

## Peer Review File

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### Reviewer A

*We thank Reviewer A for his thoughtful and detailed reading of our manuscript. We incorporated the major comments and hope this is done with satisfactory for the reviewer.*

#### Major comments

##### Comment 1:

##### 1. Introduction:

> Perhaps one paragraph which concisely describes the first-line treatment of (resectable) mesothelioma and types of surgery would improve the manuscript. In addition, perhaps the staging procedure could be of interest.

##### Reply 1:

Thank you for this comment, we agree and added the following paragraph:  
The optimal treatment approach, for patient with histologically proven MPM, according to the latest ERS/ESTS/EACTS/ESTRO guidelines (5), is defined as induction chemotherapy followed by macroscopic complete resection (MCR). Prior to define this multimodality therapy approach, patients have to undergo mediastinal staging either via mediastinoscopy or via endobronchial ultrasound to rule out lymph node metastasis. Up to date the multimodality therapy approach consists of induction chemotherapy followed by macroscopic complete resection (MCR). The preferred systemic therapy for induction is still cisplatin/pemetrexed since the landmark trial by Vogelzang et al. in 2003 (6). There are recent immunotherapy phase II/III trials, that have been investigated and shown to improve outcome for resectable malignant pleural mesothelioma. MCR is defined as either extrapleural pneumonectomy (EPP) or (extended) pleurectomy/decortication ((E)PD).

##### Changes in the text:

We added changes in the Introduction section in line **96-111**

##### 2. Patients and methods:

##### Comment 2:

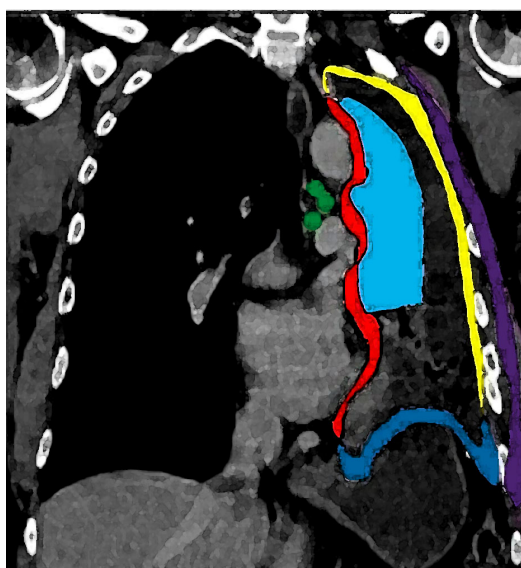
> The authors refer to figure 2, which I don't find very illustrative. I suggest to insert a better image, not necessarily based on a CT image; a drawn illustration may be clearer.

Reply 2:

Thank you for this comment, and since this illustration is not sufficiently clear, we have made changes and given it a more "descriptive look" by editing the CT image and drawing the lines more accentuated.

Changes 2:

Figure 2 is replaced.



3. Patients and methods:

Comment 3:

> The thoracic cavity was divided into 6 sections, one neo-pleural thickening (mediastinum) and one neo-pleural thickening. Perhaps to avoid confusion the latter should be renamed to neo-pleural thickening (chest wall) or (lateral)?

Reply 3:

Thank you, as described in Figure 2, there is only one Neo-pleural thickening, which was misleadingly described in the "patients and Methods" section. We tried to clarify the "Mediastinum" section in a more detailed way. We clarified this as follow:

*"The thoracic cavity was divided into the following sections: chest wall (CW), mediastinum (MED/pleura) diaphragm (Di), lung parenchyma (LP), neo-pleural thickening (exceptional mediastinal, (N-PT)) and lymph node (LN) (figure 2). Discrimination between the six locations are also demonstrated in figure 2."*

Changes 3:

Changes/Adaption/Renaming has been made throughout the whole manuscript.

4. Patients and methods:

“Each progression in the sense of tumor growth seen in one of the above-mentioned regions on imaging was declared as a relapse/metastasis.”

Comment 4:

> Sometimes infection may mimic local progression. What if a lesion disappeared at the next evaluation?

Reply 4:

We do agree on this important fact, and have indeed observed disappearance of some lesions in FU-imaging. Therefore, we never based our decision on a single image but on serial imaging, and in some cases tried to achieve histological confirmation.

Changes 4:

We added the above mentioned comment in the “patients and methods” section in line 163-165.

