Long-Term Survival Analysis of Pleural Mesothelioma Patients Undergoing Surgery: Brief Report From a Tertiary Referral Centre

Riccardo Orlandi,[1] Giovanni Leuzzi,[2] Luigi Rolli,[2] Michele Ferrari,[2] Alessia Stanzi,[2] Camilla Valsecchi,[3] Ugo Pastorino[2]

Abstract

Objectives: to date, no consensus has been reached on the surgical gold-standard in pleural mesothelioma (PM). We retrospectively reviewed our experience as a tertiary referral centre, to compare short- and long-term survival of PM patients undergoing different types of surgery. **Methods:** in retrospective, observational, single-centre study, we analysed all the patients histologically diagnosed with PM undergoing surgical procedures with palliative or curative intent at IRCCS Istituto Nazionale dei Tumori of Milan, Italy, from January 2003 to December 2020. The primary study endpoint was 10-year overall survival (OS) in three different types of resections: extra-pleural-pneumonectomy (EPP), pleurectomy/decortication (P/D), partial-pleurectomy/pleural-biopsy (PP/B). Secondary endpoints were postoperative hospital stay and postoperative 30-day and 90-day mortality rates. The survival function was estimated using Kaplan-Meier, and the Log-rank test was used for testing differences. Univariable and Multivariable Cox regression models were implemented to estimate Hazard Ratio (HR) for all variables of interest. **Results:** 243 consecutive patients were enrolled, EPP was performed in 49 (20.2%), P/D in 58 (23.8%), PP/B in 136 (56.0%) patients. The median follow-up time was 19.8 months. 10-year OS was significantly better for P/D group (16%, Log-Rank test $p<0.0001$) compared to PP/B (1.8%) and EPP (0%). No statistically significant differences were found among the 3 surgical groups in 30- and 90-day mortality rates. At multivariable analysis, gender (male, HR=1.58), type of resection (P/D, HR=0.55) and surgery date (recent years, HR=0.61) were found to be independent prognostic factors for OS. **Conclusions:** in PM, lung-sparing curative approach (e.g. P/D) should be preferred in highly selected patients and in highly experienced centres, whenever appropriate. Anyway, when P/D is not indicated, adopting palliative/conservative management (e.g. PP/B) could ensure comparable results as extremely aggressive surgeries (e.g. EPP). The aim of surgery in PM should not be reaching complete resection, but rather accomplishing significant resection allowing to complete the multimodality treatment in highly selected patients in experienced centers.

Clinical Lung Cancer, Vol. 25, No. 1, e5–e10 © 2023 The Author(s). Published by Elsevier Inc.

Keywords: Pleural mesothelioma, Thoracic surgery, Pleurectomy/decortication, Extrapleural pneumonectomy, Surgical oncology, Pleura

Introduction

Although being one of the few cancers with well-known etiopathogenetic factor, pleural mesothelioma (PM) is still among the deadliest neoplastic diseases worldwide, hardly reaching 10 months overall survival if untreated.[1,2] Its best treatment option has been a matter of debate for the last 40 years. Nowadays the multimodality approach, comprising surgery, chemotherapy, and radiotherapy, still fails in achieving satisfying results. Further-

Abbreviations: CI, Confidential interval; EPP, Extrapleural Pneumonectomy; ECOG, Eastern Cooperative Oncology Group; HR, Hazard Ratio; IASLC, International Association for the Study of Lung Cancer; IMIG, International Mesothelioma Interest Group; ISTAT, Italian national Statistical Institute; IRCCS, Scientific Institute for Research, Hospitalization and Healthcare; LOS, Length of Stay; OS, Overall Survival; PM, Pleural Mesothelioma; P/D, Pleurectomy/Decortication; PP/B, partial pleurectomy/pleural biopsy; PSS, Performance Status Scale; RCT, Randomized Controlled Trial; SEER, Surveillance, Epidemiology, and End Results; VATS, Video-assisted Thoracic Surgery.

