	Number of Patients Pleurectomy Decortication (P/D) n = 1,512	Number of Patients Extrapleural Pneumonectomy (EPP) n = 1,391
Borasio P, 2008	Retro (1989-2003)	Italy	270/124	28-93; median = 64	Epithelial = 246 (67.2%), biphasic = 84 (23%), sarcomatous = 36 (9.8%), indeterminate = 28		12	15
Yan TD, 2009	Retro (1984-2007)	Australia	390/66	66 ± 10	Epithelial = 185 (40%), sarcomatoid/biphasic = 183 (40%), unknown = 88 (19%)		250	59
Mineo TC, 2010	Retro (1987-2007)	Italy	63/14	27-82; 61.3 ± 10	Epithelioid = 50, biphasic = 17, sarcomatoid = 10	I = 21, II = 36, III = 20	44 (10 subtotal)	27
Luckraz H, 2010	Retro (1980-2010)	UK	180/28	58.9 ± 9.8	Epithelial	I, II, III	90	49
Friedberg JS, 2011	Retro (2004-08)	USA	19/9	27-81	Epithelioid n = 17, sarcomatoid = 2, biphasic = 3	III, IV (85.7 %)	14	14
Rena O, 2012	Retro (1998-2009)	Italy	24/35	56 ± 11 (EPP); 58.5 ± 9.5 (P/D)	Epithelial = 29	I, II	37	40
Nakas A, Waller D, 2012; Nakas A, Meyenfeldt E, 2012; [Martin-Ucar AE, 2007]	Retro	UK	181/31	14-72; median = 59	Epithelioid = 160, biphasic = 52		85	127
Lang-Lazdunski L, 2012	Retro (2004-2011)	UK	x	x	Epithelioid & nonepithelioid	I- IV	61	25
Lindenmann J, 2012	Retro (2000-2009)	Austria	47/14	34-82; mean = 63.7	Epithelioid = 48 (78.7%), sarcomatoid = 3 (4.9%), biphasic = 10 (16%)		41	3
Bedirhan MA, 2013	Retro (2001-13)	Turkey	58/18	30-76 (mean 53.2)	Epithelioid = 60		45	31
Bovolato P, 2014	Retro (1982–2012)	Italy	374/129	62.5 (P/D); 58.7 (EPP)	Epithelial 81%	I: 9.5%; II: 27.6%; ≥ III: 19%; unk: 43.7%	202	301

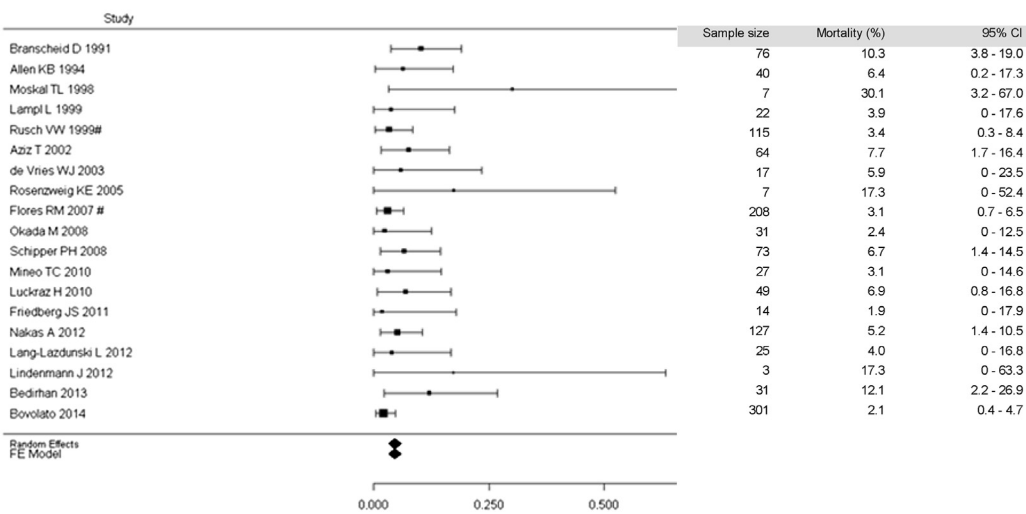
[a] Partial overlapping of the data sets.

IORT= intraoperative radiation therapy; mdn = median; PDT = photodynamic therapy; unk = unknown.

