Extrapleural pneumonectomy (EPP) *vs.* pleurectomy decortication (P/D)

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Abstract: Surgical techniques for treatment of malignant pleural mesothelioma (MPM) have improved over the decades. The main surgical principle was accepted as macroscopic complete resection. This principle was achieved with extrapleural pneumonectomy (EPP) and extended pleurectomy/decortication (P/D). Mortality and morbidity are higher following EPP with supraventricular arrhythmias, pulmonary embolism, bronchopleural fistula and pulmonary failure being the most common, while prolonged air leak is frequent following P/D. Completion of multimodality treatment was also shown to be a prognostic factor. Many different neoadjuvant and adjuvant protocols were applied with limited effect on prognosis. While locoregional recurrence is more common following P/D, EPP patients typically recur in contralateral hemithorax and abdomen. Hemithoracic radiation following EPP was the only effective technique shown to decrease locoregional recurrence. However, neither surgical technique (EPP *vs.* P/D), nor types of multimodality treatment protocols were found to be prognostic in MPM. Epithelioid histology, metastasis to extrapleural lymph nodes and completion of multimodality treatment were prognostic in most of the series. In conclusion, based on the current evidence, the choice of a less morbid and mortal procedure (P/D) seems to be the logical choice in the treatment of MPM.

Keywords: Extrapleural pneumonectomy (EPP); pleurectomy/decortication (P/D); malignant pleural mesothelioma (MPM)

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Introduction

The technique of tumor resection for malignant pleural mesothelioma (MPM) is one of the most debated topics in thoracic surgery. Pleuropneumonectomy was first applied in MPM by Dr. Butchart and reported the results of 29 patients in 1976 (1). En bloc diaphragm and pericardial resection was performed in most cases. In five early cases, diaphragm was not completely excised. Diaphragm and pericardial reconstruction was performed in 24 and 15 patients respectively. Hospital mortality was 31% and only 3 patients survived 2 years or longer, reaching 3, 5 and 6 years. The significance of histologic subtype in the course of the disease was also evident at that time with the following statement:

"Small numbers make statistical analysis unhelpful but it is interesting to note that 100% of mesenchymal tumors had already reached stage IV at the time of death, whereas two of epithelial tumors (28.6%) were still in stage I in spite of long histories".

The peri- and post-operative results of pleuropneumonectomy/extrapleural pneumonectomy (EPP) were improved in later decades and this also translated to a better survival rate in long term.

Pleurectomy/decortication (P/D) is one of the first surgical techniques defined in Thoracic surgery and has been used extensively for palliation of MPM. One of the first reports was from Memorial Sloan Kettering Center and in 17 patients who underwent P/D and had epithelioid tumors, median survival was 21 months, whereas it was 11 months for biphasic and sarcomatoid tumors (2). In the

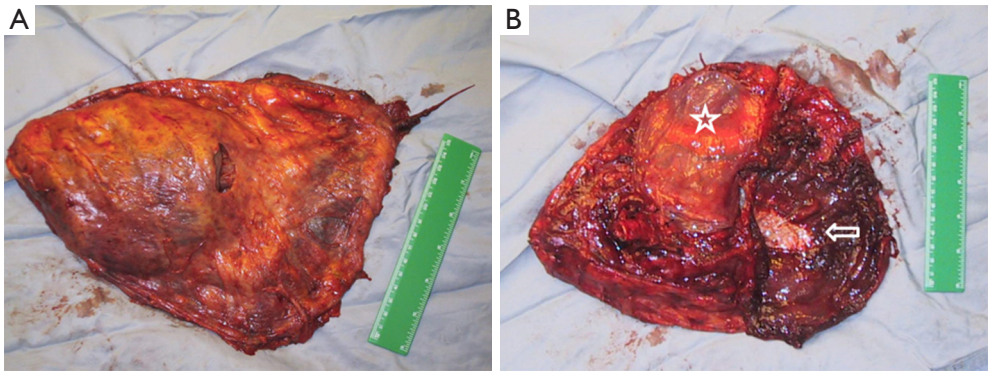

Figure 1 A left EPP specimen. (A) Costal surface; (B) En bloc resection of the pericardium (star) and diaphragm (arrow) has been performed along with parietal and visceral pleura and the left lung. EPP, extrapleural pneumonectomy.

following decades technique of P/D was refined to extended P/D with resection of diaphragm and pericardium while sparing the lung (3).

