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The surgical-based treatment of malignant pleural mesothelioma: a literature review of a still ongoing debate

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【**Abstract**】 **Background and Objective:** Pleural mesothelioma is an aggressive disease with poor prognosis due to the tendency to relapse. Despite the lack of uniform protocols of therapy, surgery remains the cornerstone of multimodal treatment. Nevertheless, the debate on which is the optimal choice for surgical-based approach lasts over time and is based over the oncological benefits of obtaining a theoretical greater radicality rather than preserving the anatomical integrity in view of further treatments. This review is intended to summarize the topics of this dispute still ongoing. **Methods:** A review on the PubMed/Medline literature database of the different surgical approach was carried out, screening all the publications in English from 2000 to 2021. The search strategy has been focused on comparative studies of surgical techniques to understand if and how the choice of the type of surgery to be offered in the forefront has changed over the years. **Key Content and Findings:** Within the multimodal strategy the goal of surgery, performed with radical intent, is to achieve the macroscopic complete removal. Two procedures are aimed to this purpose: the lung-sacrificing surgery as the extrapleural pneumonectomy and the lung-sparing surgery as the pleurectomy/decortication extended or not to resection/reconstruction of diaphragm and pericardium. Many centers today have abandoned the most radical procedure in favor of the most conservative, but the superiority of one technique over the other remains controversial. **Conclusions:** In the absence of comparative randomized trials, the choice of surgical technique is determined by the experience of individual centers and by the attitude of surgeons. Further research is needed to standardize treatment protocols and to define the role of surgery in the context of multimodal therapy.

【**Key words**】 Pleural mesothelioma; pleurectomy/decortication; lung-sparing surgery; extrapleural pneumonectomy

Introduction

Malignant pleural mesothelioma (MPM) originates from the serous lining cells of the chest and its pathogenesis is related in the majority of cases to professional or environmental asbestos exposure[1]. MPM is considered a rare tumor with an annual incidence of 1.6 cases/100,000 in Europe with almost 9,000 new diagnosis/year and a 5-year survival around 4–7%[2-4]; in USA an incidence rate of 3,200 new diagnosis/year was reported[5]. The

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trends observed, showed that in Europe, after the ban of asbestos, the incidence rate of this disease is decreasing[6], conversely in developing countries that have re-launched the production of materials containing asbestos[7] a rise of disease burden is expected in coming decades[8]. According with pathologic criteria, MPM is distinguished in epithelial, sarcomatoid, biphasic and desmoplastic subtypes[9], that differ for clinical behavior, response to therapy and survival outcomes. The median survival from diagnosis is less than 7 months for untreated patients undergoing palliative care[10]. Multiple studies on radical surgery are focused on the epithelial subtype which is related to most favorable survival results and is considered a prognostic factor for improved outcomes after the surgical-based treatment. For selected patients with resectable disease, current protocols of the upfront treatment are founded on a multimodal strategy that combines different approaches including surgery, chemotherapy and radiotherapy (trimodal approach). The two main surgical options for MPM are the lung-sacrificing procedure as extrapleural pneumonectomy (EPP) and the lung-sparing procedure as the pleurectomy/decortication (P/D) which can be extended (EP/D) if diaphragmatic and pericardial resection/reconstruction is required for tumor infiltration. For years the surgical treatment of MPM has been characterized by the pursuit of radicality to obtain the control of the resection margins through the removal of the structures of the entire hemithorax as with EPP. Nevertheless, the expected oncological benefit did not correspond to an increased life expectancy. The higher invasiveness of EPP turned out to be related mainly to a higher perioperative morbidity and mortality, while the recurrence rate remained similar between the two techniques. The lung-sparing procedures as P/D and EP/D are not defined by uniform protocols and several attempts have been made over time to standardize the technique. The proponents of lung-sparing surgery have assumed that is possible to be more conservative and at the same time to aim for the macroscopic complete removal (MCR) of the tumor burden with the purpose to preserve as much anatomy as possible. This would allow patients to be eligible for further therapy in case of relapse, with an improvement in quality of life and overall survival. The debate about what should be the surgery of choice for MPM operable patients has not ended and currently international guidelines still define both techniques as recommended treatment options to achieve the MCR of disease. We present the following article in accordance with the Narrative Review reporting checklist (available at https://www.thecjts.cn/article/view/10.3877/cma.j.issn.2095-8773.2022.04.01/rc).

