

Peer Review File

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Reviewer A

Overview and general recommendation:

Although the main points of this paper are excellent and worthy of publication, some of them may be misleading to readers, so please correct them.

P2 L5

Conclusions: EPD/HITOC may be feasible and safe for localized epithelioid pleural mesothelioma. Changing the surgical approach to a less radical lung-sparing technique clearly improved overall survival compared to trimodal EPP.

This conclusion can be justified from the contents of this paper.

Unfortunately, we do not understand your statement on this. You may have forgotten a "not". Therefore, we have softened the wording.

Materials and Methods

P3 L9

EPP between February 2001 and June 2012 (EPP cohort)

The above notation differs from the notation in Table 1. Please check it.

Thank you very much for recognizing this typo. According to the correct time range in the text, we have corrected the year in Table 1 to 2001.

Cytoreduction by extended pleurectomy/decortication

P4 L13

Patients with macroscopic tumor residuum above 1 cm³ were classified as macroscopically incomplete (R2).

Please indicate the number and ratio of R1 and R2 cases in EPD (N = 57).

We have added a paragraph to the text and included the numbers (page 11, lines 6-8). The parameters are already shown in Table 3 (macroscopic complete (R1) n=51; macroscopic incomplete n=6).

Within a multimodal treatment approach, patients received four cycles of adjuvant platin-based chemotherapy in combination with pemetrexed starting four to six weeks after cytoreductive surgery.

Why 4 cycles of adjuvant CDDP/PEM chemotherapy? Please explain the reason.

The number of therapy cycles as well as the chemotherapeutical agents used were defined on an interdisciplinary basis according to the ASCO Guidelines 2018 recommending four to six cycles of pemetrexed/platin-based chemotherapy in context of multimodal treatment (10.1200/JCO.2017.76.6394). Two currently recruiting randomized clinical trials in adjuvant setting (ClinicalTrials.gov Identifier: NCT04177953 and NCT04996017) allow four cycles of

chemotherapy. Thus, our standard post-operative approach consists of four cycles of pemetrexed and cisplatin or carboplatin, also based on the NSCLC adjuvant chemotherapy paradigm. We have added an explanation of our decision making at that time regarding number of therapy cycles and substances for adjuvant chemotherapy to the text (page 8, lines 13-20).

P4 L18

Hyperthermic Intrathoracic Chemoperfusion

Four 28 Ch chest tubes were placed in the thoracic cavity before the anterolateral thoracotomy was closed. Hyperthermic perfusion was achieved at 42°C using a RanD Performer HT (RanD S.r.l.; Medolla, Italy). Cisplatin (200 mg in 250 mL 0.9% saline solution) was added into the 4750 mL 0.9% saline solution. HITOC was performed for 60 minutes at 42°C. The total perfusate volume was 5000 mL. The final cisplatin concentration was 40 mg/L. The flow was set to 1000 mL/min.

Please explain the universality of the HITOC procedure by citing references.

Please comment on whether this technique is feasible in other facilities.

We added three citations to underline the universality of the HITOC procedure. Moreover, we commented on the feasibility of the procedure in other facilities (page 8, line 28 & page 9, lines 1-3).

Standard palliative chemotherapy

P4 L31

In patients with progressive disease, grade 3–4 toxicities, or cumulative toxic doses, the ongoing therapy was stopped or changed to second line.

How many patients and what percentage of patients moved to the second line?

Please indicate the second line regimen.

In total, 45 patients (80.3%) moved to second line chemotherapy: 4 patients due to toxicities (7.1%), 17 because of disease progression during treatment (30.4%), and 24 due to cumulative dosis of platin-based chemotherapy (42.9%).

The second line regimen at our institution during the analyzed period was vinorelbine or gemcitabine monotherapy. This information was also added to the text (page 9, lines 12-13).

3. Results

P5 L7

The difference in performance status before surgery or before chemotherapy initiation was significant: the proportion of patients with an Eastern Cooperative Oncology Group (ECOG) status of 1 was higher in the EPP and CTx group than in the EPD/HITOC group.

Please consider the impact of the above results on the conclusions of this paper.

Thank you for this relevant point. We added our consideration on this topic to the discussion section and discussed it as a limitation of the study (page 16, lines 19-25): “As a limitation, we cannot rule out that the observed differences of performance status between the three groups might have influenced overall survival.”