Technical definition

The chaos of surgical terminology in MPM was standardized and refined by International Association for Study of Lung Cancer Thoracic domain and published in 2011 (3).

In this report, EPP was defined as en bloc resection of the parietal and visceral pleura with the ipsilateral lung, pericardium, and diaphragm (*Figure 1*). According to the group's recommendation, in cases where the pericardium and/or diaphragm are not involved by tumor, these structures may be left intact. This is well in accordance with the reports from Butchart in 1976 and Sugarbaker in 1999 (1,4). In a retrospective cohort 314 patients who underwent EPP or P/D, there was no evidence of diaphragm involvement in 119 (38%) of the patients (5).

The technique of pleurectomy that involved resection of diaphragm and/or pericardium was defined as radical or extended P/D in several papers and the recommendation was to use the term extended P/D. Extended P/D was defined as parietal and visceral pleurectomy to remove all gross tumor with resection of the diaphragm and/or pericardium. The suggestion was to use the term "extended" rather than "radical", as the latter implied a completeness of resection with added therapeutic benefit. However, there is currently insufficient evidence that resection of the pericardium and diaphragm provides either.

P/D was defined as performance of parietal and visceral pleurectomy and removal of all gross tumor without removal of diaphragm and pericardium whereas partial P/D was defined as partial removal of parietal and/or visceral pleura for diagnostic or palliative purposes but obviously leaving gross tumor behind.

Comparison of EPP with P/D

We have several retrospective studies comparing EPP with P/D, but these two techniques have not been compared in a prospective randomized trial. The underpowered randomized trial of MARS, compared EPP with a group of patients who mainly received chemotherapy and other not specified surgical interventions. The four studies that have specifically focused on the comparison of EPP and P/D are shown in *Table 1* (6-8).

Despite the limitations of retrospective studies, these studies show that morbidity and mortality is higher following EPP, while survival figures are similar.

Morbidity

Morbidities related with EPP is much different than P/D. Removal of the lung, hemidiaphragm and ipsilateral pericardium leads to a significant hemodynamic and respiratory challenge and leads to cardiorespiratory complications specific to the procedure. Most common complication following a P/D is prolonged air leak which is related with the trauma to the lung tissue while peeling of the pleura. The morbidities seen in large EPP and P/D series are shown in *Table 2*.

Mortality and reasons for mortality

The frequency and causes of mortality are different in EPP

Table 1 Retrospective comparison of the results of EPP and P/D

Primary author and year	Total number of patients	Number of patients (EPP/PD)	EPP/PD morbidity (%)	EPP/PD mortality (%)	Median survival
Flores, 2008 (6)	663	385/278	10/6.4	7/4	12/16*
Burt, 2014 (7)	225	95/130	Higher in EPP[α]	10.5/3.1	NS
Batirel, 2016 (8)	130	42/66	20/5	7/2	18.3/14.6
Sharkey, 2016 (9)	362	133/229	Higher in EPP[α]	6/3.5	12.9/12.3

Two of the studies (7,8) compared the results of two periods following an intentional transition from an EPP predominant practice to a P/D predominant practice. *, P<0.001; [α], early and late reoperation, bleeding, bronchopleural fistula, ARDS, Sepsis, atrial arrhythmias, right heart failure and ileus were significantly higher in EPP patients, whereas prolonged air leak was higher in P/D patients. NS, not stated.

and P/D. High risk of bronchopleural fistula in right sided EPP was usually associated with sepsis and subsequent pulmonary and multiorgan failure (11). Pulmonary embolism was also a leading cause of mortality in patients who underwent EPP. In the report by Sugarbaker, deep vein thrombosis was observed in 21/328 patients (6.4%), which resulted in pulmonary embolism in 5 (1.5%) of the patients (13). In most series, P/D patients were older, with higher comorbidities and limited pulmonary function (7). As a result, P/D patients had more atelectasis, pneumonia, prolonged air leak, localized infections, pulmonary embolism and empyema which can lead to mortal situations. Frequency and causes of mortality are listed in *Table 3*.