5. Patients and methods:

“In our cohort, each lesion was measured by the perpendicular diameter on axial CT 121 imaging by two surgical staff members independently”

Comment 5.1:

> What if they disagreed?

Comment 5.2:

> What if a lesion had an irregular shape and had the smallest diameter on axial CT?

Reply 5.1:

Thank you very much, in cases of disagreement, the two surgical staff members discussed and analyzed these cases together and additionally consulted the senior staff surgeon.

Reply 5.2:

Thank you for this point raised. In some cases, especially the ones that have been referred from external institutions, coronal or sagittal slices were absent. Axial slices are universally available on all CT scans. Since our aim is that the LR-score can be used as an universal tool for MPM worldwide, we measured recurrence site on axial imaging only.

It might be one of our limitations in this study.

*“In some cases, especially the ones that have been referred from external institutions, coronal or sagittal slices were absent. Axial slices are universally available on all CT scans. To ensure a broad and worldwide application, all measurements were therefore performed on axial image slices.”*

Changes 5:

We added a sentence within the “limitations and strength” (last paragraph of the discussion section **in line 367 -371**).

6. Table 1:

Comment 6:

> According to table 1 15 patients were not treated by multimodality treatment, although this was required for inclusion. Why were these patients not excluded from the study or what was the reason to keep them in?

Reply 6:

Thank you for this careful reading of our manuscript. We apologize for this mistake. The initial table 1 was not the final version with the final analysis. Nevertheless, Multimodality therapy stated as no in our database, also includes patients, that have not fully completed all cycles (3-4) of induction chemotherapy and this was the case in some of the patients.

Changes 6:

Table 1 is replaced.

7. Discussion:

Comment 7:

37 of 165 patients were excluded due to insufficient data; this is 1 in 5 and might also be considered a limitation of this study (possible bias).

Reply 7:

Thank you for this remark, this may be true, but acting as a referral center, it was not possible to obtain all available data and of equal quality for each patient from referring centers. Therefore, 37 of 165 patients were excluded due to insufficient data and this might also be considered a limitation of this study as a possible bias. We added this part in the “limitation and strength” section.

Changes 7:

We added a sentence in the “limitation and strength” section in line 371-375.

8.

Comment 8:

Could the authors speculate on why local recurrence is more common in the lymph nodes and (lateral) neopleura compared to the mediastinal neopleura?

Reply 8:

This is a very interesting point raised and should be more elaborated in the manuscript as suggested.

*“A reason that local recurrence seems to be more common in the lymph nodes and (lateral) neopleura than at the mediastinal pleura might be an easier access for histological biopsies leading to an “overdiagnosis” of these localizations. Secondly, we can speculate, surgically approaching the lateral pleura is easier and more radical by pleurectomy than the mediastinal pleura and therefore microscopic residues may remain easier there.”*

Secondly, the pleural/lymphogenic spread is different and the pleural is removed. One could assume that analogous to lung cancer, we sometimes encounter “skip N2”. In MPM, we speculated that N2 skip lesions for lymph node metastasis would be more prominent mediastinal than hilar.

Changes 8:

The above written paragraph is added in the Discussion section in line 348-354.

Minor comments

1. Abstract:

“Patients with  $LRS \leq 4$  had a longer survival undergoing radiotherapy or local surgery for second line treatment whereas patients with  $LRS > 4$  if they underwent chemotherapy.”

Comment 1:

> This sentence is grammatically not correct. If using “whereas” a verb is missing.

Reply 1:

We corrected it.

Change 1:

In the result section of the abstract, line 78.

*Patients with  $LRS \leq 4$  had a longer survival undergoing radiotherapy or local surgery for second line treatment whereas patients with  $LRS > 4$  only if they underwent*

*chemotherapy.*

2. Introduction:

“Patients diagnosed with malignant pleural mesothelioma (MPM) have a high risk of local recurrence even after multimodality therapy approach.”

Comment 2:

> Are 4 references, 2 of which seem to be guidelines, required to make this statement?

Reply 2:

Thank you for this remark, due to the partly inconformity of the therapy approaches for patients diagnosed with malignant pleural msothelioma, we wanted to highlight these difficulties by referring to different guidelines.

Change 2:

None

3. Introduction:

“Based on the extension of peritoneal carcinomatosis established by Sugarbaker’s peritoneal cancer index (PCI), a thoracic spread pattern was mirrored and tailored for recurrent pleural mesothelioma.

Comment 3:

> A single reference to Sugarbaker is enough.

