Peer Review File
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Reviewer A

The authors have produced an impressive analysis of a complex collection of data and they make an important conclusion which has clinical relevance.
They need to address a few more specific points -

1. what were the respective surgical selection criteria in the two time periods and did they differ? Is this a benefit of regionalized specialism?

Reply 1: Stage, histology, and baseline testing of echocardiogram, FEV1 and DLCO surgical selection criteria were similar between groups, but more nuanced surgical selection in the early group is not known. Charlson comorbidity index and ECOG did not differ in surgical patients between the early and later cohorts (Table 2). There was a non-statistically significant trend towards older age in the later surgical cohort. With greater experience of mesothelioma cases, patients who are older may be candidates for surgery in the hands of a skilled surgical team, a benefit of regionalization.
Changes in text: Table 2 notes similar surgical selection criteria between the two time periods. We have included age of surgical patients between both early and later cohorts. We included additional information regarding surgical selection criteria in our methods section: "Surgical selection criteria were similar in the two cohorts." (page 4, lines 10-11)

2. Why was there such a high proportion of non-epithelioid MPM resected? Was this unexpected?

Reply 2: Thank you for this question. If determined to be resectable, our surgeons will consider operating on patients with bi-phasic histology. NCCN guidelines recommend consideration of surgery in patients with early-stage disease with biphasic histology. Another cause of increased number of patients with non-epithelioid histology was that a few patients initially had VATS biopsy results showing epithelioid histology preoperatively with final histology diagnosis from surgical pathology resection indicating non-epithelioid histology. One patient in the later cohort with sarcomatoid histology with a low burden of disease elected to proceed with PD. Overall, this was not an unexpected result given our surgeon's selection criteria as above and discrepancies that may have occurred between the biopsy and surgical pathology.
Changes in text: "Select patients with bi-phasic histology underwent surgery, in addition to patients with epithelioid histology." (page 4, lines 11-12)

3. What were the details of resectional path stage?

Reply 3: We included all patients who were intended to undergo a complete macroscopic resection. Most patients received R1 resection with the exception of 2 patients, who had R2 resections.
Changes in text: We have included details of resectional pathological stage in the text: "Both, EPP and PD operations performed in both study periods were curative intent and consisted of gross complete macroscopic resection (R1). Operations involving extensive tumor invasion or partial resections (R2) were included in this study and went on to receive systemic therapy." (page 5, lines 22-25)

4. What was the incidence of R2 resection and how was this managed?

Reply 4: Out of 54 patients who underwent surgery, two patients had R2 resections in the later period. We did included operations involving extensive tumor invasion or partial resection in our study. It was difficult to ascertain R2 resections in the early period due to surgical documentation.
Changes in text: We did include R2 patients in the study and have noted their inclusion and management in the methods section: "Operations involving extensive tumor invasion or partial resections (R2) were included in this study and went on to receive systemic therapy." (page 5, lines 24-25)

Reviewer B

Thank you very much for submitting this manuscript to the Journal of Thoracic Disease titled: "Improving outcomes in Malignant Pleural Mesothelioma in an integrated health care system". This work highlights and underpins the importance of the multidisciplinary team in the management of malignant pleural mesothelioma. I think that this is an important contribution to the literature, however, there are some areas that I think could be improved to make it more relevant and therefore I suggest a major revision.

The authors of the article have divided the cohort of 368 patients into two time periods: 2009 – 2014 and 2015-2020. The reason for this is that there was regionalisation of mesothelioma surgery to one surgeon from 2014 and the development and the initiation of the mesothelioma MDT in 2017. The authors come to the conclusion that multimodality treatment of MPM improves survival.

I have the following comments that I would like to be addressed:

Introduction (Page 3):

1. Line 6: “histologic subtypes”. I think this would read better using: histological subtypes.

Reply 1: Thank you for this comment.
Change in text: “histological subtypes” (page 3, line 5)

2. Line 8: “…localized MPM due to limited number of…”. Localized MPM is a discrete and separate entity that is much rarer than the more commonly seen diffuse MPM. From my reading, the authors do not focus solely on the localised form of mesothelioma and therefore, I would consider removing the word localized to encompass MPM in its entirety (both localized and diffuse).