P5 L12

The distribution of the tumor TNM stage is provided in Table 2.

Please answer the following questions about the contents of Table 2.

CTx(N=56)

ΣI/II 38(68%) vs ΣIII/IV 18(32%)

More than half of these cases are operable. Why didn't they lead to surgery? Please comment.

EPD/HITOC(N=57)

ΣI/II 44(77%) vs ΣIII/IV 13(23%)

This includes more than 20% of cases where surgery is not recommended.

Please explain the reason.

Concerning the proportion of T1/T2 tumors in the chemotherapy cohort, patients did not proceed to surgery due to progressive disease during chemotherapy, comorbidities, or patient refusal.

Within the proportion of T3/T4 tumors in the surgical cohorts, most of the patients showed tumor infiltration of the mediastinal fat, the pericardium, or solitary nodules of tumor invading the thoracic wall. This extension of tumor infiltration was diagnosed in most of the cases during surgery and not preoperatively. The amount of tumor tissue and potential infiltration into surrounding structures can only be reliably diagnosed during surgery. Preoperative radiologic staging is often misleading in mesothelioma patients as shown by Gill et. al: in more than 60% of patients pathological and clinical staging is discordant (10.1093/jnci/djx175).

We added the following paragraph to the text (page 10, lines 17-24): “Within the proportion of T3/T4 tumors in the surgical cohorts, most of the patients showed tumor infiltration of the mediastinal fat or the pericardium or solitary nodules of tumor invading the thoracic wall. These structures have been resected and pericardium was replaced if necessary. Concerning the proportion of T1/T2 tumors in the chemotherapy cohort, patients did not undergo surgery due to comorbidities, high local tumor burden on computed tomography scan, patient refusal, and grade 3-4 toxicity during chemotherapy within a neoadjuvant treatment concept. T4 tumors in the EPP group showed unexpected infiltration of the esophagus in one case and transmural infiltration of the pericardium in all other cases.” Moreover, we discussed this issue citing the above-mentioned reference.

Survival

P5 48

Stratification of the treatment cohorts showed a higher OS in both surgical cohorts than in the CTx cohort (Figure 2B).

Table4

Therapy (CTx ref.) EPP P=0.440 HR:0.806 (95%CI 0.467–1.393)

There is a discrepancy between the results in Figure 2B and those in Table 4.

Why can you draw the following conclusions from the above results?

EPP improved the survival of the patients better than 50 CTx, from 15.5 to 24 months.

To avoid misunderstanding, it is important to emphasize that it was not statistically significant.

The discrepancy between results in Figure 2B and Table 4 are explained by univariate analysis in Figure 2B on the one hand and multivariate cox-regression analysis in table 4 on the other

hand.

Using Kaplan-Meier analysis, survival after EPP was significantly better compared to CTx alone. This univariate analysis is displayed in Figure 2. In multivariate analysis, only EPD/HITOC but not EPP remained as an independent and significant prognostic factor for OS (Table 4) as described on page 12 line 20-23.

4. Discussion

P7 43

There is still no clear evidence on the impact of surgery on survival in patients with pleural mesothelioma compared to chemotherapy. There is only one randomized study, the MARS I trial, that showed no advantage of EPP over chemotherapy alone.

As noted, EPP is generally described as a very harmful operation.

Types of surgery post-neoadjuvant chemotherapy for pleural mesothelioma.

Kuribayashi K, Doi H, Kijima T.

Expert Rev Respir Med. 2019;13(12):1189-1194.

Citing the above review, you should comment on the need for EPP for mesothelioma in the future.

We included the citation into the manuscript and commented on the need for EPP in the future (page 16, lines 16-18).

Reviewer B

This is a well-written descriptive manuscript of a single institution's experience with surgery and chemotherapy for the treatment of mesothelioma. I do have the following suggestions:

1) The contextualization of the Checkmate 743 does not paint a full picture. There was not a significant benefit from IO among the epithelioid patients. Not sure if this justifies the use of IO as the adjuvant for surgery. Rather, discussion of the chemo-IO approaches is missing. This is more likely to be promising as a perioperative therapy for epithelioid mesothelioma.

Thank you for this relevant issue. We added the missing effect of IO for epithelioid subtype in the Checkmate 743 to the text. We are also not sure if chemo-IO will be the ideal adjuvant treatment for resected epithelioid mesothelioma. Due to missing other options to increase survival, we hope to get this question answered by results from the NICITA trial.