Search strategy and study selection

The authors independently used the PubMed-Medline database to review the literature about the surgical-based treatment of pleural mesothelioma published in English from 2000 to 2021. The search strategy for the selection of the studies was conducted with the following queries ("lung-sparing"[All Fields] AND ("mesothelioma"[MeSH Terms] OR "mesothelioma"[All Fields] OR "mesotheliomas"[All Fields] OR "mesothelioma, malignant"[MeSH Terms] OR ("mesothelioma"[All Fields] AND "malignant"[All Fields]) OR "malignant mesothelioma"[All Fields])) AND ((2000:2021[pdat]) AND (english[Filter])) (("pleurectomies"[All Fields] OR "pleurectomy"[All Fields]) AND ("extrapleural"[All Fields] OR "extrapleurally"[All Fields]) AND ("pneumonectomy"[MeSH Terms] OR "pneumonectomy"[All Fields] OR "pneumonectomies"[All Fields]) AND ("mesothelioma"[MeSH Terms] OR "mesothelioma"[All Fields] OR "mesotheliomas"[All Fields] OR "mesothelioma, malignant"[MeSH Terms] OR ("mesothelioma"[All Fields] AND "malignant"[All Fields]) OR "malignant mesothelioma"[All Fields])) AND ((2000:2021[pdat]) AND (english[Filter])) and 262 potentially relevant publications were identified. Among them 109 articles were excluded by title, because duplicates or not in accordance with the topic. The remaining abstracts were reviewed for the eligibility, and 36 publications were excluded due to the article type (conference communication, case report, multimedical article) or because deemed not relevant to the subject of this review. Finally, 117 full-text articles were evaluated for the present report. The selection process is shown in *Table 1* and the algorithm is reported in *Figure 1*. Additional articles and the most recent guidelines were retrieved from references and selected with the authors agreement.

Table 1 Search strategy summary

Items	Specification
Date of Search	January 2021
Databases and other sources searched	Medline/PubMed resources
Search terms used (including MeSH and free text search terms and filters)	Search: pleurectomy extrapleural pneumonectomy mesothelioma Filters: English, from 2000–2021; search: lung-sparing mesothelioma Filters: English, from 2000–2021
Timeframe	From 2000 to 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Filters for research: language, timeframe; inclusion criteria: all publications dealing with surgical treatment of MPM especially if focused on the comparison between the different techniques; exclusion criteria: Case Report, articles about modalities of treatment different from surgery
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	All authors were involved in the selection process. The screening of the publication was conducted independently by each. Agreement has been reached on the basis of shared choice criteria

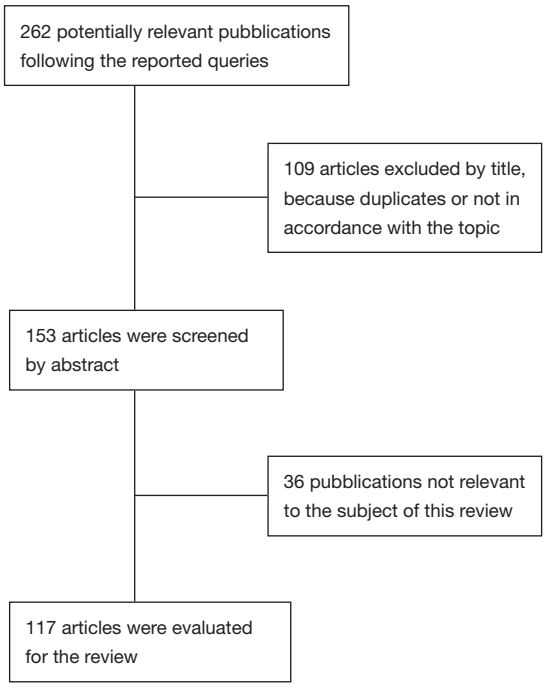

Figure 1 Algorithm of search strategy and study selection.