Written informed consent to the procedure and the use of clinical data for scientific purposes were obtained from all patients before the operation. The study was conducted in accordance with the Declaration of Helsinki. Ethics Committee Approval was deemed unnecessary by local laws. We present the following article in accordance with the STROBE reporting checklist.

[1]Department of Thoracic Surgery, University of Milan, Milan, Italy
[2]Division of Thoracic Surgery, IRCCS Istituto Nazionale dei Tumori Foundation, Milan, Italy
[3]Division of Statistics, IRCCS Istituto Nazionale dei Tumori Foundation, Milan, Italy

1525-7304/$ - see front matter
https://doi.org/10.1016/j.cllc.2023.10.010

Submitted: Aug 20, 2023; Revised: Oct 18, 2023; Accepted: Oct 22, 2023; Epub: 24 October 2023

Address for correspondence: Riccardo Orlandi, MD, Department of Thoracic Surgery, University of Milan, Via Festa del Perdono 7, Milan, 20122 Italy. Tel.: +39 0399050359.
E-mail contact: riccardo.orlandi@unimi.it

more, it offers the most significant advantages only in highly selected patients, often impairing their quality of life. In the setting of available surgical procedures, pleurectomy/decortication (P/D), extrapleural pneumonectomy (EPP), partial pleurectomy (PP) and pleural biopsy (PB) represent the main options, considering the latter two palliative techniques, while the former two curative approaches. To date, no consensus has been yet reached regarding the surgical gold-standard, since each procedure has its pros and cons. In this scenario, while eagerly waiting for publication of new prospective RCTs, we retrospectively reviewed our nearly 20-years database as a tertiary referral centre,[3] comparing short- and long-term survivals of PM patients undergoing surgery, either with palliative or curative intent.

Materials and Methods

We designed a retrospective, observational, single-center study, analyzing all the patients histologically diagnosed with PM undergoing surgical procedures with palliative or curative intent at the IRCCS Istituto Nazionale dei Tumori of Milan, Italy, from January 2003 to December 2020. All the histological diagnoses of PM were reviewed by expert panel. We retrospectively retrieved all data available on demographic information, surgical details, postoperative outcomes, and long-term follow-up of enrolled patients. The follow-up time was calculated from the date of surgery to the date of death or last follow-up. The primary study endpoint was 10-year overall survival (OS) in 3 different types of resections: EPP, P/D, partial pleurectomy/pleural biopsy (PP/B). Secondary endpoints were postoperative hospital stay and postoperative 30-day and 90-day mortality rates. Each surgical procedure was classified in accordance with the latest recommendations for uniform definitions from the International Association for the Study of Lung Cancer (IASLC) International Staging Committee and the International Mesothelioma Interest Group (IMIG).[4] P/D consisted of parietal pleurectomy including chest wall, diaphragmatic and mediastinal pleura, together with decortication of visceral pleura, eventually associated with excision of diaphragm and/or pericardium. Patients with both Eastern Cooperative Oncology Group (ECOG) Performance Status Scale (PSS) < 2 and clinical burden of disease limited to visceral and/or parietal pleura (resectable disease) were offered this procedure. EPP consisted of excision of lung, ipsilateral hemi-diaphragm, and pericardium en-bloc with parietal pleura. Patients with ECOG-PSS < 2 and disease involving the lung (still resectable disease) underwent EPP. PP/B was performed through mini-thoracotomy or video-assisted thoracic surgery (VATS) approach and consisted of partial excision of parietal and/or visceral pleura, eventually associated with talc poudrage. Patients with or ECOG-PSS of 2 to 3 or advanced/metastatic disease (unresectable disease), largely involving lung, or local lymph nodes or with distant metastasis, were offered this procedure. P/D and EPP were aimed at reaching macroscopic complete resection, whereas PP/B was for diagnostic or palliative purposes.