Mortality rate after EPP was significantly high (>10%) in the early years , however in most experienced centers the mortality rate lowered to less than 5% in the last decade (1,13,17). In the study from the database of the Society of Thoracic Surgeons, EPP mortality was 6.5% in high volume (>5/year) centers, whereas it was 12.5% in low volume centers.

P/D is almost always associated with low mortality rate. Lang-Lazdunski reported no mortality at 30 and 90 days in 102 patients (10), however when intraoperative heated chemotherapy was added mortality was 11% (5/44) in a prospective patient series from an experienced center (18). This high mortality rate was attributed to advanced age and limited pulmonary function.

Impact of multimodality treatment and treatment compliance

Multimodality treatment is now considered the standard of care in MPM. Various treatment schemes have been used including neoadjuvant, intraoperative and adjuvant treatments. One of the first reports that utilized adjuvant high dose radiation (54 Gy) was the phase II study by Rusch and colleagues (19). The study started with 88 patients. Sixty two underwent EPP, 5 had P/D and 21 had exploratory procedures only. Postoperative mortality was 7.9% (7/88). Adjuvant radiation was administered to 57 patients which showed a very high compliance rate (85%) among resected patients. There is a recent experimental protocol that involves administration of neoadjuvant intensity modulated radiation of 25 Gy in 5 days followed by EPP. The results were very promising in epithelioid tumors with a median survival of 51 months (20). The studies about types of multimodality treatment and treatment compliance are shown in *Table 4*. The types of treatment are extremely variable between the series, despite one study showing a significant difference for adherence to adjuvant treatment after EPP versus P/D (14), the other studies failed to show any significant difference (8,9).

Survival outcomes

Prognosis following MPM surgery is still very dismal with most of series reporting two year survival rates less than 40%. The most important prognostic factor is histology with epithelioid disease (4,6,8,10,15), followed by N0 status (8,15,24). Multimodality treatment and female gender were also identified as prognostic factors in a few studies (6,8,12,24). Interestingly only two studies (one P/D and one EPP series) reported macroscopic complete resection to be prognostic factor (4,10). When published data was analyzed, addition of surgery to a multimodality treatment protocol resulted in a survival extension of a maximum of 9 months (25). Long term survival was analyzed in two studies. Eighteen percent of

Table 2 Major and minor complications in retrospective EPP and P/D patients series

Author and year	Number of patients, type of study	Treatment and type of surgery	Major complications, n (%)									Minor complications (n, %)
			Total	Empyema	BPF	Chylothorax	Patch failure	Bleeding	Pulmonary embolism	ARDS	Other	
Lang-Lazdunski, 2015 (10)	102, single center	Multimodality treatment + P/D	30 (29.4)	2 (1.9)		4 (3.8)				1 (0.9)	1 (0.9)	Prolonged air leak (17, 16.7); pneumonia (10, 9.8); atrial fibrillation (2, 2.0)
Lauk, 2014 (11)	251, multicentric	Neoadjuvant Chemotherapy + EPP	76 (30.3)	35 (13.9)	20 (8.0)	13 (5.2)	12 (4.8)	9 (3.6)	9 (3.6)	3 (1.2)	0	Atrial fibrillation (67, 26.7); pneumonia (6, 2.4)
Spaggiari, 2014 (12)	518, Multicentric	Induction chemotherapy in 271 patients, Adjuvant therapy in 373 patients + EPP	136 (26.3)	12 (2.3)	14 (2.7)	5 (1.0)	17 (3.3)	39 (7.5)	NS	NS	NS	Atrial fibrillation (97, 18.7); need for bronchoscopy (62, 12.0)
Burt, 2014 (7)	95, multicentric	P/D	NS	1 (0.8)					2 (1.5)	1 (0.8)		Prolonged air leak (22, 23.1); pneumonia (3, 3.2); atrial fibrillation (11, 11.5)
Sugarbaker, 2004 (13)	328, single center	EPP	198 (60.4)	8 (2.4)	2 (0.6)	NS	20 (6.1)		5 (1.5)	12 (3.6)	NS	Atrial fibrillation (145, 44.2); deep vein thrombosis (21, 6.4)

BPF, bronchopleural fistula; ARDS, acute respiratory distress syndrome; NS, not stated.