The debate

The first study on surgery proposed to patients with resectable MPM was published in 1976 by Butchart and colleagues[11]. Twenty-nine patients underwent EPP with a perioperative mortality of 31% and a major complications rate of almost 45%. In their report 3 patients (as 10%) survived for more than 2 years. In 1970s, when the standard management for this disease was aimed to relieve symptoms and the use of chemo- and radiotherapy was limited, this experience had the task to reappraise the role of surgery with radical intent. Nevertheless, the mortality and the complications rate appeared too high in view of a rapid recurrence of disease or of perioperative death. In a historical series of 1976, Wanebo and colleagues[12] proposed for the first time a trimodal approach including P/D performed with debulking purpose in combination with external irradiation and systemic chemotherapy to prevent recurrences. In 1982, McCormack and colleagues[13] showed the results of their protocol of treatment including P/D combined with intraoperative and postoperative radiotherapy. The reported advantage of this approach was related to the preservation of lung function associated with a control on residual tumor burden brought by the intraoperative implantation of radioactive material. The 1-year reported survival rate was 49% with a median survival of 21 months. From these first experiences the debate on which is the optimal surgical procedure to treat MPM has started and, as result of the current lack of randomized clinical trials, the exact impact on survival of the different type of surgery has not been conclusively defined. In 1990s, Rusch and colleagues[14-16] compared the outcomes of patients undergone P/D and EPP, in the historical series of the Memorial Sloane-Kettering Cancer Center. In the

conclusion of their work, they stated that only a limited amount of selected patients can be considered eligible for EPP due to the higher perioperative morbimortality carried by a more extensive resection and that a greater radicality did not have a significant impact on recurrence and survival rates. Among the two approaches, EPP is a highly standardized technique based on the resection *en-bloc* of the lung, pleura, diaphragm and pericardium. The proponents of EPP have claimed that this procedure offers more oncological benefit, leaving behind less microscopic residual disease and moreover facilitates the use of radiation therapy in case of local relapse, avoiding the toxicity on the lung[17-19]. The disadvantages are related to the relatively poor quality-of-life with a higher mortality risk and to the rate of perioperative cardiopulmonary morbidities. Lung-sparing surgery, on the other hand, is recognized to be safer in terms of perioperative morbidity and mortality if compared with EPP[20-22], and when diaphragm and pericardium can be saved because not involved by the disease, excludes the risk of complications for the prosthetic reconstruction. Additionally, preserving both lungs, this approach provides a better physiologic reserve to tolerate further treatments when recurrence occurs. The principal dispute around P/D or EP/D concerns the control of resection margins and the theoretical risk of leaving microscopic burden of tumour in the preserved lung[23]. The issue on the least radicality is heavily dependent on the variability of the nomenclature regarding the lung-sparing techniques[23-25]. To date, the most recommended version, proposed by IMIG and IASLC committees in 2011, is to define the removal of the entire parietal and visceral pleura as EP/D if the involvement of diaphragm and/or of pericardium requires the resection and the prosthetic reconstruction[26]. Before this attempt to uniform the terminology, the lung-sparing surgery definition could differ between centers and, as a consequence, for long time it was not possible to compare results and outcomes of this technique.

EPP

The EPP consists of *en-bloc* resection of the whole pleura, lung, ipsilateral hemidiaphragm, and pericardium. This surgical technique is approached via a posterolateral thoracotomy through the bed of the resected sixth rib. The sites of previous diagnostic surgical access are removed. First of all, a blunt dissection is performed in the extrapleural plane between the parietal pleura and the endothoracic fascia. Whenever a localized chest-wall infiltration is found, this area is resected. From the apex, the mediastinal pleura is stripped down towards the hilum. Anteriorly, the pericardium is opened and excised. Subsequently, all hilar vessels, as well as the bronchus, are treated in a standard fashion as in a typical intrapericardial pneumonectomy. Posteriorly, the extrapleural dissection is carried on towards the hilum with the dissection of the posterior part of the pericardium. The paratracheal, paraoesophageal and infracarinal lymph nodes are resected. The hemidiaphragm is completely resected at its insertion to the chest wall, and is subsequently reconstructed by a prosthetic mesh. This graft or a xenopericardial patch might be used for the reconstruction of the pericardium.