Written informed consent to the procedure and the use of clinical data for scientific purposes were obtained from all patients before the operation. The study was conducted in accordance with the Declaration of Helsinki.[5] The vital status and date of death were obtained through the Istituto Nazionale di Statistica (ISTAT, SIATEL 2.0 platform), which is updated within 3 months from death. Data were expressed as mean (standard deviation), median (interquartile range) and percentage, whenever appropriate. Proportions were compared by chi-square test or Fisher's exact test, as appropriate. For continuous data, Wilcoxon-Mann-Whitney test was applied. The survival function was estimated using Kaplan-Meier, and Log-rank test was used for testing differences. Univariable and Multivariable Cox regression models were implemented to estimate Hazard Ratio (HR) and 95% Confidence Interval (CI) for all variables of interest. *P*-value of less than .05 was considered statistically significant. All analyses were performed using Statistical Analysis System Software (Release SAS:9.04; SAS Institute, Cary, North Carolina, USA).

Results

A total of 243 consecutive patients were enrolled in the study. EPP was performed in 49 (20.2%), P/D in 58 (23.8%), PP/B in 136 (56.0%) patients, respectively. Patients' characteristics according to type of surgery are summarized in Table 1. 34.2% patients were female, without statistically significant differences between groups (26.5% vs. 39.7% vs. 34.6%, respectively, *P* value .36). The median age was 65, showing significant trend towards younger age in those undergoing EPP compared to those undergoing P/D or PP/B (61.1 vs. 65.9 vs. 68.7 years, respectively, *P* value $<.0001$). The surgical approach has significantly changed over the years (*P* value $<.0001$) due to substantial withdrawal of EPP, whereas the numbers of P/D and PP/B have basically unchanged. The median postoperative length of stay (LOS) was 6 days, which significantly increased in line with the increasing complexity of type of resection (*P* value $<.0001$): 5 days for PP/B, 8 days for P/D, and 13 days for EPP, respectively. Although 30 and 90-day mortality rates were higher for EPP patients (6.1% and 10.2% vs. 0% and 1.7% vs. 0.7% and 5.1%, respectively for EPP, P/D and PP/B), no significant differences were found among the 3 surgical groups as well as in the 3 different period. The median follow-up time was 19.8 months. Globally, 218 (89.7%) patients died during the study period. Median survival in the whole population was 19.9 months: 14.5, 28.2, and 18.6 months for EPP, P/D and PP/B, respectively. OS at 10 years was significantly better for P/D group compared to PP/B and EPP (16% vs. 1.8% vs. 0%, respectively, *P* value $<.0001$) (Figure 1). The univariable Cox regression model (Table 2) showed that male gender was associated with shorter OS (HR = 1.71 [95% CI: 1.28-2.29]), when compared to female one; whereas P/D and surgery performed in more recent years were positively associated with longer OS (HR = 0.40 [95% CI: 0.27-0.61), and HR = 0.54 [95% CI: 0.38-0.77], respectively). At multivariable analysis, gender, type of resection and surgery date were found to be independent prognostic factors for OS: males showed shorter OS than females (HR = 1.58 [CI 95%: 1.17-2.14]), patients undergoing P/D experienced better OS compared to those undergoing EPP (HR = 0.55 [CI 95%: 0.35-0.88]) and individuals operated in more recent years had better OS compared to those operated between 2003 and 2008 (HR = 0.61 [CI 95%: 0.41-0.90]).