Table 3 30- and 90-day mortality rates and causes of mortality in various series

Author and year	Total number of patients and procedure	30-/90-day mortality rate, n (%)	Causes of mortality (n)
Sharkey, 2016 (9)	229, extended P/D	8 (3.5), 21 (9.2)	Multiorgan failure secondary to sepsis. Respiratory failure, MI, Pulmonary embolism
Infante, 2016 (14)	72, extended and partial P/D	1 (1.3), 3 (4.2)	Empyema and pneumonia
Lauk, 2014 (11)	251, EPP	12 (5.0), 21 (8.0)	Pulmonary embolism most common
Gomez, 2013 (15)	136, EPP	11 (8.0), NS	ARDS, pneumonia sepsis most common
Neragi-Miandoab, 2008 (16)	64, extended and partial P/D	2 (3.1), NS	Aspiration pneumonia
Sugarbaker, 2004 (13)	496, EPP	20 (4.0), NS	Pulmonary embolism [6], ARDS [4], MI [3], unknown [3], cardiac herniation, renal failure, cardiac arrhythmia, HIT (1 each)

ARDS, acute respiratory distress syndrome; MI, myocardial ınfarction; HIT, heparin ınduced thrombocytopenia; NS, not stated.

Table 4 The types of treatment and compliance of patients with neoadjuvant and adjuvant treatment in patients undergoing surgery for mesothelioma

Author and year	Type of surgery	Type of MM treatment	Total number of patients	Patients who completed treatment [%]	Non-surgical treatment mortality
Infante, 2016 (14)	EPP, extended P/D, exploratory	Trimodality treatment	91, 47, 25	28 [31], 33 [70], 6 [24]	None
Rimner, 2016 (21)	P/D	Neoadjuvant chemotherapy, adjuvant pleural IMRT	45	27 [60]*	None
Batirel, 2016 (8)	EPP, P/D, exploratory	Trimodality treatment	130	114 [88]	Not stated
Lang-Lazdunski, 2015 (10)	P/D	Neoadjuvant and adjuvant chemotherapy	102	83 [81]$^{\alpha}$	None
Spaggiari, 2014 (12)	EPP	Neoadjuvant and adjuvant therapy	518	271 [52.3] and 373 [72]	Not stated
Bölükbas, 2013 (22)	Extended P/D	Adjuvant chemoradiation	78	36 [46]	Not stated
Gomez, 2013 (15)	EPP	Adjuvant hemithoracic IMRT	136	86 [63]	None
Stahel, 2015 (23)	EPP	Neoadjuvant chemotherapy, adjuvant high dose RT	154 (113 had EPP)	54 [35] eligible for RT	1 patient died of pneumonitis

$^{\alpha}$, adjuvant chemotherapy; *, only 21 underwent P/D, 8 extended and 13 partial P/D.

the patients (n=117) survived longer than 3 years after EPP and median age, epithelioid histology and hematologic criteria (normal White blood cell count, hemoglobin and platelets) were found to be significant prognostic factors (26). Another multicentric study on EPP showed that 23% of patients lived longer than 3 years and similarly age and histology were significant prognostic factors followed by no history of asbestos exposure and metastatic/normal lymph node ratio (27). In another study, patients who had stage III MPM and underwent radical pleurectomy followed by chemoradiation, 37% survived longer than 3 years (22). Two-, five-year and median survivals following surgical treatment of MPM are presented in *Table 5*. In these series, progression free survival was less than one year. As seen in *Table 5*, the treatment protocols were significantly different between the series, but other than a few series with limited number of patients, median and long term survivals were almost identical between EPP and P/D.

