Surgery in Mesothelioma – Where Do We Go after MARS?

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The role of surgery in the management of malignant pleural mesothelioma remains controversial. Surgical resection consists of different procedures for diagnostic or therapeutic reasons. The latter includes either an extrapleural pleuropneumonectomy (EPP) or lung-sparing operations like debulking of the parietal and visceral pleura by pleurectomy/decortication (P/D) or extended pleurectomy/decortication, in which further debulking of the diaphragm or pericardium is included. Because of the modest outcome of surgery as single-modality therapy, combinations of chemotherapy, surgery, and radiation therapy were initiated as a new treatment strategy to improve prognosis. The observations that patients treated with P/D had an equal to better outcome than those treated with EPP, and that EPP with perioperative chemotherapy was better than EPP alone, raises the issue whether performing a P/D with perioperative chemotherapy would result in a further improvement of outcome with a lower operative mortality than with EPP and perioperative chemotherapy. This is the rationale for the next European Organisation for Research and Treatment of Cancer trial exploring the feasibility of P/D with perioperative chemotherapy.

Key Words: Malignant pleural mesothelioma, Extrapleural pleuropneumonectomy, Extended pleurectomy/decortication, Lung-sparing procedures, Multimodality treatment.

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Malignant pleural mesothelioma (MPM) is a rare and aggressive disease arising from the pleural mesothelium, with a median natural history of less than 1 year.[1] Worldwide incidence rates are expected to increase and peak in the year 2020,[2] although a leveling off has been observed in some industrialized countries.[3] Only chemotherapy has been shown to improve the outcome significantly.[4,5] In 2005, Maziak et al.[6] systematically reviewed the surgical evidence from 32 studies and case series with either a retrospective or a prospective design. They did not retrieve randomized trials or guidelines, and the heterogeneity of the treatments administered precluded a pooling of the outcome data. The role of surgery hence remains controversial. In this article, we will review and interpret the key publications relating to the subject as a background of the next randomized phase 2 trial conducted by the European Organisation for Research and Treatment of Cancer.

SURGERY IN MPM

Surgery in mesothelioma can be performed for diagnostic and therapeutic reasons.[7–9] In the former, a gross biopsy of the pleura is obtained either by video-assisted thoracoscopic surgery or open (mini)thoracotomy. Therapeutic surgery in mesothelioma involves different procedures[10]:

1. Extrapleural pleuropneumonectomy (EPP) involves the "en bloc" resection of the parietal and visceral pleura with the homolateral lung, pericardium, and diaphragm and with repair of diaphragm and/or pericardium using synthetic patches. In a systematic review of 34 series including 2462 patients from 26 institutions, median overall survival after EPP ranged from 9.4 to 27.5 months and median disease-free survival from 7 to 19 months.[1] Relapses do occur mostly locally suggesting incompleteness of resection. Overall perioperative mortality rates ranged from 0 to 12%, and overall perioperative morbidity rates ranged from 22 to 82%. Operative time ranged from 3.25 to 6.5 hours and the duration of hospitalization from 8 to 43 days. Despite these sobering figures, 45% of U.S. and 23% of European thoracic surgeons still believe in cure by EPP alone.[11]
2. Lung-sparing procedures consist of the resection of the pleura without removing the lung. The procedure can be palliative to control fluid accumulation (pleurodesis by partial parietal pleurectomy) or aim at radicality when a cytoreduction of all macroscopic tumor on the parietal and visceral pleura is considered (pleurectomy/decortication [P/D]).[7–9] In a systematic review of 1270 patients from 26 reports on lung-sparing extirpative surgery, Teh et al.[12] found an operative mortality of 4% and average survival rates at 1, 2, 3, 4 and 5 year of 51, 26, 16, 11, and 9%, respectively. In addition, P/D was better than best supportive care with a mean survival of 14 months versus 4.5 months.[13] Extended pleurectomy/decortication (e-P/D) is a promising new surgical procedure, which aims at maximal debulking with resection and reconstruction of the diaphragm and/or pericardium if necessary. An e-P/D can involve resection of a lobe, multiple wedges, or even a segment as long as it is lung sparing. Mortality and morbidity of this intervention are less in comparison with EPP, but the procedure currently suffers from a lack of standardization and uniformity.[14,15]

