Peer review file

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Reviewer A

Comment 1: The authors report in their introduction the prognosis of untreated mesothelioma patients. A prognosis for treated patients, e.g. with chemotherapy alone or with multimodality treatment is lacking, although this patient group reflects much more the population studies in this manuscript. This should be added.

Reply 1: Reports of literature on prognosis for all treated patients were added in manuscript references.

Changes in the text: we modified the text as advised - Line 88

Comment 2: The authors refer to the current protocols as 'with curative purpose', although they later state that radical tumour clearance is impossible. This is somewhat conflicting. Multimodality treatment protocols in mesothelioma are per se not with curative intent. Also, achieving macroscopic complete resection (MCR or R1) is not done by reducing the tumour burden. The goal always is to remove all visible tumour. If you expect R2 resection (which is also reducing the tumour burden), you should not perform surgery.

Reply 2: Thanks for your observation. We changed in the text.

Changes in the text: we modified the text as advised - Line 93

Comment 3:

The authors define two lung-sparing procedures: pleurectomy/decortication and extended pleurectomy/decortication. I do not entirely agree. For me, this is the same procedure (e-P/D), with

sparing of the diaphragm and/or pericardium if possible. Again, if you expect diaphragmatic involvement, performing a pleurectomy/decortication is insufficient, so these are not 2 independent procedures from which you may select the best. The authors admit that the extent of the resection is evaluated perioperatively. I would not split the results up for those two 'procedures' but give results for all surgeries combined only, because there is not the option to choose between 'procedures'.

Reply 3: The extended pleurectomy/decortication is now the most recommended lung-sparing technique to achieve the complete macroscopic removal in case of pleural mesothelioma. For the lack of standardization, many surgeons have the attitude to resect diaphragm and pericardium systematically. We found that the preservation of the anatomy can play a favorable role in term of overall survival. For that, we proposed that the removal of the pleural layer from these structures has to be always attempted when it is deemed possible. Moreover in the study design of MARS 2 trial (Trial registration numbers ISRCTN—ISRCTN44351742 and ClinicalTrials. gov—NCT02040272) the authors defined pleurectomy/decortication and extended pleurectomy/decortication as two distinct surgical procedures. In fact, Rintoul et al. in 2014, considering pleurectomy/decortication as a distinct procedure, proposed a research on the cost/effectiveness to perform pleurectomy/decortication with preservation of the diaphragm and pericardium by thoracoscopic approach.

Changes in the text: we modified the text as advised - Line 152

Comment 4: 28 patients with biphasic histology diagnosed after surgery were excluded. Apparently, this histology was not established with VATS biopsies before pleurectomy/decortication? Please explain such a high margin of error. Multimodality studies such as EORTC 1205 allow biphasic histology, so what is the rationale to focus on epithelioid histology only if you have operated them, nevertheless. You should calculate separate OS/PFS for both subtypes.

Reply 4: Thanks for your suggestion but this could be part of another paper. Our research is based on 10 years of activity (from 2009 to 2019) and the guidelines have changed during this time. This lack of standardization did not permit to uniformly collect data on these patients. All of MPM cases were diagnosed by thoracoscopic pleural biopsies in ours and in other hospitals. The 28 cases were addressed as epitheliial MPM from other hospitals to our referral thoracic surgery unit. The histotype changed at final histology after the lung-sparing surgery. We tried to collect a cohort stratified for histotype, type of lung-sparing surgery, review of the staging following the 8th edition of TNM staging system.

Comment 5: For a single-centre study, the chemotherapy is applied heterogeneously: the rationale to replace cisplatin by carboplatin seems logical, but which criteria were used to choose either preoperative or postoperative chemotherapy? What is the rationale to give some patients 3 and some 6 cycles of chemotherapy?