(Extended) pleurectomy/decortication [(E)P/D]

This surgical procedure is performed through a thoracotomy, with consensual resection of the sites of previous diagnostic surgical access. The endothoracic fascia is separated from the parietal pleura by a blunt dissection on the extrapleural plane. This surgical maneuver is favoured by the eventual pleural thickening subsequent to previous talc pleurodesis. Particular care is dedicated to the isolation of the phrenic nerve, which is secured. The decision whether a P/D or an extended P/D is to be performed, is taken as the diaphragmatic and/or pericardial involvement are evaluated. Whenever a possible infiltration of these structures remains doubtful, a frozen section might be performed. In case of a macroscopical pathological involvement of these structures, they are resected and reconstructed via a prosthetic mesh or by a xenopericardial graft. A direct closure might also be performed after partial resection in cases of an isolated involvement. The decortication of the visceral pleura is carried out either with partially inflated or with completely deflated lung. The detachment from parenchyma is performed via a blunt dissection by means of the surgeon's fingers or with cotton balls, following the fissures and around all pulmonary vessels at hilum. Both for the control of bleeding as well as for clearance of any possible pleural residues on the chest wall, Argon beam coagulation might be used. At last lymphadenectomy is performed, with accurate exploration of hilar, mediastinal stations, internal mammary and paravertebral chains.

The MCR

Despite the long latency period from the asbestos exposure to the appearance of disease, the biological aggressiveness of MPM is without equal among thoracic tumors. The natural evolution of MPM is characterized by an ineluctable local progression which takes the form of an invasion into adjacent tissue, such as adipose tissue, skeletal muscle, contiguous structures and lung, that is one of the morphologic features to distinguish MPM from other reactive mesothelial proliferations[1,26]. With this premise, due to the diffuse nature of development of MPM, no treatment option has been proven effective if used as a single-modality with curative intent. For that a combination of different approaches for local and systemic control of disease has been proposed in a multimodal setting, with surgery playing a keystone role to achieve the maximal cytoreduction of tumor burden[27]. In MPM, a true R0 resection is theoretically impossible for the failure to control residual disease on surgical margins. The goal of surgery-based setting is to remove all gross disease to obtain the MCR which is defined as a resection of all visible and palpable disease with at least R1 margins[27]. As a consequence, any cytoreductive procedure must be supplemented with chemotherapy, radiation and/or other adjunctive methods[28-30] to try to hold the residual microscopic disease onto control. Through years EPP, as a lung-sacrificing technique, was considered more effective to attain this result but one study reported that pursuing MCR with EPP, 70% of specimens were found to have positive margins on final pathology[31]. In fact, the characteristic behaviour of MPM is to coat microscopically as a sheet all contiguous surfaces leaving a boundary of normal tissue surrounded by the disease. For that the criterion of radicality with R0 resection, valid for other solid tumors, cannot be followed in the majority of MPM cases, because if lung can be removed, other structures with the same proximity with disease are left in place[24,32]. For the lung-sparing surgery, considered less radical, concerns arose for the surgical margin control and many surgeons were doubtful that MCR could be achieved with such a technique. In 2012 Friedberg and colleagues published the results of a study on 38 patients undergoing P/D for epithelial advanced MPM (IMIG stage III/IV). MCR was attained in 97% of cases, saving the lung. The long-term outcomes of median progression free survival was 9.6 months with a median survival of 17 months. The authors concluded that the lung-sparing surgery can be part of a multimodal strategy to aim the MCR and that might be planned preoperatively for all patients, even with advanced disease, not only for those considered unfit for EPP[33].