Reply 2: We agree with this comment and have removed the term localized.
Change in text: “There is no consensus for optimal treatment of MPM due to limited number of randomized controlled trials given the rarity of this disease.” (page 3, lines 7-8)

3. Line 19: “The aim of this study was to investigate whether patients with MPM received more treatment after regionalizing MPM surgeries and institution of a MPM multidisciplinary review”. The authors have clearly outlined their primary aim of this work, however this is not supported in the conclusion as they focus on the multimodality treatment improving survival. I therefore feel that the conclusion should change to match the aim of assessing if patients received more treatment, or the primary aim needs to be changed to reflect the multimodality therapy and its effect on overall survival. This is a major amendment that requires to be addressed as currently there is a mismatch.

Reply 3: Thank you for this feedback. We agree with the reviewer’s comment. Our primary hypothesis was to determine if eligible patients with MPM would receive increased treatment in the later period. We found that increased treatment may be associated with improved survival, but this finding was limited due to the observational nature of our study. We have updated our discussion and conclusion to reflect our aims stated in the introduction. These changes in the text are noted in reply 31.
Change in text: See reply 31 for text updates to abstract, discussion, and conclusion.

4. Line 22: “We hypothesized that eligible patients with MPM would receive increased treatment.” This does not make sense to me. It requires clarification as to which group the authors expect to see an increased treatment in. I suspect that it is the later group. Please amend this.

Reply 4: Thank you for this comment. We did expect to see that eligible patients with

MPM received increased treatment in the later group as a result of surgical regionalization and the MPM bi-disciplinary review and have clarified this statement.
Change in text: "We hypothesized that eligible patients with MPM would receive increased treatment in the later cohort." (page 3, lines 22-24)

Methods:

1. Page 3, line 29: "The sample size was determined by the number…". This was not a randomised controlled clinical trial and therefore sample size is the wrong term here. I would suggest that the authors say the denominator or the number of patients included.

Reply 5: Thank you for this feedback. We have updated our statement.
Change in text: "The number of patients included was determined by the number of new diagnoses of MPM during the study period." (page 4, lines 3-4)

2. Page 4, line 1: The authors explain here that the reason for choosing the two periods are regionalization of MPM surgeries to one surgeon as one surgical centre starting in 2014. The authors have another big group recruited before 2014 and from the results, the reader can appreciate that surgery for MPM was undertaken but there is no explanation as to how this was carried out. This is an important piece of information that has been omitted. Prior to 2014, was surgery carried out at different centres, was it carried out by several surgeons performing a small volume of cases. This is extremely important for the reader to appreciate to better understand the conclusions reported in this report. Please expand on this.

Reply 6: Thank you very much for this feedback. This is an important point to clarify. Prior to 2014, surgeries were performed at two different centers and carried out by two surgeons performing a low number of annual mesothelioma cases. We have updated our text.
Change in text: "Prior to 2014, mesothelioma surgeries were performed at two sites by two surgeons with a low volume of annual mesothelioma cases." (page 4, lines 8-10)

3. Page 4, line 6: The authors outline the multidisciplinary team and state that it consisted of medical oncology representatives and thoracic surgery representatives. This is not a multidisciplinary team; it is a bi-disciplinary team. In the United Kingdom, our MDT consists of colleagues from: thoracic surgery, medical oncology, histopathology, radiology, respiratory medicine and specialist nursing teams. I would like to see the full remit of the

multidisciplinary team. If there are only the two representatives, the authors should explain why there are no other representatives. Also, in the conclusion the authors state that the MPM MDT was regular, but can the authors explicitly state what this means, i.e. was it weekly or monthly, for example?

Reply 7: Thank you for this feedback. The MPM review team consisted of both medical oncology and surgical representatives. Although this team communicated closely with pathologists and radiologists involved in each patient's case, the pathology and radiology representatives were not part of the weekly review of cases. Radiation oncology did not participate directly in the tumor board due to the low number of cases requiring radiation. In the future, we hope to include additional subspecialties as in your MDT but have limited resources to make this change at the present time.
Change in text: We have correctly updated the text to reflect the bi-disciplinary, weekly nature of the tumor board. "The bi-disciplinary team consisted of medical oncology and thoracic surgery representatives. Representatives from pathology and radiology were consulted by the tumor board as needed." (page 4, lines 15-17) To describe the frequency of tumor board review, we previously included: "The pathology reports were subsequently verified, and the cases were reviewed during the weekly bi-disciplinary tumor board." (page 4, lines 21-22)

4. Page 4, line 15: The authors stated that clinical stage was confirmed based on PETCT scanning. Is this the routine method of staging that is used for all patients? CT scans are used in other institutions and I wonder why this institution used PETCT routinely for staging purposes?