Reply 3:

We only referred to one reference by Sugarbaker (No.6). *Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. Cancer Treat Res. 1996;82:359–374.*

The number was repeated and could therefore raise the impression of a repition. We combined it.

Change 3:

We deleted the one repition of reference No.6 in the introduction section **in line 123.**

4. Patients and methods:

“Follow up was monitored by serial every 4 months...”

Comment 4:

> This sentence is not grammatically correct.

Reply 4:

Thank you for reading our manuscript that carefully. We made the changes accordingly by adding the word “imaging”.

Change 4:

Changes have been adopted in the “Patients and Methods” section in **line 149**.

5. Patients and methods:

“In our cohort, each lesion was measured by the perpendicular diameter on axial CT 121 imaging by two surgical staff members independent”

Comment 5:

> Independently

Reply 5:

Correct, we do apologize.

Change 5:

Changes have been made accordingly in the “Patients and Methods” section in **line 172**.

6. Results:

“209 patients achieved MCR following induction chemotherapy”

Comment 6:

> This is somewhat confusing. They first underwent chemotherapy, followed by surgery with MCR achieved.

Reply 6:

Yes, we understand that this might be confusing, although grammatically correct. We rephrased the sentence to “*209 patients achieved MCR after undergoing induction chemotherapy*”.

Change 6:

Changes have been made in the “Result” **section in line 231-232**.

7. Results:

“Male and epithelioid type were dominant”

Comment 7:

> Male sex

Reply 7:

We agree and made the changes accordingly.

Change 7:

The word “gender” has been added in the “result” **section in line 243.**

8. Results:

“revealed, a”

Comment 8:

> Remove comma

Reply 8:

Thank you. We apologize as we could not find this mistaken “comma”.

Change 8:

None

9. Whole manuscript:

Comment 9:

> The succession of figures seems not to be chronologically: 1, 2, 3, ... I find consecutive references to figure 1, 2, 5, 3, but no 4?

Reply 9:

Thank you for this careful observation. We ordered it correctly.

Change 9:

Changes have been made throughout the whole manuscript accordingly.

10. Discussion:

“based on the anatomical structures approached by MCR”

Comment 10:



> What does this mean?

Reply 10:

We wanted to express that MCR is performed in a standardized way by first peeling off the parietal pleura along the chest wall, followed by decortication and finished by partial resection of the pericardium and the resection of the diaphragm. However, this was not elaborated enough with the sentence and therefore we have added another statement.

Change 10:

We added the sentence:

*“ The approached anatomical structures are the ones that are incorporated in our Local recurrence score (LRS) by dividing the hemithorax into 6 regions. These structures are always approached in a standardized way, at our institution, by first peeling off the parietal pleura along the chest wall, followed by decortication and finished by partial resection of the pericardium and/or the resection of the diaphragm. Associated with each of these localizations is lymph node resection.”*

In the “Discussion” [section in line 292-300](#).

## **Reviewer B**

Comment:

Firstly, I would like to commend their efforts in the treatment of this challenging disease and their attempts to rationalize the difficult management of disease progression.

I appreciate their attempt to categorize tumour spread but there are important areas that need to be addressed -

The main limitation of the study is the lack of histological confirmation of disease progression. I note that the major site was reported to be neo-pleural thickening. This is very difficult to interpret after lung sparing surgery and scarring may well be over interpreted as tumour progression. This may be why survival after EPD was longer than EPP even though the LR score was lower. Similarly, biopsy of tumour progression may reveal epithelial-mesenchymal transition with sarcomatoid elements predominant and thus explaining inferior survival.

The use of LR score to determine further treatment is controversial and many of the authors conclusions are unjustified. The use of local therapy for any more than symptom control has not been sufficiently established and the authors should concede this. Radiotherapy has not been shown to influence survival and the authors should clearly define their indications and techniques for redo surgical excision.

The authors should consider the use of PET imaging in the assessment of disease

progression and the preferential use of tumour volumetrics over the isolated measurement of tumour dimension.

Reply:

We thank the reviewer for reading our manuscript so carefully and that the reviewer raised important points, that may be explained in a more detailed way.

We do agree that the distinction between recurrence and scarring processes etc may be very difficult even for experienced surgeons and/or radiologists. Nevertheless, we do several follow ups of imaging in an alternative manner by CT and PET/CT and only in case of non-disappearance after repeated serial imaging we conclude a recurrence. Additionally, we perform a so called baseline CT scan 4 weeks and 3 months after surgery to be able to get a better distinction between scarring processes and recurrences in the follow up period. The addition of PET/CT may be helpful for recurrences on certain spots, but for lymph nodes for example it may also lead to false positive results as they show metabolic activity for several reasons even a few months after surgery.