Pleurectomy/Decortication



Extrapleural Pneumonectomy



For each study, the square represents percent mortality; the size of the square is proportional to the size of the study; bars represent 95% Confidence Intervals

	Pleurectomy/Decortication		Extrapleural Pneumonectomy		P value^
	Sample size	Meta % mortality (95% CI)	Sample size	Meta % mortality (95% CI)	
Total (fixed effects)	1166	1.7 (0.9- 2.8)	1237	4.5 (3.2- 6.0)	<0.05
Total (random effects)	1166	1.7 (0.9- 2.8)	1237	4.5 (3.2- 6.0)	<0.05
Q (DF)	7.6 (18)		16.8 (18)		
Significance level	P = 1.0		P=0.53		
I^2	0.0		0.0		

^ p value tests the statistical difference between percent mortality

Fig 1. Meta-analysis of short-term mortality (perioperative and 30 days after surgery).

comparison group must be present. Finally, information on 2- to 5-year mortality for both intervention and comparison groups must be available.

Statistical Analysis

Percent mortality within 30 days from surgery and median survival in months after surgery were extracted from each study. When median survival was reported in days, the value was divided by 30 to convert the value to months. In order to carry out the meta-analysis computations, the "metan" command in Stata (Stata Version 10, StataCorp LP, College Station, TX) was used. The meta-analysis procedure allows us to statistically combine the results of individual studies and to produce a summary estimate that takes into account the weight (size) of each study. The combined percent perioperative mortality was calculated according to both a fixed and a random effects model; the Q statistics were used to test for heterogeneity between the studies included in the meta-analyses [4]. The I^2 statistic was used as a confirmatory test for heterogeneity with I^2 less than 25%, 25% to 50%, and greater than 50% representing low, moderate, and high degree of heterogeneity, respectively [5]. High heterogeneity across studies usually renders the summary results less valid.

Results

The search resulted in 98 eligible papers. Upon further detailed review, 71 publications were excluded; 38 due to evaluation of 1 surgical procedure and lack of a separate report of outcome data for the surgical procedures of interest, 25 papers were reanalyses of data or reviews, 7 papers measured other outcomes, and 1 paper reported 30-day survival data only. Twenty-seven articles were included [6–32], of which five [8, 9; 26–28] overlapped and relied on the same source populations and were therefore considered as 2 distinct data sets, bringing the number of distinct data sets to 24 (Table 1), for a total of 1,512 patients treated with P/D, and 1,391 treated with EPP. Several studies reported the percentage of patients who received other treatments either before or after surgery; the data are also included in Table 1.

Short-Term Mortality

The pooled estimate of the proportion of patients who died perioperatively within 30 days from surgery was calculated from 19 studies for which the information was available (Fig 1), for a total of 1,166 patients who underwent P/D, and 1,237 who underwent EPP. No statistically significant heterogeneity was observed among the studies (Q test for EPP, 16.8, $p = 0.53$; Q for P/D, 7.6, $p = 1.0$). There was a significantly higher proportion of short-term deaths in the EPP group versus the P/D group (percent mortality meta estimate: 4.5% vs 1.7%; $p < 0.05$).

Median Survival

There were 17 studies that reported median survival after surgery. The difference between median survival after P/D and EPP was plotted (Fig 2). Fifty-three percent of the studies indicated longer survival after EPP and 47% after P/D.

Long-Term Survival

Ten studies report survival at various times during the follow-up; 7 studies reported 2-year survival (Fig 3) for 622 patients who underwent EPP and 544 patients who underwent P/D. There was statistically significant heterogeneity among the studies (Q for PDD: 64.3, $p < 0.0001$; Q test for EPP: 25.2, $p = 0.003$). There was no statistically significant difference in 2-year mortality between the 2 groups (23.8% vs 25%; $p = 0.8$).

Complications

Short-term complications were reported in 15 (62.5%) of the 24 included data sets. Patients undergoing EPP experienced more postoperative complications than patients undergoing P/D. Frequent complications were local infections, systemic infections, and cardiac arrhythmia (Table 2).