2) It would be helpful if the authors address the time bias of this study. That is to say, even with the same regimen, over time, the survival of patients receiving those drugs has improved over time. It is unclear whether this is due to variations in patient selection, the efficacy of subsequent lines of therapy, earlier diagnosis, and/or better supportive care. Therefore, when indicating the "later" surgical cohort does better than the "earlier" EPP cohort, it is challenging to know how to interpret that difference. This should be discussed as a limitation of this report.

We added this issue as a limitation to the text: "Moreover, OS of patients receiving chemotherapeutic drugs has improved over time and might influence patient outcome, possibly

due to patient selection, earlier diagnosis, better supportive care as well as improved surgical technique.”

3) One challenge here that cannot be accounted for is the physician selection of treatment approach. What were the reasons that patients did not have surgery among the cohort that received only chemotherapy? Since this isn't a randomized prospective trial, surgical and non-surgical patients are not equivalent and interchangeable and there must have been something about those patients or their disease that led the team to recommend chemotherapy without inclusion of surgery. This should be identified in the results section and addressed in the discussion as a limitation of the report.

We added the reasons for not being selected for surgery to the results section. Moreover, we discussed this point as a limitation since it might influence outcome.

Reviewer C

In a retrospective study the authors have compared the overall survival (OS) of patients with malignant pleural mesothelioma (MPM) of epithelioid type, treated with two different types of surgery, trimodal extrapleural pneumonectomy (EPP) (69 patients) and extended pleurectomy/decortication combined with hyperthermic, intrathoracic chemoperfusion (EPD/HITOC) (57 patients), respectively. In their comparison they have also included 56 patients who received conventional chemotherapy.

They found that EPD/HITOC was significantly associated with longer OS and conclude that EPD/HITOC may be a safe and feasible method to treat localised epithelioid MPM.

The paper is well-written, addressing a significant topic. The balance between the sections is good, the patient categories are concisely described and the discussion is relevant to the results. However, the fact that the study is retrospective is a major drawback (as pointed out by the authors themselves). The patients are for obvious reasons not comparable (to design an ethically acceptable randomized study would in any case be delicate).

The patients who received chemotherapy differed from those who were selected for EPD/HITOC treatment regarding variables expected to be prognostic (age, ECOG, nodal involvement, TNM stage), as seen in Table 1.

However the very same variables are shown to be insignificant in the Cox regression. This outcome is counterintuitive and should be discussed in detail and the complete dataset should be available as a supplement to allow for more detailed and specific analysis. Do e.g. the expected effects, i.e. the correlation between OS and age, ECOG and nodal involvement reappear when analysing within each treatment group?

The variables age, ECOG and nodal status significantly influenced overall survival in univariate analysis. In the cox-regression analysis, variables do not keep their significance in multivariate analysis. This has been added to the text. Moreover, the dataset will be provided for more detailed and specific analysis. This was included in the data sharing agreement of the journal. In addition, we performed a cox-regression analysis for each subgroup to analyze whether the

observed effects reappear within each treatment group. The results are summarized in the tables below:

	<i>HR</i>	<i>95% CI</i>	<i>P value</i>
EPD/HITOC (n=57)			
ECOG 1	2.445	1.126–5.311	0.024
age > 70 years	1.853	0.892–3.851	0.098
N status (N0 ref.)			
N1	0.448	0.052–3.857	0.465
N2	-	-	-
female sex	1.146	0.460–2.855	0.769
stages III & IV	0.516	0.067–3.987	0.526

	<i>HR</i>	<i>95% CI</i>	<i>P value</i>
EPP (n=67)			
ECOG 1	1.195	0.697–2.048	0.518
age > 70 years	-		
N status (N0 ref.)			
N1	1.006	0.286–3.534	0.993
N2	-		
female sex	0.840	0.405–1.742	0.640
stages III & IV	0.573	0.186–1.761	0.331

	<i>HR</i>	<i>95% CI</i>	<i>P value</i>
CTx (n=56)			
ECOG 1	0.769	0.383–1.544	0.460
age > 70 years	1.045	0.533–2.048	0.898
N status (N0 ref.)			
N1	1.230	0.592–2.554	0.578
N2	1.958	0.558–6.871	0.294
female sex	0.512	0.210–1.249	0.141
stages III & IV	1.206	0.549–2.651	0.641

In the EPD/HITOC subgroup ECOG 1 performance status represents an independent negative prognostic factor for overall survival. This effect could neither be observed in the EPP nor in the CTx cohort. In the later subgroups no independent and significant prognostic factor for overall survival could be identified in multivariate analysis.