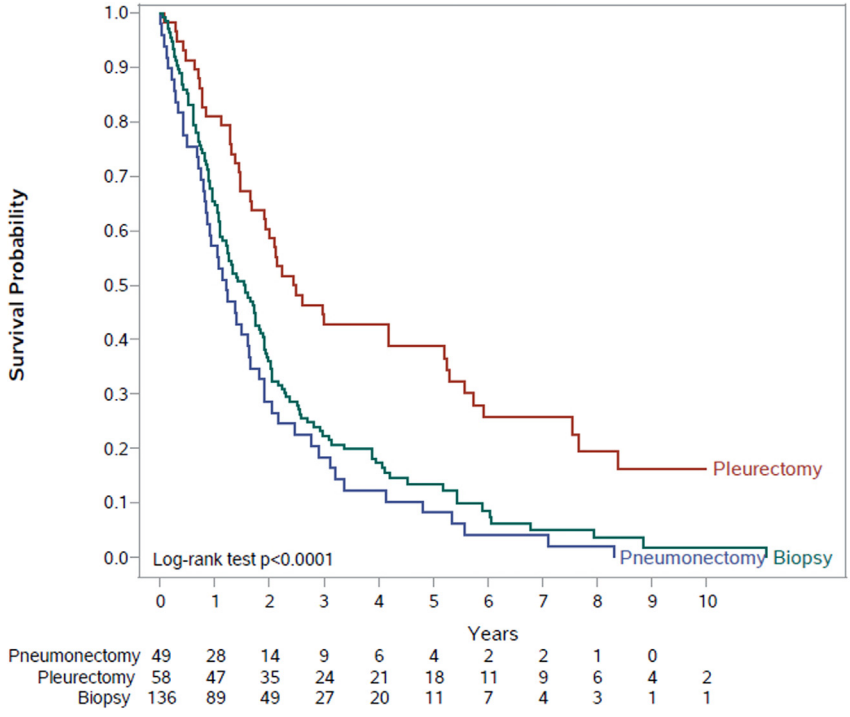
Discussion

PM is still a largely unknown disease, with well-known etiopathogenesis but with lack of in-depth knowledge of genetic and molec-

Table 1 Patients' Characteristics According to Type of Surgery

	Total N = 243	Pneumonectomy N = 49	Pleurectomy N = 58	Biopsy N = 136	*P* Value
Age, median (IQR)	65.0 (16.3)	61.1 (8.7)	65.9 (13.7)	68.7 (15.7)	<.0001
Sex, n (%)					
Female	83 (34.2)	13 (26.5)	23 (39.7)	47 (34.6)	.3576
Male	160 (65.8)	36 (73.5)	35 (60.3)	89 (65.4)	
Surgery date, n (%)					
2003-2008	104 (42.8)	36 (73.5)	15 (25.9)	53 (39.0)	<.0001
2009-2014	75 (30.9)	13 (26.5)	24 (42.4)	38 (27.9)	
2015-2020	64 (26.3)	0	19 (32.8)	45 (33.1)	
Postoperative day, median (IQR)	6 (6.0)	13 (8.0)	8 (6.0)	5 (2.0)	<.0001
Mortality, n (%)					
30-day	4 (1.6)	3 (6.1)	0	1 (0.7)	.0541
90-day	13 (5.3)	5 (10.2)	1 (1.7)	7 (5.1)	.1868

Figure 1 Ten-year overall survival according to the type of resection.



ular factors, which ultimately could explain its dismal prognosis. A SEER study[6] including more than 14,000 patients reported surgery (intended as any resection from partial to radical) as an independent prognostic factor for better survival, suggesting that multimodality treatment, when based on surgery, can benefit PM patients. The specific role of surgery is debated and even more controversial is the optimal surgical approach to adopt. Literature is confounding and studies are heterogeneous, since most have several limitations, mainly based on small sample size and retrospective analysis, with limited long-term follow-up. We have presented our nearly 20-year experience in surgically handling PM, which has allowed us to gain a very long-term follow-up, that is a rarity compared to currently published literature. According to the applied surgical technique, we have recorded different 10-year OS: 16%, 1.8%, 0%, in P/D, PP/B, and EPP groups, respectively. This difference was statistically significant, and it could be clinically relevant. Actually, patients undergoing palliative PP/B may not experience shorter survival than those undergoing aggressive EPP, and both might have worse prognosis than P/D. On the contrary, the 3 procedures seem to have low differences in 30-day and 90-day mortality rates, without any statistical

