Review Article

Appropriate treatment approaches and prognosis of pleural mesothelioma

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Abstract: The current standard-of-care treatment of malignant pleural mesothelioma (MPM) is generally accepted as systemic therapy alone. Surgery could be part of a multimodal treatment plan since it is the only modality that could render a patient without the disease. Selecting patients fit for surgery, determining the optimal operation and the additional treatments have not yet been established due to the severe variability of neoplasm itself related to the surgical techniques' variability. Even though there is an MPM staging system, the results of surgery remain to be strongly affected by other prognosticators (e.g., subtype of histology, not taken by the contemporary staging systems). Consequently, there is not a common denominator that permits careful evaluation between surgical cohorts and the definitive creation of beneficial operational approach.

Keywords: Malignant pleural mesothelioma; treatment; management; lung cancer

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Introduction

The current standard-of-care treatment of malignant pleural mesothelioma (MPM) is generally accepted as systemic therapy alone. Surgery could be part of a multimodal treatment plan since it is the only modality that could render a patient without the disease. Selecting patients fit for surgery, determining the optimal operation, and the additional treatments have not yet been established due to the severe variability of cancer itself related with the variability of the surgical techniques (1).

The complete macroscopic resection is the objective of surgical treatment. There are two attempts to attempt a radical surgery, sparing the lung or sacrificing the lung. The disadvantages of extrapleural pneumonectomy (EPP) are the quality-of-life and safety issues related to the pneumonectomy and the complications due to the prosthetic reconstruction of the pericardium and diaphragm. The safety and quality-of-life issues related to preserving both lungs, including decreased or eliminated need for prosthetic repairs are the advantages of lung-sparing surgery. The disadvantages compared to EPP include a longer time to operate, approximately leaving behindhand a higher burden of microscopic disease under the additional lung surface area, the issue of managing postoperative air leaks, the inherent variability of qualitative assessment of resection completeness, challenges to using adjuvant radiation, obstinate misunderstanding in classification, and no standardisation in method (1).

Technical definition

The confusion of MPM surgical terminology was standardised by the International Association for Study of Lung Cancer (IASLC) in 2011. EPP was well-defined as *en bloc* resection of the parietal and visceral pleura with the ipsilateral lung,

Table 1 Definitions of surgical procedures for the malignant pleural mesothelioma. Adapted from IASLC (2)

Surgical procedure	Definition
Extrapleural pneumonectomy	En bloc resection of the visceral and parietal pleura, lung, ipsilateral hemidiaphragm, and pericardium
Pleurectomy/decortication	Resection of the parietal and visceral pleura, to eliminate all gross tumours, without removing pericardium and diaphragm
Extended pleurectomy/decortication	Pleurectomy/decortication with the resection of ipsilateral pericardium and diaphragm
Partial pleurectomy	Limited removal of the parietal and/or visceral pleura for palliative or diagnostic intentions

pericardium, and diaphragm. Extended pleurectomy/decortication (P/D) was defined as parietal and visceral pleurectomy to eliminate all overall tumour as well as the resection of the pericardium and/or diaphragm (*Table 1*) (3).

Whilst surgery scarifying the lung has been unambiguously characterized and extremely standardised as EPP, attempts to standardise the procedure for lung-sparing have been restricted by the paucity of randomised trials. In the lack of data, various patterns of extensive surgery completed by P/D have in recent times emerged. At this time, there is no consensus on the ideal multimodality approach to resectable MPM. Various intraoperative treatments under investigation include hyperthermic povidone-iodine lavage, hyperthermic chemotherapy lavage, fibrin associated cisplatin, and photodynamic therapy (4).

Objectives of surgical treatment

Surgery [open or video-assisted thoracoscopic surgery (VATS) pleural biopsies] could help to achieve an MPM correct diagnosis or to palliate (VATS pleurectomy, VATS talc pleurodesis, indwelling pleural drainage placement) symptoms caused by malignant pleural effusions. Every time aggressive surgery is scheduled, it aims to remove all visible disease, increasing survival by decreasing the intrathoracic tumour burden to microscopic levels. Ideally, all MPM patients should be operated by thoracic surgeons with recognised broad experience in MPM management, regularly related to radiation and medical oncology involved in MPM clinical trials (5).

Prognostic factors and patient selection

This risk factors substantially impact on survival in MPM undertaking surgery:

- Tumour status (most evident in curative intent surgery);
- Nodal status;
- Tumour histology (epithelial with better outcomes);
- Gender and age;
- Curative intent.