In Table 1 it is unclear which of the three possible pairs is meant when reporting p-values. Please clarify.

We added the details concerning p-values for age and ECOG into table 1 to clarify which of the possible pairs is meant when reporting p-values. Details concerning survival time and significance are displayed in figure 2.

The authors might explain why they chose 70 years for splitting the age groups in the KM analysis. There were practically no 70+ patients in the EPP group acc to Fig 1.

According to the literature, older age is regularly discussed to serve as a limiting factor to proceed patients to surgery. Taking the whole patient cohort into account regardless of treatment, we wanted to analyze if increased age impacts overall survival. We chose 70 years as cutoff according to Lapido et al. (10.1016/j.jtcvs.2022.01.054) or Fournel et al. (10.1016/j.lungcan.2022.03.014) because colleagues demonstrated worse overall survival for

patients with pleural mesothelioma older than 70 years.

As Cox regression can make use of continuous variables a discussion why a binary age variable was used would be of value.

Patients younger than 70 years had significant better overall survival than older patients in univariate analysis. To analyze influence on survival in multivariate analysis, we decided to include age in the COX regression model as a binary age variable. During revision, we repeated COX regression analysis using age as a continuous variable. The results are summarized in the tables below and results were well comparable:

	<i>HR</i>	<i>95% CI</i>	<i>P value</i>
entire cohort (n=182)			
ECOG 1	1.091	0.746–1.597	0.654
age > 70 years	1.325	0.802–2.189	0.272
N status (N0 ref.)			
N1	1.296	0.704–2.385	0.405
N2	2.226	0.685–7.227	0.183
female sex	0.778	0.485–1.246	0.296
stages III & IV	1.116	0.620–2.010	0.715
therapy (CTx ref.)			
EPP	0.806	0.467–1.393	0.440
EPD/HITOC	0.428	0.245–0.748	0.003*

	<i>HR</i>	<i>95% CI</i>	<i>P value</i>
entire cohort (n=182)			
(Age continuous variable)			
ECOG 1	1.062	0.723–1.559	0.760
age	1.020	0.995–1.046	0.114
N status (N0 ref.)			
N1	1.299	0.707–2.385	0.399
N2	2.288	0.705–7.424	0.168
female sex	0.777	0.486–1.244	0.293
stages III & IV	1.079	0.605–1.927	0.796
therapy (CTx ref.)			
EPP	0.875	0.512–1.496	0.626
EPD/HITOC	0.430	0.250–0.738	0.002*

The authors point out that improved therapy results and post-surgery care over time may partly explain the longer OS for the EPD/HITOC group than for the EPP group. They also report that the EPD/HITOC patients were older. But those patients also tended to have more nodal involvement and more advanced TNM-stage. This might indicate that the indications for surgery have been widened, patients with an inherent poorer prognosis also being included. If it were so it would strengthen the conclusion that EPD/HITOC might be a good treatment option. Potential biases caused by the different time periods might be specifically addressed in the discussion.

We added the time bias as a limitation into the discussion section. In contrast to EPP, selection criteria of patients for EPD/HITOC were definitely widened. We also added this to the text.

At the end of the discussion the authors mention "some limitations". These limitations (and those I have mentioned above) are so significant for the interpretation of the results that they should be integrated and addressed in the discussion proper.

We included the limitations into the discussion to directly link important points of the limitations to the discussion as suggested.

A few minor remarks

Title: "epithelioid" should be added

The term was added to the title.

According to the text in the M&M section only patients with maximum T4N1M0 are included in the EPD/HITOC cohort but according to Table 2 there is one M1 patient

The patient with M1 status suffered from very small bipulmonal lesions. After interdisciplinary

discussion, patient underwent EPD/HITOC. Pathological analysis revealed pulmonary metastases from mesothelioma, in combination with the radiologically documented bipulmonal lesions unfortunately M1. We added this to the text.

Page 3, line 1 EPD preferable to extended PD

Thank you for this suggestion. We have changed this in the text.

Reviewer D

This is a manuscript of retrospective analysis concerning the role of surgery in the treatment of malignant pleural mesothelioma. As the authors state, the role of surgery and the surgical option is one of the most controversial topics in thoracic oncology. Although there are some limitations described in discussion, the manuscript is well-written and potentially would give important information to readers in the area.