Table 2 Univariable and Multivariable Cox Regression Model

	HR (95% CI)	
Variable	**Univariable Analysis**	**Multivariable Analysis**
Age		
<65	1 (Reference)	1 (Reference)
>=65	0.97 (0.74-1.26)	1.00 (0.99-1.02)
Sex		
Female	1 (Reference)	1 (Reference)
Male	1.71 (1.28-2.29)	1.58 (1.17-2.14)
Type of resection		
Pneumonectomy	1 (Reference)	1 (Reference)
Pleurectomy	0.40 (0.27-0.61)	0.55 (0.35-0.88)
Biopsy	0.79 (0.57-1.11)	0.96 (0.67-1.39)
Surgery date		
2003-2008	1 (Reference)	1 (Reference)
2009-2014	0.72 (0.53-0.99)	0.75 (0.54-1.05)
2015-2020	0.54 (0.38-0.77)	0.61 (0.41-0.90)

significance. Noteworthy, 10-year OS of 16% after P/D is an interesting result, which is going to be further explored and analyzed, to find out prognostic factors affecting this population, since on average in literature such a survival is reported on 3 to 5 years only.

At multivariable analysis, male gender was found to be a prognostic independent factor for shorter survival, in line with the findings from other studies.[6,7] Similarly, the date of surgery has emerged as an independent prognostic factor for survival, with the more recent years ensuring a longer survival, in accordance with results reported in literature,[6] thanks to developments in medical oncology and advances in surgical techniques. Finally, the type of surgical approach has been found out to be an independent prognostic factor, with P/D providing the best OS. EPP has been historically considered the treatment of choice in PM, prompted by the paradigm of reaching R0 resection as the only way to cure the disease. At our tertiary center, during the last decade, there has been a substantial change in the preferred surgical approach, shifting from EPP towards P/D, in accordance with the trend widespread throughout the world,[7] partly driven by personal experience but mainly based on MARS Trial,[8] which has undermined the role of EPP in PM. Our results seem to be in line with those from MARS study, as testified by similar OS reached by EPP and PP/B patients, with lower postoperative mortality and LOS for the latter's. Several centers progressively abandoned this surgical approach for a more conservative approach. P/D is a promising surgical technique, aiming at best debulking, which is yet burdened by lack of standardization and homogeneity. Five-year OS after EPP is reported to range from 0 to 24%, with postoperative mortality rate of 0% to 12% and morbidity rate of 22% to 82%.[9] On the other hand, P/D is reported to have 5-year OS of 0% to 35%, with average postoperative mortality rate of 4%.[10] Recent metanalysis[11,12] comparing P/D with EPP concluded that the former is associated with enhanced outcomes regarding 30-day mortality, median overall survival, and complications, therefore suggesting that P/D should be the preferred approach whenever possible. The reason why P/D should provide better outcomes than EPP is still a matter of debate. Some authors deem that it is related to different postoperative mortality, which is higher in EPP, others think that aiming at complete sterilization of the thorax is useless (and impossible for PM), and the real benefit could be related to time free from recurrence gained. Indeed, even if P/D patients are more prone to locally relapse, recurrences could be retreated either surgically or through radiotherapy. A recent Italian multicenter study[13] has highlighted a different OS between P/D (extended or not) and partial pleurectomy, defining the former as a valid operative option with good survival and acceptable postoperative mortality rates, and the latter as a palliative procedure without impact on survival. In this setting, the MesoVATS trial[14] highlighted that talc-pleurodesis, gained either through slurry or poudrage, is preferable to partial pleurectomy through VATS, leading to less complications, shorter hospital stay and lower costs without differences in OS. That's the reason why we have merged patients undergoing PP and those undergoing PB in the same group. A risk-benefit equation has been established in PM[15]: gain in survival time = (time gained by cytoreduction + time gained by lung reexpansion) – (time lost by operative mortality + time lost by long-term mortality of surgical procedure + time lost from accelerated death after recurrence). This equation could potentially explain even our results, since the EPP is burdened by high loss of time in operative and long-term mortality as well as death after recurrence without lung re-expansion; similarly, PP/B cannot provide valuable time by cytoreduction but can be favorable in all the other fields, finally equalizing the EPP. On the contrary, P/D seems currently to be the most balanced procedure, ensuring time in lung re-expansion and lowering perioperative and long-term postoperative mortality. Whether P/D is going to be the key surgical approach of the future, as EPP has been in the past, is still to be fully explored. Recently, findings from the UK multicenter RCT MARS-2 Trial,[16] which have been presented at the latest World Conference of Lung Cancer 2023 in