Nevertheless, biopsies, if accessible, have always been tried to obtain, if the patient was willing to do so. Nevertheless, most of the locations are not easily accessible and the decision for further adjuvant recurrence therapy has been made at our interdisciplinary tumourboard together with all mesothelioma specialists and the high suspicion of recurrence.

The decision which patients should be operated on in case of recurrence is crucial and stays an exception. The decision was always be made consensual at our weekly based interdisciplinary tumorboards and always with the same and most experienced thoracic surgeon in malignant pleural mesothelioma surgery.

The indications and techniques for redo surgical excision are in case of symptom control if not otherwise achievable and has been decided individually in every case. Additionally, if the patient rejected radiotherapy for pain control.

Furthermore, adjuvant radiotherapy as an therapy option, was recently published by our group, where 21 consecutive patients have been treated with hypofractionated radiotherapy for oligoprogressive

MPM. The median progression free survival (PFS) after SBRT was 6 months (range 0–21 months)

and the median OS from first first SBRT was 29 months (range 0–61 months).

Additionally, only one patients experienced above Grade 3 toxicities.

(Schröder C, Opitz I, Guckenberger M et al., Stereotactic Body Radiation Therapy (SBRT) as Salvage Therapy for Oligorecurrent Pleural Mesothelioma After Multi-Modality Therapy. *Front. Oncol.*, 26 September 2019. <https://doi.org/10.3389/fonc.2019.00961>)

Changes:

Changes have been made in the “Limitation and strength” section **in line 389-406**.

“In this challenging disease, pathological findings are well known as a prognostic factor in any therapeutic approaches. The absence of pathological factors is one of the most considerable issues in this study. However, the definitive pathological diagnosis of local recurrence is often challenging due to postoperative situations.

The local therapies for local recurrence such as surgical excision is still controversial, however several reports revealed the efficacy of local therapies in such a situation.

The decision which patients should be operated on in case of recurrence is crucial and stays an exception. The decision was always be made consensual at our weekly based interdisciplinary tumorboards and always with the same and most experienced thoracic surgeon in malignant pleural mesothelioma surgery.

Furthermore, adjuvant radiotherapy as a therapy option, was recently published by our group, where 21 consecutive patients have been treated with hypofractionated radiotherapy for oligoprogressive

MPM. In this retrospective single-institution study the feasibility of a SBRT approach for oligorecurrent MPM was proven.”

**Reviewer C**

I compliment the authors on their attempt to design a prediction model to aid in the selection of treatment for patients with recurrent disease.

As they state themselves: this model should be tested prospectively before any recommendations can be done.

Some comments:

Comment 1:

Figures mentioned in 'statistics' are 'results' and should be mentioned accordingly

Reply 1:

Thank you for this carefull observation. We ordered it correctly.

Change 1:

Changes have been made throughout the whole manuscript accordingly.

Comment 2:

Please mention the median follow up time in the results section

Reply 2:

Thank you for this point raised.

Median follow-up: 58.6 months, calculated via reverse Kaplan Meier.

We added the FU time in the result section in line.

Change 2:

FU time was added in the “Result” **section in line 250-251.**

Comment 3:

Table 2: define 'MST'

Reply 3:

We apologize for this mistake. The initial definition was MST (Median survival time), but we changed it for a better understanding to PRS (Post recurrence survival time), but forgot to change it in this table 2.

Change 3:

We changed MST to PRS (as used in the whole manuscript) and added the definition in the table’s legend.

Comment 4:

line 54: From 2001 until 2017, 128 consecutive MPM patients with LR undergoing macroscopic.... : who underwent OR after undergoing

Reply 4:

Thank you, we made the changes accordingly and rephrased the sentence:

*“From 2001 until 2017, 128 consecutive MPM patients with LR who underwent macroscopic complete resection by extrapleural pneumonectomy (n=61) or by (extended) pleurectomy/decortication (n=67), were included in the present analysis.”*

Change 4:

Changes have been made in the “Abstract Result” **section in line 65-69.**

Comment 5:

line 63: whereas patients with LRS > 4 if they underwent chemotherapy: a word seems to be missing in this sentence

Reply 5:

We corrected it.

Change 5:

In the result section of the abstract, **line 78**.