It looks natural that survival of patients treated by chemotherapy is the poorest. The reviewer want to know the policy of judging the patients of MPM whether resectable or unresectable in their institution.

For judgment concerning resectability, the affected hemithorax should not show a relevant shrinkage and tumor mass within the contrast-enhanced computed tomography should not infiltrate into non-resectable structures (heart, vertebral spine, etc). We added a paragraph to the methods section. Moreover, important cardiac and pulmonary comorbidities as well as individual patient preferences were taken into consideration.

p6, line 31: 'The survival' should be changed as ' The median survival.'

Thank you for this suggestion. It was added to the text.

p6, line 34: 'epithelial' should be changed as 'epithelioid'

Thank you for detection of this typo. Epithelial was corrected to epithelioid.

Reviewer E

Interesting retrospective data from a single centre in Germany that switched from EPP to EPD.

(1) Why did you not operate some of the chemotherapy patients, as their cTNM suggests operability (55% T2 disease, 23% T3 disease; both are considered operable)? This more limited disease usually performs better, so I am a bit disappointed in the poor OS. Was this group perhaps suffering from a larger number of comorbidities?

The patients did not undergo surgery due to comorbidities, patient refusal, or progressive disease during chemotherapy. We added this to the results section.

(2) Why did you operate on T4 disease? Landmark papers (Krug, Weder, Van Schil, Treasure +

ongoing EORTC 1205 trial) excluded these patients. Or were this all upstaged TNMs? It would be interesting to see and compare the clinical TNM for surgical patients, as this is important in deciding whether to operate or not.

The reason for surgery on T4 tumors was unexpected infiltration of tumor to the esophagus in one case and also unexpected transmural infiltration of the pericardium in all other cases. Since clinical TNM usually “understages” pathologic TNM, pTNM is much more accurate. In most cases, the extension of tumor infiltration was diagnosed during surgery and not preoperatively. Since preoperative radiologic staging is often misleading in mesothelioma patients by “understaging” mesothelioma patients as shown by Gill et. al. with more than 60% of patients having discordant c- and p-stage. The amount of tumor tissue and potential infiltration into surrounding structures can only reliably be diagnosed during surgery.

(3) The authors report that improvement in salvage therapy and perioperative management could explain (partially) the improvement in OS from EPP to EPD. Could improvement in surgical experience not be the major factor, given the chronological evolution and the high number of re-interventions in the EPP group (not explicitly reported in the landmark trials, but 1 in 4 seems very high)?

For sure surgical experience can improve surgical outcome for mesothelioma patients. But during the years, only a small number of experienced surgeons performed surgery on mesothelioma patients at our institution. EPP is known to be associated with high perioperative morbidity and the morbidity rate / re-intervention in our EPP cohort is well comparable to the existing literature (e.g. 10.1016/j.lungcan.2013.11.026). From our point of view, general improvement in surgical experience may not be a major factor explaining the reduced morbidity rate in the EPD cohort. The lung-sparing surgical approach of EPD might be responsible for the reduced perioperative morbidity and fewer re-interventions.

(4) Why was the ECOG score in EPD significantly better compared to EPP, whereas generally EPD is only performed in very fit patients? As ECOG PS is a well-known prognostic factor, this might partially explain why EPD outperformed EPP.

ECOG in EPP patients might be affected by neoadjuvant chemotherapy. Since ECOG has no significant effect on overall survival in multivariate analysis, a relevant impact on our study results seems to be rather unlikely. We added this issue to the discussion as a potential limitation of the study.

(5) I think the only safe conclusion is that switching from EPP to EPD is not associated with worsening OS or increased complications. This is not the first paper published on the subject. I miss a reference to such a paper, e.g. Batirel (2016)

We included the publication of Batirel and colleagues to the manuscript (10.1016/j.jtcvs.2015.09.121). In addition, we added a statement to the discussion.

(6) "Mesothelioma is associated with asbestos exposure". This is not entirely correct, as in some cases hereditary factors or radiotherapy plays a role. No data are reported on asbestos exposure (which is reported in some trials).

We added hereditary factors and radiotherapy as reasons for mesothelioma development to the

text. In the EPD cohort 60% of patients (n=34) had asbestos exposure whereas 26% of patients had no known exposure and in 14% of patients the status of asbestos exposure remained unclear.