Singapore,[17] even questioned its role in the management of PM, showing higher risk of death, more serious complications, poorer quality of life and higher costs for patients undergoing (extended) P/D after induction chemotherapy compared to those undergoing chemotherapy alone. These results seem to be practice-changing, but, while waiting for the definitive publication of the Trial, from the available data, we can notice that patients enrolled in the "surgical arm" experienced less than 20% 5-year OS, which is about half of that experienced by our patients, maybe due to different selection criteria. This finding suggests that P/D may still represent a valid therapeutic option in the next future in highly selected patient and in highly experienced centers, within a multimodality approach, at least until highly effective chemotherapeutics will be discovered.

Besides its retrospective monocentric nature and the relatively small sample size enrolled, this study presents other significant limitations: lack of information about comorbidity data, stage, histology, and adjuvant/neoadjuvant treatment. In order to keep the central message as clear as possible, providing a cross-sectional real-world scenario of our tertiary referral center without wandering in speculative elements, we decided not to include such information in this brief report. Furthermore, the long span of study period may have introduced confounding elements: different surgeons' techniques as well as progressive evolution of medical treatment, such as improvement of immunotherapy, might have influenced the reported outcomes. These limitations, which will be soon addressed in further in-depth analysis, prevent us from drawing generalizable conclusions at the moment. Nonetheless, this is one of the studies with the longest postoperative follow-up period and accurate assessment of deaths through the ISTAT national platform, ensuring a unique 10-year OS, which is worth to be shared with the scientific community.

In conclusion, currently PM is still a challenging disease with awful prognosis. Until proven otherwise, multimodality treatment is the therapeutic approach of choice in PM, when feasible. The evolution of medical therapy has not changed the natural history of the disease yet, and surgery may still have a role in its treatment. Based on our results, lung-sparing approach (eg, P/D) should be preferred in highly selected patients compared to other surgical options, whenever appropriate. Anyway, when P/D is not indicated, adopting a palliative/conservative surgical management (eg, PP/B) could ensure comparable long-term results as extremely aggressive surgeries (eg, EPP), which have been demonstrated to be uncapable of reaching radicality at the cost of an unbearable increase of morbidity and mortality risks. The aim of surgery in resectable PM should not be longer reaching a macroscopic or microscopic complete resection, but rather accomplishing a significant resection allowing to complete the multimodality treatment in highly selected patients in experienced centers. Further studies are needed to better address this interesting issue.

Clinical Practice Points

- The benefit of surgical treatment in Pleural Mesothelioma is still debated and even more questioned is the surgical gold standard, due to the lack of studies with long-lasting follow-up.
- Lung-sparing approach (e.g. pleurectomy/decortication, P/D) should be preferred in highly selected patients compared to other surgical options, whenever appropriate, ensuring the best 10-year overall survival; anyway, when P/D is not indicated, adopting a palliative/conservative surgical management (e.g. partial pleurectomy/pleural biopsy) could ensure comparable long-term results as extremely aggressive surgeries (e.g. extra-pleural pneumonectomy).
- Curative surgery for Pleural Mesothelioma should be performed only in highly selected patients in highly experienced centers, preferably through lung-sparing approach.

Disclosure

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Acknowledgments

The authors did not receive support from any organization for the submitted work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2023.10.010.