Reply 5: This article describes 10 years of activity in mesothelioma surgery. The guidelines and the recommendations for Oncologists and Surgeons have changed many times over years. The adjuvant setting is older if compared to the neoadjuvant, which today represents the first choice in multimodality protocols. For that, we indicated that this diversity, due to very long time span, could be a possible bias and a limitation of this research. Our thoracic surgery Unit has been for years the referral center for mesothelioma patients coming from nationwide, for this reason was not possible to achieve a uniform protocol for induction chemotherapy which has been valid since 2009. For the best of our knowledge the only phase II randomized study on neoadjuvant versus adjuvant chemotherapy in pleurectomy/decortication for MPM is the EORTC 1205 as you cited in comment 4. The results of this EORTC trial will be available in December 2021.

Comment 6: Considering the inclusion criteria: T3 is allowed. Could you clarify whether focal chest wall lesions were excluded or not? What was the rationale to exclude all ipsilateral nodal

involvement (N1-2) for surgery? These can be resected, perhaps incompletely, but this is also the case for the pleura. Lymph node involvement was not as strongly associated with relapse, as compared to the T descriptor.

Reply 6: For all patients, clinical and pathological staging were reviewed considering the 8th edition of the TNM staging. In the T descriptor, T3 is defined by multiple features, among which, focal resectable lesions invading soft tissue of the chest wall. Patients staged as T3 were included in our analysis. However, for the N descriptor, the 8th edition of the TNM staging collapsed the ipsilateral nodes involvement in the N1 category. We excluded N2 from surgery because this category defines the contralateral nodal involvement.

Changes in the text: we modified the text as advised - Line 275

Comment 7: I note there are 9 surgeons among the authors. How many of those actually performed the procedures? Had all these surgeons previous experience with mesothelioma surgery, or could there have been a learning curve?

Reply 7: In our team 3 senior surgeons have routinely performed mesothelioma surgery for twenty years. As many surgeons did, they shifted from the systematic use of extrapleural pneumonectomy to the lung-sparing procedures approximately 10 years ago. This experience is synthetized in this research.

Comment 8: The authors use frozen sections to determine the extent of the resection. To my knowledge, this is not the standard procedure for e-P/D (e.g. not part of the standardized protocol as in EORTC 1205). How likely is it that a frozen section is false negative?

Reply 8: The frozen sections were required following the surgeon's choice, in the event that the presence of infiltration of the tumor was doubtful. When it was difficult to peel the pleural sheet off, the involvement of the diaphragm and of the pericardium had to be proven by frozen section. In our experience we did not encounter any false negative, for all required frozen sections, the result was

confirmed at final histology report.

Changes in the text: we modified the text as advised - Line 133

Comment 9: Under ‘methods’ results are given, such as the % of e-P/D or the number of patients included, mean age, % asbestos exposure, ... This should come under ‘results’.

Reply 9: We changed in the text.

Changes in the text: we modified the text as advised - Line 172

Comment 10: The authors state that all histopathologic reports were reviewed according to the eighth edition of TNM staging system. This means that cTNM was done under TNM 7 and pTNM under TNM 8. This may be somewhat confusing?

Reply 10: This paper shows ten years of activity with lung-sparing surgery in pleural mesothelioma. For all patients, the clinical staging and the pathological staging were both reviewed following the 8th edition of TNM classification. We corrected this possible confounding factor in the text.

Changes in the text: we modified the text as advised - Line 120

Comment 11: It seems somewhat odd to start the results with complications, as this article primarily focusses on outcome. A small table containing relevant complications seems more appropriate.

Reply 11: Thanks for your suggestion. We added a new table for complications in the text.

Comment 12: Follow-up was done with chest CTs every 4-6 months. This gives quite long FU intervals and might affect RFS as first PD usually is asymptomatic. In 17% of patients no RFS could be calculated!