Reply 8: Thank you for this clarifying question. We use both CT and PET/CT for staging. All patients received initial CT for staging, followed by PET/CT to clarify nodal and distant involvement if surgery was considered. Staging with CT, followed by PET/CT for further surgical evaluation is supported by NCCN guidelines (PMID: 29346042).
Change in text: "During the bi-disciplinary virtual review, clinical stage was confirmed based on CT scan with subsequent PET/CT scan performed as needed for surgical consideration. Pathology was reviewed with clear documentation on specific histology (epithelioid, biphasic, or sarcomatoid) on the pathologic report, and referrals were made to the designated mesothelioma surgeon, medical oncology and/or radiation oncology when appropriate, based on NCCN guidelines." (page 4, lines 25-29, page 5, line 1)

5. Page 4, line 16: "…specific histology (epithelioid, …)". The authors use epithelial and epithelioid to describe the same histopathological subtype of MPM. This needs to be standardised throughout the manuscript for coherence. I would prefer to see epithelioid over epithelial.

Reply 9: We agree with this comment and have changed all epithelioid histopathological subtype to epithelioid.
Change in text: see pages 3, 7, 8, 12, 13

6. Page 4, line: 20: "Twelve patients had missing MPM stage due to incomplete staging imaging". I understand from the tables that 8 of these occurred in the earlier time period studied and that 4 (2%) occurred in the later time period. This is difficult to understand as one of the major aspects of the MDT is to stage the disease as this reflects the treatment that patients will potentially receive. I would like further explanation of this. Furthermore, the authors chose to include these patients details in the analyses and I have major reservations about this. The main reason for this is that the authors have later analysed the data using multivariable logistic regression and Cox proportional hazards regression modelling after adjusting for stage. This introduces uncertainty in an already small group of patients. I don't understand why the authors did not exclude those patients with no staging recorded. This will require a major amendment.

Reply 10: We appreciate the reviewer's comments. Patients in both periods who did not have initial staging completed were ineligible for treatment due to age, comorbidities, performance status or patient preference. These patients and their care teams elected not to pursue staging imaging. We agree with your concerns and have excluded patients with missing stage information.
Change in text: We have updated Figure 2 and Tables 3 and 4, excluding patients with missing staging data and noted this change in the methods text.
"Patients with missing stage were excluded from the final analyses." (page 5, lines 5-6)
Figure 2. Survival of All Patients by Treatment Type in Early Period (2009-2014) (A) and Later Period (2015-2020) (B)
1. Multimodality treatment includes surgery and systemic therapy with or without radiation. 2. Systemic only includes systemic treatment with or without radiation. 3. Surgery only includes surgery with or without radiation. 4. No treatments administered.
Figure 2A.

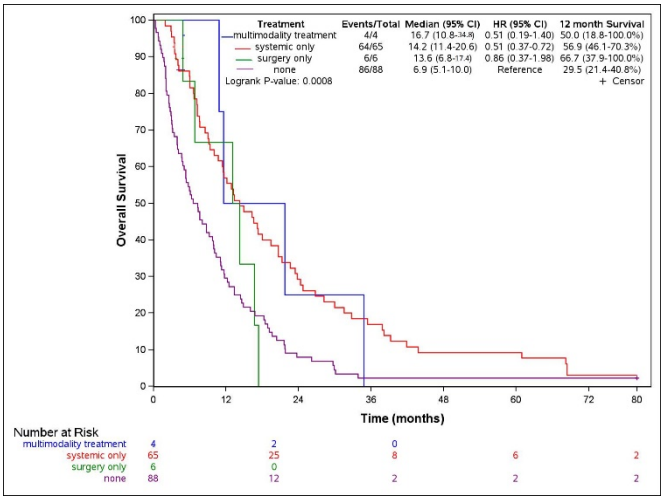


Figure 2B.