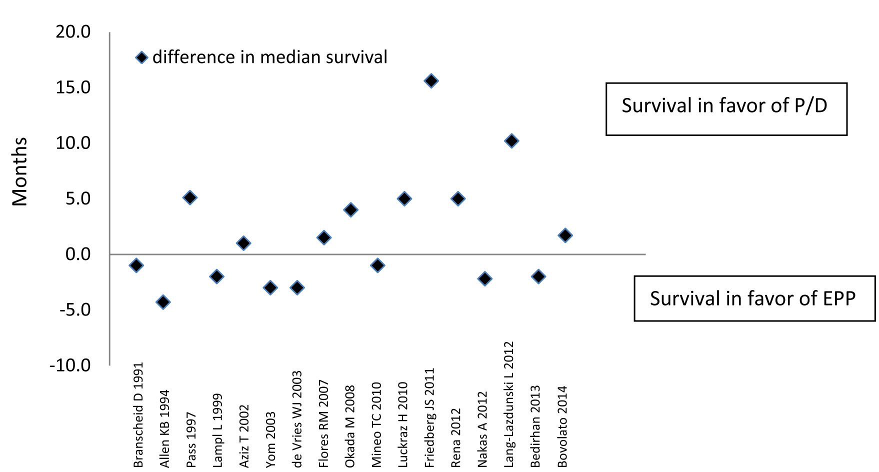
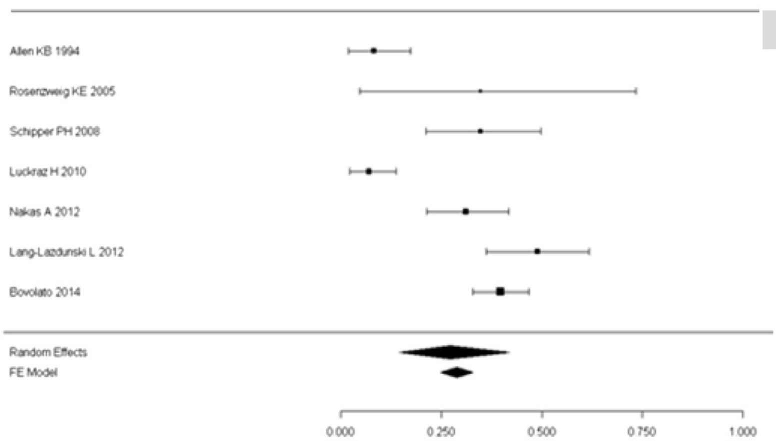


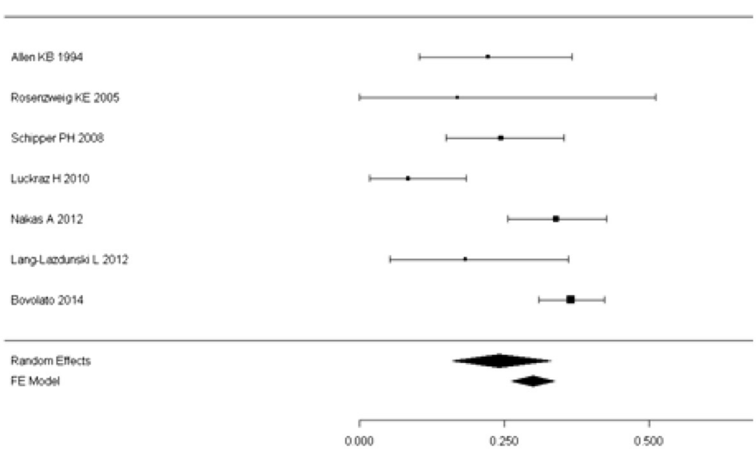
Fig 2. Difference in medial survival between pleurectomy decortications (P/D) and extrapleural pneumonectomy (EPP) (number of studies = 17).

Pleurectomy/Decortication



Sample size	Mortality (%)	95% CI
56	8.2	1.9 - 17.5
6	34.7	4.7 - 73.4
44	34.8	21.1 - 49.8
90	7.0	2.2 - 13.8
85	31.2	21.5 - 41.7
61	49.0	36.2 - 61.8
202	39.7	32.8 - 46.8

Extrapleural pneumonectomy



Sample size	Mortality (%)	95% CI
40	22.2	10.3 - 36.8
7	17.0	0 - 51.2
73	24.5	14.9 - 35.3
49	8.4	1.7 - 18.5
127	34.0	25.7 - 42.7
25	18.3	5.2 - 36.2
301	36.6	31.0 - 42.3

For each study, the square represents percent mortality; the size of the square is proportional to the size of the study; bars represent 95% Confidence Intervals

		Pleurectomy/Decortication		Extrapleural Pneumonectomy	P value
	Sample size	Meta % survival (95% CI)	Sample size	Meta % survival (95% CI)	
Total (fixed effects)	544	28.8 (25.0-32.9)	622	30.0 (26.3-33.8)	0.7
Total (random effects)	544	27.3 (14.7-41.9)	622	24.2 (16.1-33.1)	0.2
Q (DF)	64.3 (6)			25.2 (6)	
Significance level	P<0.0001			P = 0.003	
I^2	90.7 %			76.9 %	

Fig 3. Summary estimate of 2-year percent survival after extrapleural pneumonectomy versus pleurectomy decortications (number of studies = 7) (∧ = p value tests the statistical difference between percent mortality; Q, I^2= statistical tests for heterogeneity.)