Reply 12: There is no evidence that a benefit could derive from a early treatment of asymptomatic relapse when compared to the treatment of relapse with symptoms. For that the available guidelines

have not suggested an optimal frequency of follow up controls after surgery. On the basis of the limited protocols for second line treatments, for the best of our knowledge, an intensive follow up out of clinical trials is not recommended. The percentage of patients lost in follow up could be a possible bias of the study.

Comment 13: The rate of R2 resection was almost 15% for e-P/D. This is quite high. Perhaps patients who were unlikely to benefit were operated on, nevertheless? Are there any data on cTNM for these patients?

Reply 13: The lung-sparing surgery in mesothelioma is defined for cytoreductive purpose. In these patients the goal is to reach a complete macroscopic tumor removal with at least an R1 resection. In some doubtful cases after a pleurodesis and after the neoadjuvant chemotherapy, at clinical staging, is not possible to establish if tumor infiltrates the extrapleural structures. The risk is to exclude from surgery the potentially resectable patients. For that the R2 incomplete surgery in our research is the result of the unexpected interaoperative findings as described in the paper.

Comment 14: The median time of survival = median OS. Was the OS calculated from the surgery to death, or from completion of treatment to death in patients receiving adjuvant chemotherapy?

Reply 14: The outcomes considered (OS and RFS) were calculated from the date of surgery (as reported in the main text at row 168 in data collection paragraph).

Changes in the text: we modified the text as advised - Lines 160, 197, 214

Comment 15: In a comparison of the different surgical techniques, OS was found to be improved ($p=0.007$) when diaphragmatic and pericardial resections were avoided (Fig.2). This is true, but dishonest. OS was better in case a less extensive resection could be performed, meaning that no tumor extending to the diaphragm or the pericardium (higher stage) is beneficial. This should not be an invitation to avoid diaphragmatic resection (e-P/D) if necessary!

Reply 15: This remark (see comment 3) could have been addressed also to those who proposed the extended pleurectomy/decortication versus the extrapleural pneumonectomy. The lack of a standardized technique for MPM led to a great variability of attitudes among surgeons. Some are more oriented to perform systematically EP/D with the resection of the diaphragm and pericardium, others prefer to carry out a P/D to save the structures at least in the lower stages of disease. In our population, the different stages are equally distributed in each group of surgery. Helped by a statistician, that is one of the co-author, we calculated with a chi-square test if there was a stage more represented in P/D rather than in EP/D. The result was not significant with a p=0.189. Moreover, as reported by a joint NCI-IASLC-MARF task force (recorded as reference), the preservation of the normal anatomy would bring itself benefits to improve survival, providing to patients a better state of health to increase the tolerability of further treatments in case of relapse. It is also stated that to save diaphragm and pericardium could become a goal for a standardized surgical-based strategy. In our research, the results align with these observations and we try to confirm the statement that the preservation of the structures should be always attempted.

Comment 16: OS according to TNM, was this pTNM or cTNM? Could the authors hypothesize on why OS was better for IIIB compared to IIIA?

Reply 16: OS was calculated according to pTNM. The result of a better OS for IIIB staged patients, if compared to those staged as IIIA, was surprising. We can hypothesize that the incomplete resection leaving a gross residual of tumor burden can have a different impact depending on the location. Moreover in patients with IIIA stage the recurrence appears as a new onset disease, in IIIB cases the residual tumor is left behind during surgery. This could make some difference in terms of OS but further studies on biology of mesothelioma are needed.

Comment 17: The legends for the images are minimal. Please explain more in detail what can be seen. In figure 3 staging, TNM staging groups are given. Given the fact that it contains a stage IIIB, this means pTNM. Please make these legends more clear.

Reply 17: Thanks for your suggestion. We tried to clarify the image legends

Changes in the text: we modified the text as adivised. From line 535

Comment 18: A table on baseline characteristics should not contain results or complications of surgery. Results and demographics should be presented in two different tables.

Reply 18: We followed your remark to correct the tables in the manuscript

Comment 19: Results from this study are not compared to similar studies with EPP or e-P/D. This must be done.