Since the impact of surgery as an extension of overall survival is needed but lacking, the overall survival without substantial morbidity negative influence on the quality-of-life. Institutional and practice bias will have a considerable impact on surgical approaches. Therefore, the selection in the accrual and recording of small multimodality trials makes it challenging to include neoadjuvant/adjuvant treatments (6).

Preoperative evaluation

MPM patients judged for EPP are staged with positron emission tomography/computed tomography (PET/CT) to evaluate lymph nodes or metastases to other organs. The avidity of PET of the pleural tumour correlates with survival, with higher avidity correlated with reduced survival. Enlarged and/or PET-positive mediastinal lymph nodes are assessed with cervical mediastinoscopy or endobronchial ultrasonography. Even though some centres perform in all patients routine staging mediastinoscopy, others have abandoned since the inconstant pleural nodal drainage with a random pattern of lymph nodes metastases and the absence of sensitivity of cervical mediastinoscopy for discovering extrapleural nodal spread. Chest magnetic resonance is frequently accomplished to assess for thin transdiaphragmatic, chest wall, or transmediastinal invasion of the tumour. The presence of a transdiaphragmatic extension of the tumour and/or ascites deserves additional evaluation (e.g., laparoscopy for staging since intraabdominal tumour precludes surgery). The residual preoperative evaluation should determine the capability to tolerate EPP. Spirometry and diffusion lung capacity should be completed. Quantitative ventilation/perfusion scan is usually performed to evaluate perfusion to the affected lung. The product of

the forced expiratory volume in 1-second and the proportion of perfusion to the contralateral lung is the predicted postoperative forced expiratory volume in 1-second. A stress test (detection of coronary artery disease with inducible myocardial ischemia) and an echocardiogram (Doppler of pulmonary artery pressure) should also be completed (7).

Surgical technique

Extrapleural pneumonectomy

EPP was continuously achieved through double lateral thoracotomy (first access through IV–V intercostal space, other access through VII–VIII intercostal space) with *en bloc* excision of the parietal pleura with the whole lung, ipsilateral pericardium and hemidiaphragm. The diaphragm was rebuilt with a synthetic dual mesh or with bovine pericardium placed on the resected diaphragm. The pericardium was recreated both on the left sides and on the right side to avoid cardiac torsion using a bovine pericardium or synthetic mesh. Lymph nodes dissection should always be done. Surgery was continually done within four weeks after the last cycle of induction chemotherapy (8).

Pleurectomy/decortication

P/D comprises two parts. The first half, from the thoracotomy to the end of the extrapleural dissection, is like EPP. Visceral pleurectomy is typically started at the lateral segment of the lower lobe (a broad flat plane). First, a 5 to 10 cm long incision in the visceral pleura using a blade or scissors was made. The visceral pleura is peeled off from the parenchyma. Sometimes, the parietal pleura is naturally dissected. Then, very soft blunt dissection using swabs or dry gauze is recommended. Dissection of the interlobar vessels is generally straightforward. Dissection at the apex and base is often tricky, requiring sharp dissection. In minimal resection of the pericardium and diaphragm, the direct suture is desirable. Else, the pericardium is reconstructed with a 0.1 mm Gore-Tex patch. The diaphragm is restored with a 2 mm Gore-Tex patch. Air leaks are unavoidable in P/D. Massive air leaks from detectable airways should be stitched (9).

Comments

The surgeon in the diagnosis and palliation of MPM have a prominent role. In properly carefully chosen patients with the appropriate risk profile, as part of a multimodality concept, surgical resection (P/D or EPP), should be offered only if performed in low mortality/high-volume centres (10). Nevertheless, current literature favours P/D to EPP since P/D is a procedure with smaller mortality and morbidity. Lung preservation should be achieved whenever possible. The Clinical Practice Guidelines of the European Society of Medical Oncology (ESMO) on MPM do not encourage a detailed procedure to implement a complete macroscopic resection (11). The National Comprehensive Cancer Network (NCCN) guidelines indicate P/D safer than EPP in early-stage disease with favourable histology but do not achieve on which procedure is oncologically enhanced because of the lack of adequately intended well-performed randomised controlled trials (12).

Nonetheless, the decision to do EPP or P/D should not be made until surgical exploration (13). Literature accounts yield evidence that the achievement of EPP in skilled referral centres, as a part of multimodality treatment, depends on a suitable patients selection with appropriate variables and technically favourable settings to decrease the typically high perioperative mortality and morbidity and recover the overall survival (14). Consequently, a P/D should be evaluated to undergo EPP if, during surgery, an extensive lung infiltration was discovered. The patient should be informed about EPP, not only during informed consent discussion, and preoperative functional assessments must be performed (15,16).