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MULTIMODALITY THERAPY

Because of the incompleteness of the resection as single-modality therapy, combinations of chemotherapy, surgery, and radiation therapy were initiated as a new treatment strategy to improve prognosis.[16] Historically, the adjuvant strategy was explored first. Sugarbaker et al.[17] reported on 183 patients from a retrospective single institutional series, treated with EPP followed by variable adjuvant chemotherapy regimens consisting of either doxorubicin or cyclophosphamide, with or without cisplatin, or carboplatin and paclitaxel. While the reported median overall survival time of 19 months and the 5-year survival rate of 15% are within the previously reported range, subgroup analyses in different prognostic categories showed an impressive outcome in completely resected pN0 epitheloid cases. It is, however, unclear whether these analyses were performed on intention-to-treat basis or merely reflects the survival of the fittest.[18]

In a retrospective series from three U.S. institutions, undergoing EPP with or without any kind of adjuvant treatment, Flores et al.[14] observed an improved outcome in those patients receiving adjuvant chemotherapy, postoperative radiotherapy (PORT), or both. Of the 384 patients who had either an EPP or P/D, 207 received adjuvant therapy, including 130 who had radiation without chemotherapy, 35 who had chemotherapy without radiation, and 42 who received both chemotherapy and radiation. The type of surgical resection (EPP versus P/D) did not significantly influence the survival. The greatest survival difference was seen in patients who underwent multimodality therapy with surgery compared with patients who underwent surgery alone (median survival: 20 versus 10 months). Patient and treatment selection may, however, account for the observed effect.[19]

A number of promising single institutional series with neoadjuvant chemotherapy resulted in the conduct of three prospective multicenter phase 2 studies of EPP in multimodality treatment (Table 1).[20–22] The fraction of patients completing the planned treatment was 50 to 71%, and the fraction of patients completing the neoadjuvant chemotherapy and EPP was 74 to 84%. PORT was the biggest challenge to overall treatment time with a median duration of 184 days in one series, of which 30 to 84 days interval between the resection and the beginning of PORT.[22] Quality of life was monitored in the Swiss study, where approximately 80% of the patients reported psychological morbidity, physical symptoms, and worsening of activity after surgery, followed by a recovery back to the baseline level.[20]

In a systematic review of 349 patients from seven series treated with EPP and any adjuvant treatment, Cao *et al*. observed a median overall survival of 13 to 24 months and a perioperative mortality of 0 to 11%. Presence of N2 lymph node involvement is a significant prognostic factor as compared with N0 to N1 disease.[1] In 286 patients treated with neoadjuvant chemotherapy and analyzed according to the intention-to-treat principle, they found a median overall survival for the intention-to-treat population of 14 to 25.5 months and a perioperative mortality of 0 to 7%, both in the same range as with the adjuvant strategy.[1]

MESOTHELIOMA AND RADICAL SURGERY

The controversy on the role and effectiveness of EPP in the management of MPM lead to the design of the Mesothelioma and Radical Surgery (MARS) trial.[23,24] Patients were scheduled to receive three cycles of chemotherapy and to be restaged thereafter. Then, patients were assigned either to EPP followed by postoperative hemithoracic irradiation or to the no-EPP group, consisting of continued oncological management, which could include chemotherapy, palliative radiotherapy, or palliative surgery (pleurodesis). The EPP procedure was centralized in a limited number of participating high volume centers with experienced thoracic surgeons. To power this trial for the outcome of overall survival, an accrual of 670 patients was required. As the feasibility of allocating patients between a surgical and nonsurgical approach was questioned, a randomized phase 2 trial was first initiated in

TABLE 1. Prospective Multicenter Phase 2 Studies of Radical Multimodality Treatment in Early-Stage Mesothelioma

Variable	SAKK trial[20]	U.S. trial[21]	EORTC 08031[22]
N/n institutions	61/6	59/11	77/9
Induction regimen	Three cycles of cisplatin/ gemcitabin	Three cycles of cisplatin/ pemetrexed	Four cycles of cisplatin/ pemetrexed
Compliance to induction chemotherapy (%)	95	93	83
EPP	45 (74%)	42 (74%)	54 (70%)
Operative mortality (%)	2.2	6.5	7
PORT completed	36 (59%)	37 (65%)	40 (52%)
Median OS (ITT)	19.8 m	18.4 m	16.8 m
Median OS (PP)	23 m	NA	29.1 m
Local relapse (% PP)	NS	6 (16%)	11 (28%)
Median PFS (ITT)	13.5 m	13.9 m	10.1 m
Median overall survival time (days)	NS	184	NS

SAKK, Schweizerische-Abeitsgemeinschaft für Klinische Krebsforschung; EORTC, European Organisation for Research and Treatment of Cancer; EPP, extrapleural pneumonectomy; ITT, intention to treat; NA, not analyzed; NS, not stated; OS, overall survival; PFS, progression free survival; PORT, postoperative radiotherapy; PP, per protocol.