Reply 19: we modified the text as requested.

Changes in the text: we modified the text as advised - Line 237, 245

Small errors:

- There is a difference between perioperative (during surgery) and preoperative (before surgery). This error is made several times. Also, if stating that chemotherapy is preoperative, also stating that it is induction is somewhat a tautology and could be left out

- Both mean and median age are reported in the manuscript. This is not relevant.

- OS and in particular RFS should be written in full before using the acronym.

Reply. To Small Errors. Thanks. We reviewed the main text.

Reviewer B

Comment 1. what was the accuracy of intraoperative frozen section analysis of resection margins?

Reply 1. In all the frozen sections, we performed we had a 100% confirmation in the definitive pathological report. Only one case was ambiguous because there was a pathological relapse on the site of resection despite the negative frozen section confirmed by the final report.

Comment 2. what was the effect on survival of the following - preoperative clinical assessment of tumour thickness the timing of chemotherapy - induction vs adjuvant the relative importance of preserving the diaphragm vs achieving macroscopic complete resection

Reply 2. The timing of chemotherapy was difficult to analyze because of the heterogeneity of chemotherapy treatments applied; it's due to various afferent oncology units from the entire national territory. Regarding the evaluation of tumour thickness, this parameter was unavailable for a conspicuous part of the sample due to not-routinary reporting of this value on the pathological reports until last decade. At last, we preserved diaphragm only with no evidence of large or multifocal involvement of the structure.

Comment 3. were survival data calculated from diagnosis or post resection?

Reply 3. Survival data were calculated starting from surgery (as reported in the main text at row 168 in data collection paragraph)

Changes in the text: we modified the text as advised - Line 160, 197, 214

Reviewer C

In this manuscript, the authors evaluated 155 consecutive patients with malignant pleural mesothelioma (MPM) who underwent lung-sparing surgery comprising pleurectomy/decortication (P/D) or extended pleurectomy/decortication (eP/D). Most of the patients underwent induction chemotherapy. eP/D was performed in 56.1%.
Overall median survival time was 34 months. On multivariate analysis pN status and P/D were predictive factors for survival. The authors conclude that lung-sparing surgery by P/D or eP/D is a valid option in multimodal management of patients with epitheloid MPM.

Comments:

- although this is a retrospective study with its inherent selection bias, the results of this large series of well-performed operative procedures are worth reporting; an advantage of this series is that the 8th TNM classification of MPM was used - lines 39-40 and 111-112: how was the choice made between induction and adjuvant chemotherapy? Line 39 only mentions carbo-alimta; why was cisplatin-alimta (for the latter product better use generic name pemetrexed) not preferred for patients who could tolerate it?
- line 82: “curative purpose”: this cannot be achieved in MPM; better use “To obtain maximal tumor clearance”
- line 122: why was a vertical thoracotomy used which is at right angle with the skin folds and prone to incisional complications?
- line 168 RESULTS: how much was intraoperative blood loss? Any difference between P/D and eP/D?
- lines 43, 130-131 and 251: how accurate is frozen section analysis for MPM as usually, special stainings are required?
- throughout manuscript substages should be indicated by capital letters: IA, IB, etc. - lines 198-199: P/D had a better survival than eP/D but the latter had more pronounced disease extent; this should be mentioned

- reference 3: was updated in 2020
- references should be uniform: sometimes volume numbers are indicated, or initials before last name instead of the reverse
- survival figures: number of patients at risk should be indicated at the bottom - the language is generally good but some typing errors should be corrected; examples include line 131 cytology, line 138 surgeon's choice, 141 lymph nodes