Outcomes

The EPP has been the gold standard of MPM surgery for years. From the first attempt reported by Butchart and coll. the technique of EPP has improved leading the perioperative mortality to decrease from 31% to 15% in 1980s[15,34] to finally reach 4.5%[35] in the years 2000. Despite this progress, the outcomes following EPP always showed a higher rate of morbidity and a poorer quality of life when compared to the alternative surgical techniques[20,36-37]. In all the most referenced comparative analysis, summarized in *Table 2*, the morbimortality defined as 30-day mortality and complication rate increased for patients following EPP. The most common adverse events were respiratory failure (ARDS), cardiac arrhythmias and complications related to defects in the prosthetic reconstruction of the diaphragm and pericardium. The comparative studies between lung-sacrificing and lung-sparing surgery have been intensified only since the 2000s. The difficulty to compare the outcomes was due to the not uniform definition of lung-sparing procedures and to selection bias on study population. In fact, for decades EPP was considered the standard for the surgical-based strategy and P/D represented the alternative option for early stages of disease or for those patients unfit for the more extensive resection. Flores *et al.* in 2007[38] in their retrospective research, analyzed the outcomes of 945 MPM patients treated with a multimodal approach, among them 384 underwent surgery with EPP or P/D. In this cohort, the decision to perform P/D was made for those patients with poor pulmonary function having a minimal tumor burden on visceral pleura. With these selection criteria, the short-term outcomes revealed a lower morbimortality (3% *vs.* 5%) and a slightly improved median survival (15.8 *vs.* 14.4 months) in favor of P/D. In 2008 Flores and colleagues[40] in one of the largest investigations on the comparison of EPP *vs.* P/D, analyzed the outcomes of 663 MPM patients. Even though EPP group presented favorable prognostic factors as the biggest proportion of epithelial histotype and patients receiving multimodal therapy, the Cox-model adjusted for histology, stage,

gender, and multimodality therapy, showed a hazard ratio (HR) of 1.4 for EPP compared with P/D (P<0.001). In Luckraz series[42], were included only patients undergone surgery aimed to achieve the MCR. The results of this research showed that no operative technique is curative in itself, nevertheless P/D combined with chemotherapy and radiotherapy was the strongest predictor of prolonged survival (HR =3.6) and conversely, EPP alone was an independent risk-factor for decreased survival (HR =9.2) at the Multivariate analysis. The concerns about the reaching of MCR by lung-sparing surgery have been overcome by Friedberg and coll. In 2011, they assumed that Lung-sparing procedures, which was defined Radical Pleurectomy in this study, can be performed to obtain the maximal cytoreduction also in patients in advanced stages of MPM (III e IV AJCC/IMIG staging system) and therefore no longer only in the early stages, resulting in an improved survival for the radical pleurectomy group[30]. Lang-Lazdunsky and colleagues[45] in 2012 published a comparative analysis on 79 patients with epithelial MPM treated with EPP versus (E)P/D. They found a significant survival benefit when lung was preserved (P<0.004) and moreover a similar survival outcome between EPP-group and patients with an incomplete macroscopic cytoreduction (R2 resection) was reported. Lung-sparing surgery was proposed as first choice in surgical-based strategy. However, despite the most favorable results in terms of quality of life[36] and in short-term outcomes although not statistically significant, final conclusions have not been reached yet to propose P/D instead of EPP and several studies did not find any difference in median and overall survival between the two techniques[43-49], with the result of supporting the discussion on which is the optimal option for the resectable MPM.

Table 2 Comparative studies on outcomes: lung-sparing *vs.* lung-sacrificing surgery