References

1. Bovolato P, Casadio C, Billè A, et al. Does surgery improve survival of patients with malignant pleural mesothelioma?: a multicenter retrospective analysis of 1365 consecutive patients. *J Thorac Oncol*. 2014;9(3):390–396.
2. Leuzzi G, Rea F, Spaggiari L, et al. Prognostic score of long-term survival after surgery for malignant pleural mesothelioma: a multicenter analysis. *Ann Thorac Surg*. 2015;100(3):890–897. doi:10.1016/j.athoracsur.2015.04.087.
3. Flores RM, Zakowski M, Venkatraman E, et al. Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center. *J Thorac Oncol*. 2007;2(10):957–965. doi:10.1097/JTO.0b013e31815608d9.
4. Rice D, Rusch V, Pass H, et al. Recommendations for uniform definitions of surgical techniques for malignant pleural mesothelioma: a consensus report of the international association for the study of lung cancer international staging committee and the international mesothelioma interest group. *J Thorac Oncol*. 2011;6(8):1304–1312. doi:10.1097/JTO.0b013e3182208e3f.
5. World Medical AssociationWorld Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191–2194. doi:10.1001/jama.2013.281053.
6. Taioli E, Wolf AS, Camacho-Rivera M, et al. Determinants of survival in malignant pleural mesothelioma: a surveillance, epidemiology, and end results (SEER) study of 14,228 patients. *PLoS One*. 2015;10(12):e0145039. doi:10.1371/journal.pone.0145039.
7. Batirel HF, Metintas M, Caglar HB, et al. Adoption of pleurectomy and decortication for malignant mesothelioma leads to similar survival as extrapleural pneumonectomy. *J Thorac Cardiovasc Surg*. 2016;151(2):478–484. doi:10.1016/j.jtcvs.2015.09.121.
8. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the mesothelioma and radical surgery (MARS) randomised feasibility study. *Lancet Oncol*. 2011;12(8):763–772. doi:10.1016/S1470-2045(11)70149-8.
9. Cao CQ, Yan TD, Bannon PG, McCaughan BC. A systematic review of extrapleural pneumonectomy for malignant pleural mesothelioma. *J Thorac Oncol*. 2010;5(10):1692–1703. doi:10.1097/JTO.0b013e3181ed0489.
10. Teh E, Fiorentino F, Tan C, Treasure T. A systematic review of lung-sparing extirpative surgery for pleural mesothelioma. *J R Soc Med*. 2011;104(2):69–80. doi:10.1258/jrsm.2010.100345.
11. Taioli E, Wolf AS, Flores RM. Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. *Ann Thorac Surg*. 2015;99(2):472–480. doi:10.1016/j.athoracsur.2014.09.056.
12. Magouliotis DE, Tasiopoulou VS, Athanassiadi K. Updated meta-analysis of survival after extrapleural pneumonectomy versus pleurectomy/decortication in mesothelioma. *Gen Thorac Cardiovasc Surg*. 2019;67(3):312–320. doi:10.1007/s11748-018-1027-6.
13. Marulli G, Breda C, Fontana P, et al. Pleurectomy-decortication in malignant pleural mesothelioma: are different surgical techniques associated with different outcomes? Results from a multicentre study. *Eur J Cardiothorac Surg*. 2017;52(1):63–69. doi:10.1093/ejcts/ezx079.

14. Rintoul RC, Ritchie AJ, Edwards JG, et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. *Lancet*. 2014;384(9948):1118–1127. doi:10.1016/S0140-6736(14)60418-9.
15. Flores RM. The mesothelioma surgery shift. *J Thorac Cardiovasc Surg*. 2016;151(2):485–486. doi:10.1016/j.jtcvs.2015.10.054.
16. Lim E, Darlison L, Edwards J, et al. Mesothelioma and radical surgery 2 (MARS 2): protocol for a multicentre randomised trial comparing (extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma. *BMJ Open*. 2020;10(9):e038892. doi:10.1136/bmjopen-2020-038892.
17. Lim E, Waller D, Lau K, et al. *Plenary Session 3: Presidential Symposium PL03.10, Late-Breaking Abstract WCLC2023*. MARS 2: a multicentre randomised trial comparing (extended) pleurectomy decortication versus no radical surgery for mesothelioma; 2023.