Reviewer C

- Answering your question about chemotherapy times and protocols, this point is difficult to clarify due to the large timeframe of our sample and the heterogeneity of Oncology Units referring patients to our center. In the last case, some of these patients came to our attention already treated with antiblastic drugs. **Changes in the text:** we modified the text as advised
- Line 82: thank you for your suggestion. **Changes in the text:** we modified the text as advised
- Line 122: in our experience, vertical thoracotomy guaranteed an acceptable surgery field exposure and the advantage of a total muscle sparing approach. Surgical wound complications were negligible.
- We reported both the necessity for re-surgery because of haemothorax and the need for hemotransfusion; no differences were detected between these subgroups. The Argon beam coagulation was largely used following surgeon's decision.
- In all the frozen sections, we performed we had a 100% confirmation in the definitive pathological report, but one case was ambiguous with pathological relapse on the site of resection. No special stainings were required.
- "throughout manuscript substages should be indicated by capital letters". Thank you for your suggestion, we will correct it. **Changes in the text:** we modified the text as advised -

Line 185, 206

- As described in Result's first paragraph, the different pathological stages were equally represented for each type of surgery and the patients' distribution was balanced in the two groups.
- About references: thank you for your suggestions, we will correct it.
- IBM SPSS statistical analysis software did not allow number at risk along and 95% confidence intervals. For the better readibility we preferred to leave just the Kaplan-Meier curves.
- We are going to correct typing errors, thank you for your suggestions. **Changes in the text:** we modified the text as advised - Line 137, 143, 146

Reviewer D

Thank you for submitting this paper to Journal of Thoracic Disease, I was pleased to receive it as a reviewer and read with great interests.

P/D (pleurectomy/decortication) for malignant pleural mestothelioma (MPM) has been widely accepted for another surgical option from extrapleural pnemonectomy (EPP) as its preservation of lung function and QOL. Authors et al have assessed whether a conservative approach, through P/D, might affect the long-term outcomes such as overall survival (OS) and recurrence-free survival (RFS) compared to Extended P/D (EPD).

This paper is well written based on large cohort and beneficial for our readers, however, I have several concerns about this article.

Comment 1. Please describe the reason why 35% of patients were not able to receive induction chemotherapy. Were there any technical differences between induction and non-induction?

Reply 1. There was no thechnical difference between induction and non-induction. This variability

depends on the lenght of the period of study (2009-2019), in which the treatment protocols have not been standardized and the guidelines were not homogeneous.

Comment 2. How many specimens were investigated by intraoperative frozen section to identify the absence of tumor infiltration to the diaphragm or pericardium? It seems to be difficult because of the characteristics of MPM itself.

Reply 2. We don't have this data. A frozen section was performed at the surgeon's discretion on the areas of greatest resistance, and the amount of resection was dependent on the negative margins.

Comment 3. The results that a longer survival was observed in the early stage of disease, with pN0 and when pleurectomy/decortication was carried out, preserving diaphragm and pericardium were somewhat lacking in novelty. Why did the resection of the pericardium or diaphragm affect the overall survival and NOT the recurrence-free survival? Did the reconstruction of the diaphragm cause deaths from other diseases not MPM? What are your thoughts on this?

Reply 3. Recurrence is somewhat to be considered as inevitable, whether diaphragm and pericardium are spared or not. The reconstruction of the diaphragm/pericardium did not cause deaths from other diseases. On the other hand, the patients who underwent pleurectomy/decortication preserving diaphragm and pericardium showed to have a better compliance to adjuvant treatments after surgery, being thus able to achieve a better overall survival.

Comment 4. What treatments were given at the time of recurrence of disease and how many people could be given some treatment? Did the reconstruction of the diaphragm affect the availability of chemo or immune-check inhibitors?

Reply 4. Thank you for your question. In our population, the recurrence rate was 49%, that is 76 patients experienced a recurrence. Among them, 6,5% were treated with surgery, 57,9% of the patients were submitted to adjuvant chemotherapy, 51,3% received IMRT and 2,6% immune-

therapy (all of these treatments alone or in combination). 18 patients could not receive any treatment for recurrence and were addressed to palliative care. Among those, 14 underwent extended P/D with diaphragm and/or pericardium prosthetic reconstruction.