Study	Multimodal treatment	(E)P/D		EPP	
		30-day mortality/OM	Survival (months)	30-day mortality/OM	Survival (months)
Flores[38], 2007	Mixed	3%	15.8	5%	14.3
Schipper[39], 2008	Mixed	0%/20%; total pleurectomy	17.2; total pleurectomy	8.2%/50.7%	16
Flores[40], 2008	+/– ind CT; +/– adj RT; +/– other	4%/6.4%	16	7%/10%	12
Okada[41], 2008	Mixed	0%	17	1.5%	13
Luckraz[42], 2010	+/– adj CT; +/– adj RT	2.2%/16%	Not Reported	10.2%/41%	Not reported
Friedberg[30], 2011	Mixed	0%; radical pleurectomy	Not reached	2%	8.4
Rena[43], 2012	Mixed	0%/24%	32	5%/62%	28
Nakas[44], 2012	Mixed	3%/43%	13.4	7%/68%	14.7
Lang-Lazdunski[45], 2012	Mixed	0%/27.7%	23	4.5%/68%	12.8
Bedirhan[46], 2013	Adj CT; +/– adj RT	P/D 30-day: 4%; EP/D 30-day: 0%	P/D 15 EP/D 27	30-day: 12.9%	17
Bovolato[47], 2014	+/– CT	2.6%/10.4%	20.5	4.1%/21.6%	18.8
Infante[37], 2016	+/– CT; +/– adj RT	2.1%/26%	30	3.3%/27%	19
Sharkey[48], 2016	Mixed	3.5%/NR	12.3	6%/NR	12.9
Kostron[49], 2017	Ind CT; +/– adj RT	0%/58%	32	5%/38%	23
Miyazaki[21], 2018	Mixed	0%/44%	22.5	0%/33%	16.5
Hasegawa[50], 2019	Ind CT; +/– adj RT	1.6%/29%	43.4	3.8%/46.2%	18.5
Zhou[51], 2022	+/– ind CT; +/– adj RT	30-day: 0%	18	30-day: 11%	11

Ind CT, induction chemotherapy; Adj RT, adjuvant radiotherapy: Adj CT, adjuvant chemotherapy; OM, overall morbidity; EPP, extrapleural pneumonectomy; (E)P/D, (extended) pleurectomy/decortication.

Recurrence

Even following multimodal approach with any type of surgery as a keystone of treatment, the biologic aggressiveness of MPM makes recurrence almost inevitable. Recent studies on failure of trimodality therapy pivoted on EPP estimated that up to 75% of patients experienced recurrence with a median disease-free survival (DFS) of 13 months and a median survival of 15 months[52]. After EPP the most frequent pattern of failure is related to a distant spread involving contralateral hemithorax, peritoneum, abdomen, bone and brain with a longer DFS when compared to P/D. These data have been interpreted as a consequence of the higher control of margins attained after a more radical resection. Bellini and coll. reinforced this assumption in a recent analysis on 250 resectable MPM patients[53]. They stated that local relapse, occurring earlier than distant, is related to the larger amount of microscopic disease burden left in place after surgery. Moreover, they found that a worse DFS after EPP is associated to the advanced stages of disease in which it is likely to be more difficult to obtain the MCR. The median PRS was 14 and 8 months in the EPP and PD group, respectively. In a systematic review Cao and colleagues[54] analyzed data of 15 studies on recurrence in patients undergone (E)P/D. The principal pattern of relapse was local, occurring in 26–57% of patients and in both at local and distant sites in 6–43%. Despite the inexorable appearance of recurrence, limited data are available on second-line protocols of treatment for MPM relapsing patients after EPP versus (E)P/D and the few comparative studies are summarized in *Table 3*. Nakamura and colleagues[55] analyzed the oncologic outcomes in relapsing patients after P/D, finding a median DFS of 19 months. They reported that a DFS >12 months (HR =0.4) and the post-recurrence treatment (HR =0.2), for patients considered fit for further therapies, are favourable prognostic factors for a prolonged overall survival with a median PRS of 14.4 months. Kai and colleagues in their comparative research on 50 patients reported significant results in favour of P/D[56]. They found that when compared with EPP-group, patients after P/D had a similar DFS and improved PRS (20 months) due to the preserved pulmonary function, leading to improved OS. They suggested that the local control is possible also with the less invasive technique in the trimodal treatment setting when MCR can be achieved.

Table 3 Comparative studies on recurrence: lung-sparing *vs.* lung-sacrificing surgery

Study	n	Median OS (months)	Median DFS (months)	Median PRS (months)
Kai *et al.*[56], 2019	EPP: 29; P/D: 15	Overall: 22*; EPP: 17*; P/D: 34*	Overall: 14*; EPP: 13*; P/D: 21*	Overall: 5*; EPP: 3*; P/D: 20*
Bellini *et al.*[53], 2021	EPP: 49; P/D: 45	Overall: 33; EPP: 38; P/D: 23	Overall: 14; EPP: 20; P/D: 11	Overall: 12; EPP: 14; P/D: 8

*, time from diagnosis. OS, overall survival; DFS, disease free survival; PRS, post-recurrence survival; EPP, extrapleural pneumonectomy; P/D, pleurectomy/decortication.