Reviewer F

I congratulate the authors on the paper entitled "Multimodal therapy of pleural mesothelioma: improved survival by changing the surgical treatment approach".

This manuscript analyzed the overall survival after multimodality therapy (Neoadjuvant chemo+ Extrapleural Pneumonectomy + Postoperative radiation versus Pleurectomy Decortication+ HITOC+ Adjuvant chemo) versus chemotherapy alone for epithelioid malignant pleural mesothelioma. This is a retrospective study including 182 patients including 69 patients who underwent EPP, 57 Pleurectomy Decortication, and 56 just chemotherapy. The authors concluded that overall survival for epithelioid malignant mesotheliomas improved after surgery. Their results show greater benefit especially in the pleurectomy decortication-based multimodality group compared to chemotherapy alone. There has been a shift from extrapleural pneumonectomy to pleurectomy decortication during the last decade and the authors here suggest performing lung-sparing surgery as the preferred surgical method based on their results. The median survival in the pleurectomy decortication group here represents a very good result achieved in these patients. I praised the group for the 30- and 90-day mortality rate. This paper is interesting and important. I have some questions and suggestions for the authors:

Abstract- The abstract and manuscript should emphasize the comparison between two multimodality treatments: Trimodal EPP versus EPD/HITOC/Adjuvant chemotherapy versus just chemo. Adjuvant chemotherapy in the EPD group should be added as part of this arm.

Thank you for this suggestion. We added the adjuvant chemotherapy term to the abstract since it is part of the EPD/HITOC concept even it was not mandatory for inclusion.

Materials and Methods- Please add information about the group of patients who underwent just chemo. What were the reasons for not operating on them (The authors mentioned that patients with localized disease with a maximum clinical stage T4N1MO were eligible for surgery)?

Patients did not undergo surgery due to comorbidities, high local tumor burden on computed tomography scan, patient refusal, and grade 3-4 toxicity during chemotherapy within a neoadjuvant treatment concept. We added the reasons to the text.

How many patients underwent mediastinal staging? What were the indications for mediastinal staging?

Suspicious enlargement of mediastinal lymph nodes was clarified by bronchoscopy and transbronchial needle aspiration (TBNA) in 12 patients. Mediastinoscopy was necessary in three patients due to enlarged contralateral mediastinal lymph nodes and negative TBNA results.

How many patients underwent PET CT to exclude distant metastases in each group.

According to German guidelines PET-CT is not indicated for staging in mesothelioma patients and there is no reimbursement by the German health insurance. Therefore, only 17 patients in

the EPD/HITOC cohort and three patients in the EPP cohort underwent staging by PET-CT. All other patients were staged using bone scintigraphy and sonography of the abdomen.

How many patients underwent extended pleurectomy decortication?

55 patients underwent extended pleurectomy decortication. Two patients had no resection on pericardium or diaphragm.

How many patients received HITOC in the EPD? If not all of them, please explain why?

All of the EPD patients received HITOC. We added this to the text.

Please elaborate on the postoperative follow-up methods

After completion of chemotherapy, follow-up was conducted every three months with CT of the chest and upper abdomen.

Statistics- I suggest comparing survival between the three groups by calculating survival from the day of surgical diagnosis instead of start of treatment.

Since not all of our patients had surgical diagnosis via thoracoscopy, we wanted to unify the calculation of survival and therefore decided to calculate overall survival from the start of first treatment irrespective of treatment modality.

Results- page 5 line 2 please change EPD/HITOC to EPD/HITOC/Adj chemo.

We changed this in the text.

It seems that ECOG status was not significantly different between the Epp group versus chemo alone. 61 % of the EPP patients underwent surgery despite ECOG1. What were the reasons for not operating on patients in the CTx group?

Patients did not undergo surgery due to comorbidities, high local tumor burden on computed tomography scan, patient refusal, and grade 3-4 toxicity during chemotherapy within a neoadjuvant treatment concept. We added this to the text.

I suggest adding comparison of the clinical stages between the three groups. It would be more accurate than comparing clinical to pathological staging.

Thank you for this point, this is definitely a limitation of the study. Pathologic TNM is much more accurate since in mesothelioma the percentage of upstaged patients is known to be high (10.1093/jnci/djx175). For the chemotherapy cohort, there is no pTNM available. Since we aimed to precisely compare the two surgical cohorts, we decided to use p-stage in these cohorts.