Perioperative management

EPP anaesthesiologist preparation involves the positioning of monitors, routine lines, and an epidural catheter. Large-bore intravenous access (including a central line) and an arterial line is recommended owing to rapid hemodynamic modifications. A Swan-Ganz catheter is positioned if there is any concern regarding pulmonary hypertension. To avoid pneumothorax on the ventilated lung, central lines should be placed on the operative side. A double-lumen endotracheal tube is preferred; the latter of the bronchial blocker should be pulled back before the bronchus division. Lastly, to help in distinguishing the oesophagus intraoperatively and to decompress the stomach postoperatively, a nasogastric tube is inserted (17).

Conclusions

Progress in the surgical treatment of MPM has been

thwarted by:

- Variability in the form of operations or the reportage of operations;
- Variability in the surgical treatments;
- Variability in the recurrence treatment;
- Intrinsic variability of cancer.

Even though there is a brand new, improved MPM staging system, the results of surgery for MPM is strongly influenced by other prognosticators not taken by the current staging system (such as subtype of histology). Consequently, there is at this time no possibilities to determine a common denominator that permits laborious evaluation between surgical series and ultimate establishing which surgical approach and adjuvants are advantageous and in which sequences/circumstances used or combined.

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References

1. Friedberg JS, Culligan MJ, Tsao AS, et al. A Proposed System Toward Standardizing Surgical-Based Treatments for Malignant Pleural Mesothelioma, From the Joint National Cancer Institute-International Association for the Study of Lung Cancer-Mesothelioma Applied Research Foundation Taskforce. J Thorac Oncol 2019;14:1343-53.
2. 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;6:1304-12.
3. Batirel HF. Extrapleural pneumonectomy (EPP) vs. pleurectomy decortication (P/D). Ann Transl Med 2017;5(:232.
4. Tsao AS, Lindwasser OW, Adjei AA, et al. Current and Future Management of Malignant Mesothelioma: A Consensus Report from the National Cancer Institute Thoracic Malignancy Steering Committee, International Association for the Study of Lung Cancer, and Mesothelioma Applied Research Foundation. J Thorac Oncol 2018;13:1655-67.
5. Filosso PL, Guerrera F, Lausi PO, et al. Pleurectomy/decortication versus extrapleural pneumonectomy: a critical choice. J Thorac Dis 2018;10:S390-4.
6. Azzouqa AG, Stevenson JP. The evolution of the diminishing role of extrapleural pneumonectomy in the surgical management of malignant pleural mesothelioma. Onco Targets Ther 2016;9:7247-52.
7. Schwartz RM, Lieberman-Cribbin W, Wolf A, et al. Systematic review of quality of life following pleurectomy decortication and extrapleural pneumonectomy for malignant pleural mesothelioma. BMC Cancer 2018;18:1188.
8. Casiraghi M, Maisonneuve P, Brambilla D, et al. Induction chemotherapy, extrapleural pneumonectomy and adjuvant radiotherapy for malignant pleural mesothelioma. Eur J Cardiothorac Surg 2017;52:975-81.
9. Hashimoto M, Hasegawa S. Surgical technique of

pleurectomy/decortication. Shanghai Chest 2018;2:44.
10. Opitz I, Weder W. Pleural mesothelioma: is the surgeon still there? Ann Oncol 2018;29:1710-7.
11. Baas P, Fennell D, Kerr KM, et al. Malignant pleural mesothelioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26:v31-9.
12. Ettinger DS, Wood DE, Akerley W, et al. NCCN Guidelines Insights: Malignant Pleural Mesothelioma, Version 3.2016. J Natl Compr Canc Netw 2016;14:825-36.
13. Domen A, Berzenji L, Hendriks JMH, et al. Extrapleural pneumonectomy: still indicated? Transl Lung Cancer Res 2018;7:550-5.
14. Spaggiari L, Marulli G, Bovolato P, et al. Extrapleural pneumonectomy for malignant mesothelioma: an Italian multicenter retrospective study. Ann Thorac Surg 2014;97:1859-65.
15. Opitz I, Weder W. A nuanced view of extrapleural pneumonectomy for malignant pleural mesothelioma. Ann Transl Med 2017;5:237.
16. van Gerwen M, Wolf A, Liu B, et al. Short-term outcomes of pleurectomy decortication and extrapleural pneumonectomy in mesothelioma. J Surg Oncol 2018;118:1178-87.
17. Wolf AS, Flores RM. Extrapleural pneumonectomy for pleural malignancies. Thorac Surg Clin 2014;24:471-5.

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