50 patients.[23] Of 112 patients registered over 3 year, only 50 were randomized, because of incomplete registration, disease progression, or withdrawal by the patient. Despite obtaining informed consent before randomization, four patients changed their minds, another three patients refused EPP, and one patient randomized to the non-EPP group had EPP in a non-MARS center and died postoperatively because of multiorgan failure.

Survival was defined from time to randomization, this means after the induction chemotherapy. The patients allocated to no-EPP had a better median and 1-year overall survival than those treated with EPP in the MARS trial and than those in a number of historical series.[24] Quality of life was also worse in the EPP-treated patients and remained so during the 2 years of follow-up.

The results of this feasibility trial have stirred the controversy even more than before, as the trial's sample size was insufficient for outcome as primary end point and could only conclude to the nonfeasibility of a phase 3 trial on this issue.[25,26] The enthusiasm to perform EPP declined in several institutions and a search for alternative surgical interventions revived.[27]

EPP VERSUS P/D

The observation that patients with MPM treated with lung-sparing surgical procedures did better than those proceeding to EPP stems from different historical series (Table 2).[14,28–38] A pooled series from three U.S. centers including 663 patients with stages I–IV MPM demonstrated essentially no survival differences, stage by stage, between P/D with a median survival of 16 months and EPP (12 months) with, however, higher local recurrence rate with P/D (65%) compared with EPP (33%). Operative mortality was 7% with EPP and 4% with P/D. This was despite the observation that the group undergoing P/D was negatively selected as considered to have a worse prognosis and to be no candidate for EPP.[14]

Lang-Lazdunski et al.[39] recently reported their prospective series of 36 patients treated with e-P/D and hyperthermic pleural lavage with povidone–iodine followed by chemotherapy and compared them with similar patients treated with EPP. Median overall survival of 23 months in e-P/D patients was significantly better than the 12.8 months for EPP. Patients with epitheloid histology had a longer survival than the nonepitheloid ones. The survival benefit was regardless of stage. The mortality rate for EPP was 4.5% and for e-P/D was nil. Morbidity of e-P/D included prolonged air leak, empyema, reaccumulation of pleural fluid, wound infection, and bronchopleural fistulas. When patients had disease progression after P/D, most of them were still able to receive further systemic therapy as opposed to patients having had EPP, who were often too unwell to receive any active treatment.

Finally, a retrospective analysis of the International Association for the Study of Lung Cancer Mesothelioma database of 3101 patients of 15 centers from four continents showed no difference in the median survival time between EPP and P/D but in stage I patients in whom EPP was shown to result in a substantial survival benefit (40 months) compared with 23 months for a P/D.[38] With the caveats of the selection bias inherent to retrospective series, whereby fitter patients undergo more aggressive treatment and thus seem to achieve superior outcomes, these data suggest furthermore that patients receiving more than one treatment modality (that is surgery plus chemotherapy or radiotherapy) had a significant better outcome.[40]

TABLE 2. Extrapleural Pleuropneumonectomy and Pleurectomy/Decortication in Malignant Pleural Mesothelioma

Investigator (year)	No. of patients with EPP	No. of patients with P/D	Chemotherapy	Other modalities	MST EPP (months)	MST P/D (months)
Martini (1976)[28]	2	NS	Adjuvant	± PORT	2	21
Branscheid (1991)[29]	76	82	Adjuvant	–	9.3	10.4
Allen (1994)[30]	40	56	Adjuvant	RTX	13.3	9.0
Pass (1997)[31]	39	39	NS	Photodynamic therapy, immunotherapy	9.5	14.5
Pass (1998)[32]	25	23	NS	Adjuvant immunochemotherapy	14.4	22
Rusch and Venkatraman (1999)[33]	115	59	± adjuvant	± PORT	18.5	18.5
Martin-Ucar (2007)[34]	45	12	(Neo)adjuvant	PORT	15	16
Flores (2008)[14]	385	278	Adjuvant	PORT	12	16
Lucraz (2010)[35]	49	34	Adjuvant	PORT	26	30
Lang-Lazdunski (2012)[36]	22	54	Neoadjuvant	Hyperthermic pleural lavage, PORT	12.8	23
Rena (2012)[37]	40	37	(Neo)adjuvant		20	25
Rusch et al. (2012)[38]	1190	299	(Neo)adjuvant	Various	NS	NS
p stage I	75	57			40	23
p stage II	229	77			23	20
p stage III	762	97			16	19
p stage IV	124	68			12	15