Table 2. Complications After Pleurectomy Decortication and Extrapleural Pneumonectomy

Author, year	Number of cases P/D, EPP	Complications P/D	Complications EPP
Allen 1994	56, 40	26.8% (15 cases) prolonged air leakage (6), arrhythmias (5), tracheostomy (2), renal failure (2), pneumonia (1)	30% (12 cases); bronchopleural fistula (2), vocal cord paralysis (2), arrhythmias (3), tracheostomy (2), chylothorax (1), MI (1) contralateral benign pleural effusion (1), splenectomy (1), pneumonia (1)
Pass, Kranda 1997; Pass, Temeck 1997	39, 39	Supraventricular tachyarrhythmias (2)	Supraventricular tachyarrhythmias (14), bronchopleural fistulae (7)
		Postoperative pancreatitis (4), esophageal-pleural fistula (2), hemorrhage (2), diaphragmatic herniation (1), temporary left radial nerve palsy (1), wound dehiscence (1)[a]	
Aziz 2002	47, 64	Re-exploration for bleeding (1), pneumonia (1)	21% (14 cases);ARDS (6), pneumonia (4), bleeding (4), reintubation and ventilation (2)
de Vries 2003	29, 17	Empyema (1)	Atelectasis (2), prolonged air-leak (3), discharge with drainage (1), prolonged ventilation (1), large blood transfusion (3)
Rosenzweig 2005	6, 7	Pneumonitis/TE fistula (1), chest tube leak (1)	Thoracic duct leak (1) , empyema (1), wound dehiscence (1)
Okada 2008	34, 31	15%; supraventricular arrhythmias (3), respiratory infection (2),	48%; supraventricular arrhythmias (8), respiratory failure (4), respiratory infection (1), bleeding (2), heart hernia (2), bronchial stump insufficiency (2), chylothorax (2), heart failure (1), laryngeal nerve palsy (1)
Schipper 2008	44, 73	4 (9%) bleeding, respiratory failure (1), MI (1)	37 (50.5%); empyema (14), respiratory failure (10), bronchopleural fistulae, bleeding (5), orthostatic hypotension (5), ARDS (4), bowel herniation (4), MI (3), acute renal failure (3), cerebrovascular accident (3), pulmonary embolism (3), cardiac herniation (2), vocal cord paralysis (2), gastric perforation (1), heart failure (1), pleurocutaneous fistulae (1), splenic rupture (1), esophageal perforation (1), delayed gastric emptying (1), metabolic encephalopathy (1), gastropleural fistula (1)
Borasio 2008	12, 15	33% (4 cases); bleeding (2), atrial fibrillation (1), retained secretions (1)	60% (9 cases); atrial fibrillation (4), respiratory failure (3), bleeding (3), ileus (2), pneumonia (1), vocal cord paralysis (1)
Mineo 2010	44, 27	13.6% (6 cases); bleeding (4), DVT (2)	33% (9 cases); cardiac arrhythmias (4), bleeding (2), vocal cord palsy (1), DVT (2), bronchopleural fistula (2)
Luckraz 2010	90, 49	Atrial fibrillation (8)	Infections (8), bronchopleural fistula (7), atrial fibrillation (2)
Friedberg 2011	14, 14	DVT requiring anticoagulation (4) atrial fibrillation (3), chyle leak (2), pneumonia (3), respiratory failure (1), persistent air leak (1)	DVT requiring anticoagulation (6) atrial fibrillation (3), chyle leak (1), pneumonia (2), respiratory failure (2), pulmonary embolism (1), stroke (1), MI (1)
Rena 2012	37, 40	24% (9 cases); Atrial fibrillation (2), bleeding req operation (1), MI (1)	62% (25 cases); Atrial fibrillation (17), bleeding req operation (2), pneumonia (2), ARDS (1), cerebral ischemic attack (1), pulmonary embolism (1), bronchopleural fistula with empyema (1), gastric hernia after diaphragmatic prosthesis dislocation (1)
Nakas, Waller 2012; Nakas, Meyenfeldt 2012	85, 127	Reoperation (5), prolonged air leak (20), pleural sepsis (5)	Reoperation (19), pleural sepsis (8)