Page 5-line 25 Tachyarrhythmia absoluta. Does it mean Atrial Fibrillation?

Yes, atrial fibrillation and/ or atrial flutter. We changed this in the text to avoid confusion.

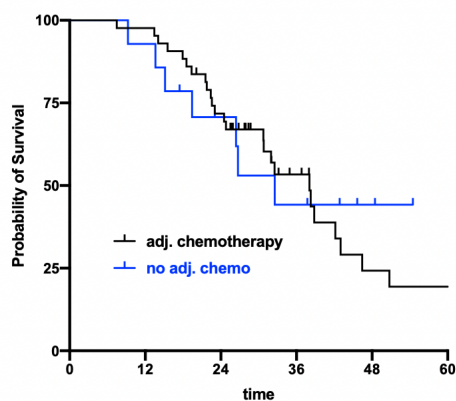
Page 5- line 37 Infected serothorax- I am not familiar with this entity (does it mean empyema?)

The term infected serothorax was changed to massive pleural effusion with compression of the contralateral lung to avoid confusion with association to empyema. Sometimes patients with elevated laboratory infection parameter and quickly rising fluid in the thoracic cavity after

pneumectomy show reduced cardiac and pulmonary function due to compression of the contralateral lung. Even after drainage of pleural fluid, symptoms quickly reappear. After thoroscopic lavage, the general condition of our patients stabilized promptly. No germs could be regrown out of the fluid and no bronchial stump insufficiency was detected. We changed the term in the text.

Page 6 line 2. In the EPD group did you notice better survival in patients who received adjuvant chemo versus patients who did not.

There was no significant survival benefit for patients with or without neoadjuvant/adjuvant chemotherapy in the EPD cohort ($p=0.55$). We noticed a trend towards better survival for patients with adjuvant chemotherapy. From our point of view, there are too few cases ($n=9$) to be able to show a difference. We added a statement to the results section.



Page 6 line 6 What is the prognostic role of ECOG 0, age below 70 and negative lymph node metastasis in each group- multimodality EPP versus multimodality EPD versus just chemo?

The variables age, ECOG and nodal status significantly influenced overall survival in univariate analysis. In the cox-regression analysis, variables do not keep their significance in multivariate analysis. This has been added to the text. Moreover, the dataset will be provided for more detailed and specific analysis. This was included in the data sharing agreement of the journal. In addition, we performed a cox-regression analysis for each subgroup to analyze whether the observed effects reappear within each treatment group. The results are summarized in the tables below:

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female sex	0.512	0.210–1.249	0.141
stages III & IV	1.206	0.549–2.651	0.641

In the EPD/HITOC subgroup ECOG 1 performance status represents an independent negative prognostic factor for overall survival. This effect could neither be observed in the EPP nor in the CTx cohort. In the later subgroups no independent and significant prognostic factor for overall survival could be identified in multivariate analysis within each group.

Discussion

Page 6 line 13-I suggest adding the NCCN, ASCO, ESTS etc... guidelines as a reference for the role of surgery in the treatment of MPM.

Thank you for this valuable point. The guidelines have been added to the text.

Line 22- How many patients received HIOTC in the EPD group? If not all of them, please explain why.

In the EPD group, all of the patients received HITOC. We added this to the methods section to avoid misunderstanding (page 9, line 3).

Line 31 – High median survival for the EPD group is seen here. It is better than the cohort from the authors' group from Munich even for the macroscopic complete resection group. I believe that the reason could be explained by the favorable novel prognostic factors in pleurectomy decortication published by the Brigham group in Annals of surgery 2020. Not just HITOC but also Adjuvant chemotherapy is an independent favorable prognostic factor.

This can definitely be a relevant point. In our cohort, there was a trend towards better survival

in the patient cohort of EPD and HITOC in combination with adjuvant chemotherapy. However, possible due to the small number of patients, there was no significant difference. We have added this and the reference to the text.

Page 7 line 10- The authors' claim for "Similar survival outcomes but worse postoperative outcomes after inductive chemotherapy than upfront surgery...." Is reinforced by the recent publication in JNCI by the duke group (The Role of Neoadjuvant Chemotherapy in Patients With Resectable Malignant Pleural Mesothelioma—An Institutional and National Analysis JNCI 2020).

Thank you, we have added this citation to the text.