*Patients with  $LRS \leq 4$  had a longer survival undergoing radiotherapy or local surgery for second line treatment whereas patients with  $LRS > 4$  **only if they underwent** chemotherapy.*

Comment 6:

line 96 'a MPM' instead of 'an'

Reply 6:

Thank you, unfortunately we could not find this mistaken spelling.

Change 6:

None

Comment 7:

line 105 'by serial' : by serial what?

Reply 7:

Thank you for reading our manuscript that carefully. We made the changes accordingly by adding the word “imaging”.

Change 7:

Changes have been adopted in the “Patients and Methods” section in **line 149**.

Comment 8:

line 121: independentLY

Reply 8:

Thank you and we do apologize. We made the change accordingly.

Change 8:

Changes have been made accordingly in the “Patients and Methods” section **in line 172**.

Comment 9:

line 122: lesionS

Reply 9:

Correct, we do apologize. We made the change accordingly.

Change 9:

Changes have been made accordingly in the “Patients and Methods” section **in line 174.**

Comment 10:

line 148 273 MPM patients: you mention 249 later on and in figure 1

Reply 10:

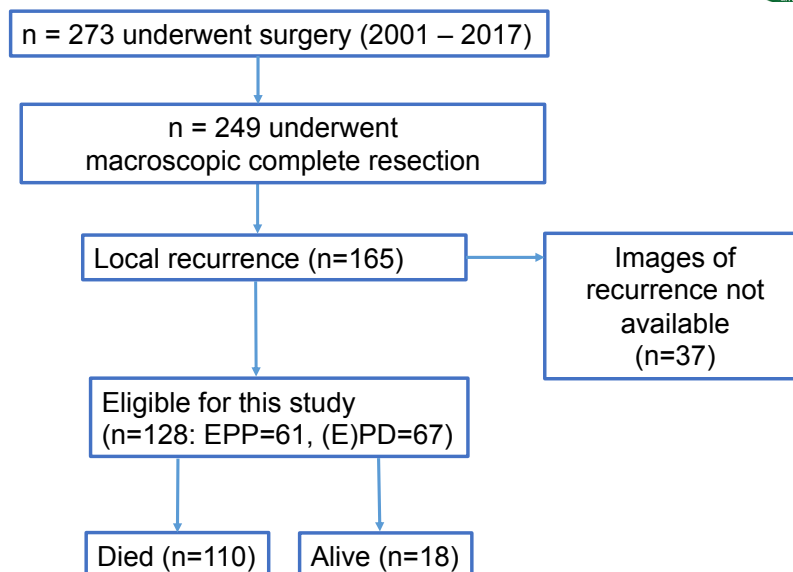
From 2001 until 2017, 273 MPM patients were diagnosed with malignant pleural mesothelioma and underwent curative intent surgery and of those *249 patients achieved MCR after undergoing induction chemotherapy (figure 1)*. Out these, 165 patients were diagnosed with LR.

Thank you for mention this, 273 patients underwent surgery with curative intent (ITT), but only 249 patients achieved macroscopic complete resection.

Changes have been incorporated in Figure 1.

Change 10:

We adapted the Flowchart/Figure 1.



Comment 11:

line 212 there is --> there ARE

Reply 11:

Thank you. We made the change accordingly.

Change 11:

We changed it in the “Discussion” section **in line 313**.

Comment 12:

line 213 'age, performance status' are not associated with worse survival, however higher age and worse performance status are. Please nuance

Reply 12:

Yes, this might be misleading and we adopted the suggested change into the manuscript.

Change 12:

We added the words “higher” and “worse” in the “Discussion” **section in line 313**.

Comment 13:

line 225: check grammar and length of sentence

Reply 13:

We separated the sentences to give more clarification.

*“We already reported comparable results in patients undergoing redo surgery for second line therapy after relapse. They had a significantly longer median PRS compared with patients receiving other types of second-line therapy (16 months vs 9 months).”*

Change 13:

We made the changes accordingly in the “Discussion” section in **line 339-342**.

Comment 14:

line 236 'and distribution': this statement cannot be made. A discussion about LRS  $\leq 4$  but situated at the chest wall or LN should be written if you want to make this statement.

Reply 14:

Thank you for this point raised. We do agree and rephrased the sentence:

*“Another point that supports these therapeutic approaches is the distribution of the recurrence if situated at the chest wall or LN and if represented in a LRS of  $\leq 4$ .”*

Change 14:

We changed the sentence in the “Discussion” **section in line 345-346**.