EPP, extrapleural pneumonectomy; IMRT, intensity-modulated radiotherapy; IORT, intraoperative radiotherapy; MST, mean survival time; NS, not stated; P/D, pleurectomy/decortication; PORT, postoperative radiotherapy; RTX, radiotherapy.

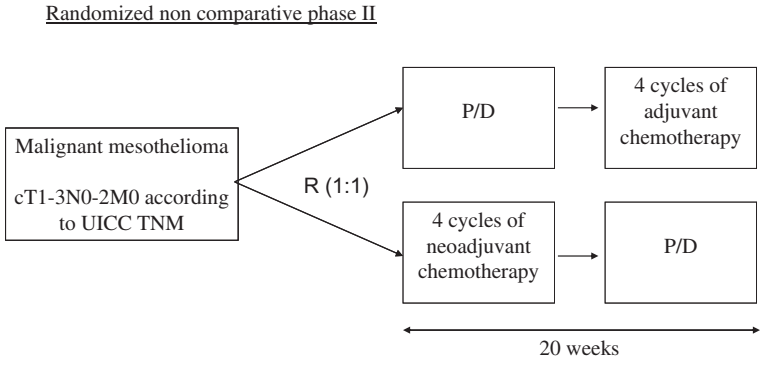

FIGURE 1. Design of European Organisation for Research and Treatment of Cancer 1205: a randomized noncomparative trial of P/D with (neo-)adjuvant chemotherapy. P/D, pleurectomy/decortication.

• P/D: pleurectomy / decortication
• chemotherapy will consist of pemetrexed (500 mg/m²) and cisplatin (80 mg/m²) given 3-weekly.
Arm A: 4 cycles of adjuvant chemotherapy started at 4 – 6 weeks postoperatively.
Arm B: 4 cycles of neoadjuvant chemotherapy will be administered. Patients without PD will proceed to surgery within 6 weeks of d1 of cycle 4 of chemotherapy.

NOVEL STRATEGIES – WHERE DO WE GO AFTER MARS?

Since P/D has been repeatedly associated with similar to better outcome than EPP, and EPP accompanied by perioperative chemotherapy and radiotherapy was better than EPP alone, the question arises whether P/D as part of a multimodality treatment further improves outcome (Table 2). The mechanism whereby P/D results in a better outcome than EPP remains unsolved. Some argue that the operative mortality, which is typically higher with EPP, is the cause. Others speculate that a maximal cytoreduction is not necessary because survival rates are determined by the time before the relapse of MPM. Comprehensibly, lung-sparing surgery can be responsible for better survival rates. P/D patients tend to recur more locally, and these relapses can be retreated either surgically or by radical radiotherapy, suggesting that the improved outcome of P/D might be related to this relapse pattern. However, the data of P/D as part of a multimodality treatment are mostly extracted from retrospective selected series spanning several decades, with different drugs, not analyzed according to the intention-to-treat principle and require prospective confirmation.

The UK investigators will investigate the role of extended P/D in a "MARS-2" trial wherein this surgical procedure will be added to standard induction chemotherapy and randomly compared with chemotherapy only.[41] The Lung Cancer Group of the European Organisation for Research and Treatment of Cancer will conduct a randomized phase 2 trial in patients with early-stage MPM randomizing between four cycles of neoadjuvant chemotherapy (cisplatin/pemetrexed) followed by P/D or P/D followed by four cycles of the same chemotherapy given in adjuvant setting (Fig. 1).[42] This study will evaluate whether immediate or deferred P/D in combination perioperative chemotherapy is feasible and safe. Primary end point is the rate of success being defined as any registered patient who has received four cycles of chemotherapy and has undergone P/D and is alive at 20 weeks after registration without evidence of progression, relapse, or toxicity higher than grade 3 according to the Common Toxicity Criteria. To power this study at 90% a sample size of 64 patients is necessary, 32 in each arm. It is hoped that both these trials will allow to clarify the role of P/D before embarking on the necessary phase 3 in which EPP and P/D are compared.

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