Comment 5. Median follow-up (20 months) seems to be not enough for discussing the overall survival even for MPM.

Reply 5. Our median follow-up was depending on about one third of our population showing recurrence-free survival interval less than 12 months. This represents one of the most important prognostic factors affecting overall survival.

Reviewer E

I am delighted to review your manuscript as long-term outcomes after lung-sparing surgery for epithelial mesothelioma. Breda et al presented the long-term outcomes after pleurectomy/decortication in consecutive 155 epithelial mesothelioma patients. They mentioned that standard P/D and pN-status were independent prognostic factors, and also macroscopic complete resection, TNM stage and pT-status were significantly related to relapse. However, the results of this study would not be enough to support your conclusions, especially standard P/D as an independent prognostic factor. I would like to ask follows questions.

Comment 1. Patient characteristics according to type of surgery (P/D vs eP/D) would be needed to discuss. I guess P/D group had larger number of cT1 or/and pT1patients compared to eP/D group.

Reply 1. The statystical analysis of the patients in the two surgical groups (P/D vs EP/D) revealed that there is not a significant p-value for the distribution of the pathological stages between the two procedures. The stages are equally represented in the two groups (chi-square test p=0.189).

Comment 2: You should describe the reason why standard P/D was correlated with favorable outcomes. Only "Preserving normal organ" would not be enough to clarify.

Reply 2: The lack of a standardized technique for MPM led to a great variability of attitudes among surgeons. Some are more oriented to perform systematically EP/D with the resection of the diaphragm and pericardium, others prefer to carry out a P/D to save the structures at least in the lower stages of disease. The extended pleurectomy/decortication is now the most recommended lung-sparing technique to achieve the complete macroscopic removal in case of pleural mesothelioma and many surgeons are still oriented to resect diaphragm and pericardium systematically. In our analysis, we proposed that a less invasive resection could have benefit in term of overall survival and do not affect the recurrence rate. It is unclear how the preservation of the normal anatomy plays a role in increasing of the long-term outcomes, or the reason why it makes more tolerable further treatments in the context of multimodal management of this disease. In a recent article (recorded as reference) the IASLC committee for the research on mesothelioma, proposed a system to standardize the surgical treatment. It is claimed that the macroscopic complete resection can be achieved preserving pericardium and diaphragm. The authors stated that the outcomes after lung-sparing surgery are potentially proportional to the amount of normal anatomy and this may correlate with OS, perhaps by establishing a more robust state of health in anticipation of the inevitable recurrence.

Comment 3. Median follow-up period was too short to assess the survival such as 5-years survival.

Reply 3. Our median follow-up is affected by a shorter survival rate of a third of our cohort. These patients presented a recurrence-free interval shorter than 12 months. We found that the occurrence of a relapse within1 year from surgery is a detrimental prognostic factors.

Comment 4. Patient at risk should be added.

Reply 4. If you are meaning that patient at risk should be added in the legend of the figure of Survival, we used a software (the most used in his different versions) for statistical analysis that did not permit the over-writng in the figure. For reason of readibility we did not add in the image. (See Reply to Reviewer C).

Comment 5. Your cohort includes the patient who received induction chemotherapy, I guess that induction chemotherapy. Is there any correlations between induction chemotherapy and type of surgery or clinical outcomes.

Reply 5. The recent guidelines on the treatment of MPM did not specifically recommend induction chemotherapy versus adjuvant in the surgical-based multimodal strategy. In the period of our research (2009-2019) we considered generally perioperative chemotherapy without distinction between the different approach, which for that were not investigated in correlation with the type of surgery. The impact of chemotherapy is still a matter of debate and only the ongoing study EORTC 1205 whose preliminary results are expected for December 2021, may define the exact role of the systemic treatment in the context of multimodal management.