Table 5 Survival figures in various series that utilized EPP or P/D as surgical treatment

Author and year	Type of surgery, histology	Type of treatment	Number of patients (n)	Median survival (months)	2-year survival rate (%)	5-year survival rate (%)
Rimner, 2016 (21)	P/D, all	Neoadjuvant chemotherapy, adjuvant pleural IMRT	27	23.7	59	NA
Batirel, 2016 (8)	EPP, P/D, exploratory, all	Trimodality treatment	130	17.8	32	14
Lang-Lazdunski, 2015 (10)	P/D, all	Neoadjuvant and adjuvant chemotherapy	102	32	63	23
Stahel, 2015 (23)	EPP, all	Neoadjuvant and adjuvant treatment	151	15	NA	NA
Spaggiari, 2014 (12)	EPP, all	Neoadjuvant and adjuvant therapy	518	18	41	14
Sugarbaker, 2014 (24)	EPP, epithelioid	Multimodality treatment	529	18	39	14
Bölükbas, 2013 (22)	Extended P/D, all	Adjuvant chemoradiation	78	32	NA	25
Gomez, 2013 (15)	EPP, All	Adjuvant hemithoracic IMRT	136	14.7	32	NA
Flores, 2008 (6)	EPP, P/D, all	Multimodality treatment	663	14	NA	12

Recurrence data

Despite the improvements in overall survival over the decades, the recurrence pattern following surgical treatment of MPM has stayed the same. Only high dose hemithoracic irradiation and IMRT has proved to change the recurrence pattern following EPP (15,19). In those patients, locoregional recurrence has decreased dramatically and most of the recurrences occurred distally, in contralateral hemithorax or abdomen. In a phase II study of 62 patients who underwent EPP and high dose hemithoracic radiation, 54 recurred and only in 7 there was locoregional recurrence, whereas recurrence occurred distally in 30 patients (19). In another series of 136 patients who underwent EPP, 86 also had hemithoracic IMRT. Only 2 patients had only locoregional recurrence. Fifty one patients had distant recurrence with contralateral hemithorax being the most common followed by abdomen (15).

In another series, 169 patients underwent EPP (heated intraoperative chemotherapy rate of 78%) and 62% were epithelioid. Recurrences in ipsilateral hemithorax, contralateral hemithorax, abdomen and other sites were exactly the same in their 1997 and 2015 reports (28,29). Around 70% of the patients had locoregional, 50% had abdominal and 35% had contralateral hemithoracic recurrence. Thus local chemotherapy did not lead to any difference in terms of recurrence patterns.

In patients who underwent extended P/D and postoperative chemoradiation, only locoregional recurrence occurred in 47% of the patients, followed by distant and both (14% each) (22). When two practice periods were compared, EPP predominant period had more distant recurrences, while P/D predominant period had more locoregional recurrences (8).

In a novel technique that involves administration of accelerated neoadjuvant hemithoracic IMRT, EPP was performed in 62 patients subsequently. Survival was very good for epithelioid histology patients. Only 30 patients had recurrence and ipsilateral hemithoracic recurrence was seen in 8 patients and these were in patients with biphasic histology and clinical T4N2 disease. Remainder of the recurrences were in the contralateral chest or abdomen (20).

Despite the changes in recurrence patterns, in most of the series this does not translate to any survival advantage between the two techniques.

Final word

The surgical technique in MPM aims to achieve a macroscopic complete resection. The best technique to achieve this was with EPP in the beginning. The technique of EPP, a morbid and risky procedure, has been refined over time and became a procedure with acceptable morbidity and mortality. However, technique of P/D has also improved

with diaphragmatic and pericardial resection and acceptable macroscopic complete resection can also be achieved with P/D in the current era. The morbidity and mortality is much less following P/D. In several large patient series of EPP and P/D, there was no difference in terms of long term survival. The main prognostic factors were epithelioid histology, extrapleural lymph node metastasis and completion of multimodality treatment. Based on the current evidence, the choice of a less morbid and mortal procedure (P/D) seems to be the logical choice in the treatment of MPM.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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