(*Continued*)

Table 2. Continued

Author, year	Number of cases P/D, EPP	Complications P/D	Complications EPP
Lang-Lazdunski 2012	61, 25	27.7%; arrhythmia (2), persistent air leak (10), chylothorax (4) ARDS (1)	68%; Arrhythmia (7), reoperation for bleeding (2), bronchopleural fistula/empyema (2), pulmonary embolus (1), ARDS (1), pneumonia (1), vocal cord palsy (1), Horner syndrome (1), late septicemia (1)
Bovolato 2014	202, 301	21.6% (65 cases); atrial fibrillation (32), bleeding (13), chest infection (4), bronchopleural fistula (3), pulmonary embolism, (3), displacement of diaphragmatic prosthesis with herniation (3), respiratory insufficiency (2), DVT (2), ARDS (1), cerebral ischemia (1), wound infection (1)	10.4% (21 cases); atrial fibrillation (9), prolonged air leak (5), bleeding (3); MI (2),controlateral pleural effusion (1), paraplegia (1)

[a] These complications are reported in general, not assigned to one or the other surgical procedure.

ARDS = acute respiratory distress syndrome; DVT = deep vein thrombosis; EPP = extrapleural pneumonectomy; MI = myocardial infarction; P/D = pleurectomy decortication; TE = tracheoesophageal.

Comment

This meta-analysis of published data comparing these 2 surgical techniques for pleural mesothelioma demonstrates that perioperative 30-day survival is significantly better after P/D than after EPP. The difference persists, although it is not statistically significant, at 2 years. Overall, differences in survival between the 2 procedures are modest but favor P/D in both the short and long terms. Given the complexity of technique and increased physiologic strain of EPP, significant improvement in survival should be demonstrated in order to warrant the increased risk. However, the summary meta-analysis performed here suggests that survival is in fact worse with EPP.

In an environment that lacks randomized clinical trials comparing the 2 surgical approaches [33], the current work is the largest comparative study conducted to-date, including 1,512 patients treated with P/D and 1,391 treated with EPP. Two systematic reviews have been previously published, but both were subject to significant limitations. One review [3] included studies that analyzed either one or the other procedure (without comparing the 2) rather than excluding studies that did not compare the 2 surgical techniques. A recent meta-analysis [2] that included studies comparing the 2 procedures was incomplete (only 7 trials were analyzed). While the present analysis supports the results of the latter, this meta-analysis represents a much more comprehensive evaluation of the current literature. Finally, other systematic reviews have concentrated on the outcomes of one [34] or the other [35] surgical procedure, but do not consider the comparison of the 2.

The present study is a reanalysis of published data, and, as such, has some limitations. In each study, the choice of one or the other surgical procedure may have been dictated by clinical reasons, such as the stage, histology, age of the patient or the presence of comorbidities; these same factors may have independently impacted survival. If such selection bias exists it cannot be accounted for and adjusted in the meta-analysis. Another limitation is that the studies did not report 90-day mortality, a metric that is now considered clinically important. Only 7 studies reported 2-year mortality, and even fewer followed the patients for 5 years. The summary estimate at 2 years is very heterogeneous, indicating that other factors such as variations in the basic surgical approach or in the surgeon ability, the degree of specialization of the center performing surgery, or the standardization of data definition across institutions, may have played a role. Finally, another limitation is that due to the retrospective nature of the meta-analysis, data on multimodal treatments, induction and adjuvant treatments, Photodynamic Therapy (PDT), intrapleural chemotherapy, or intrapleural povidone iodine in addition to surgery were available as percent out of the total sample but not on an individual basis, and therefore could not be systematically considered and analyzed; it is established that chemotherapy can substantially prolong life in responders. Additional treatment may have been applied differentially to patients in the 2 surgical groups and may have affected the outcome. Another aspect that could not be considered because the information was not reported in the original articles is a comparison of the most common causes of intraoperative death P/D versus EPP.

In conclusion, the reanalysis of a large number of studies comparing pleurectomy decortication to extrapleural pneumonectomy suggests that pleurectomy decortication is associated with a 2 $^{1}/_{2}$ -fold lower short-term mortality (perioperatively and within 30 days) than extrapleural pneumonectomy. Pleurectomy decortication should therefore be preferred when possible.

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