Discussion

The role of surgery at the center of the multimodal setting for the treatment of MPM has been recognized as a predictor of prolonged survival in several studies[47]. Nevertheless, Flores and coll. in their analysis of the Surveillance, Epidemiology, and End Results database, found that surgery was offered only to 22% of patients diagnosed with MPM between 1990 and 2004, and only 40% of them underwent surgery at tertiary care hospitals[57]. Due to the tendency of this disease to tissue infiltration and the frequency to relapse, surgery is aimed to achieve the maximal cytoreduction that might be attained through the removal of the all structures in the hemithorax by EPP or by mean of P/D, a less extensive resection limited to pleural sheets to preserve lung and as much anatomy as possible. For years EPP has been considered the gold standard of surgical treatment for the theoretical oncological benefit brought by a higher control on resection margins after a more radical procedure. But several studies showed that the greater risk of complications and perioperative death associated to EPP was not balanced by a longer life expectancy[22]. In 2011 in the MARS trial, 50 patients were randomized in two arms, undergoing EPP and no-EPP, as non-surgical

approach[58]. This controversial study showed that patients randomly assigned to non-surgical group had a longer median and 1-year overall survival than those undergone EPP, who, moreover, have perceived their quality of life as worst throughout the 2 years of follow-up. The trialists concluded that the higher radicality offered through EPP within trimodal therapy did not grant an oncological advantage and possibly was harmful for patients when compared to surgical alternatives. Consequently, questions have arisen as to whether the aggressiveness of EPP can still be justified, and many centers have shifted their orientation to develop a less invasive techniques to preserve the anatomy for a better tolerance to further treatments in the event of relapse[59-61]. Through years, P/D has gained ground as a lung-sparing procedure, sustained by the intuition that maintaining the physiologic cardiopulmonary function the postoperative complications could be decreased, improving the quality of life in resected patients. In their proposal to standardize the lung-sparing technique, the joint NCI-IASLC-MARF task force recommended that every effort should be made to preserve as much normal anatomy as possible, to maximize the benefit of the tumour cytoreduction following P/D[24]. How much is the potential effect of the intact cardiopulmonary function remains unclear[36,62-63] and further research is needed to evaluate whether it has an impact on oncological outcomes also in advanced stages of disease. In recent years we are witnessing a change of perspective in which the role of surgery has passed from a theoretical research of radicality to a more conservative approach to maximize the benefits of a multimodal strategy[59-61]. Nevertheless, although many institutions in Asia, Europe and North America have adopted P/D as first-line choice in surgical-based treatment, the discrepancy in guidelines recommendations does not always provide a support to clarify which surgical option is to prefer[64-67]. For the ASCO guidelines of 2018, P/D is the first-line option to achieve the maximal cytoreduction, while EPP should be offered to selected patients in high-volume centers. This recommendation is presented with a strong evidence-based level of quality. The ESMO indicated that surgery with radical intent should be offered for MCR in the context of multimodal strategy. Both techniques, EPP and P/D, are recommended with an intermediate level of evidence, due to the lack of randomized comparative studies. For the British Thoracic Society (BTS) guidelines, EPP should not find any indication in the management of MPM and P/D might be performed only in a clinical trial setting. The ERS/ESTS/EACTS/ESTRO task force experts suggested that surgery can be considered only for high selected patients and as a part of controlled clinical trials whenever possible. For radical intent extended P/D rather than EPP is the preferable option for patients at early stage, with epithelial histotype, without contralateral lymph-node involvement (stages I to III following the 8th TNM edition). For all these guidelines the huge variability of outcomes and the conflicting results in the reviewed studies did not consent to reach a high quality of evidence and the grading system for recommendations is not uniformly adopted. In addition, the lack of comparative studies not retrospective or based on well-standardized protocols brought multiple bias that affected the conclusions of the analysis and more consistent data derived from randomized research are needed. To date the choice to perform EPP or (E)P/D for resectable patients with MPM is still widely dependent on institutions attitude and surgeons experience.

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