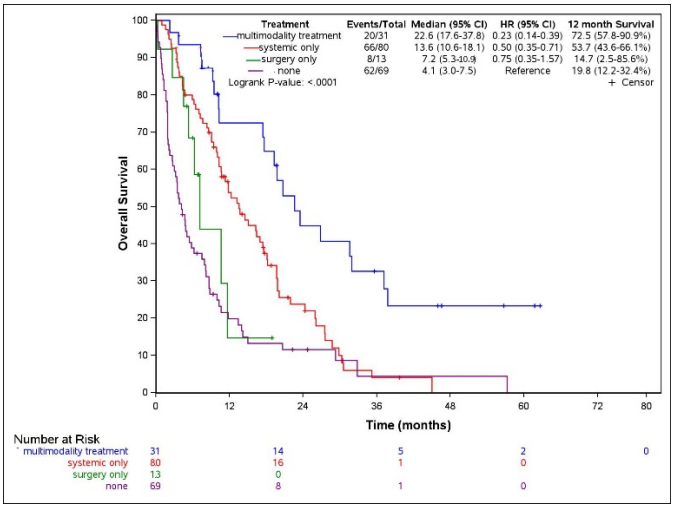


Table 3. Factors associated with receiving any treatment

Variables	Adjusted Odds Ratio (95% CI)	P-value
Study period		
2015-2020	3.25 (1.93-5.49)	<.0001
2009-2014	Reference	
Age at Cancer Diagnosis, years		
18-64	Reference	
65-74	1.29 (0.58-2.86)	0.533
75-84	0.32 (0.15-0.65)	0.002
>=85	0.10 (0.04-0.25)	<.0001
Male vs Female	1.77 (1.00-3.14)	0.048
Charlson Comorbidity Index (CCI)		

0-3	Reference	
4-6	0.54 (0.30-0.99)	0.046
7+	0.38 (0.20-0.70)	0.002
Histology		
Epithelial	1.78 (1.08-2.93)	0.023
Biphasic, Sarcomatoid, Other	Reference	
Stage		
I/II	1.04 (0.63-1.70)	0.888
III/IV	Reference	

Table 4. Cox Proportional hazard models in Overall Population

Variables	Adjusted Hazard Ratio (95% CI)	P-value
Study period		
2015-2020	0.99 (0.77-1.26)	0.916
2009-2014	Reference	
Any Treatment vs none	0.57 (0.44-0.73)	<.0001
Age at Cancer Diagnosis, years		
18-64	Reference	
65-74	1.21 (0.84-1.74)	0.308
75-84	1.86 (1.30-2.67)	<.001
>=85	2.33 (1.51-3.59)	<.001
Male vs Female	1.02 (0.78-1.33)	0.893
Charlson Comorbidity Index (CCI)		
0-3	Reference	
4-6	0.86 (0.65-1.14)	0.293
7+	1.27 (0.94-1.71)	0.122
Histology		
Epithelial	0.71 (0.56-0.89)	<.001
Biphasic, Sarcomatoid, Other	Reference	
Stage		
I/II	0.62 (0.49-0.78)	<.0001
III/IV	Reference	

7. Page 4, line 26: The authors state that more PD were performed in the later period whilst EPP was the more frequent operation in the early period. The authors state that this was due to changes in practice at our institution. I wonder how much of this change was due to the result of the MARS trial run in the UK. There was a large paradigm shift across the world from EPP to EPD. I would like to better understand why there was a change in practice.

Reply 11: Thank you for this comment. Yes, due to the results of the MARS trial, the surgical teams shifted to largely performing PD. The surgical team preferred PD due to lower complication rate and morbidity and mortality seen with PD.
Change in text: "More extrapleural pneumonectomies (EPP) were performed during the early period, and more pleurectomy/decortications (PD) were performed in the later period due to changes in practice at our institution, related to influences from the MARS trial results (8)." (page 5, lines 8-11)

8. Page 4, line 31: the authors state that PD consisted of extended radical parietal and visceral pleurectomy and then go onto say complete lung decortication. To my mind a radical visceral and parietal pleurectomy is synonymous with a complete lung decortication. I would therefore remove complete lung decortication to omit tautology.

Reply 12: We agree with the reviewer's comment and have omitted tautology.
Change in text: "PD consisted of exploratory thoracotomy, extended radical parietal and visceral pleurectomy, resection of the pericardium with reconstruction with bovine pericardium mesh, complete resection of the diaphragm with reconstruction using porcine-derived acellular dermal matrix (Strattice Reconstructive Tissue Matrix) mesh, and complete mediastinal lymph node dissection." (page 5, lines 14-19)

9. Page 5, line 5: The authors state that both EPP and PD operations were performed in both study periods were done with curative intent and consisted of gross complete macrsoscopic resection (R1). This sentence is contradictory. It is very well understood that surgery for MPM is not curative and is palliative. The ESMO guidelines state that an R0 resection is considered a curative resection. In MPM, the best resection that can be achieved is an R1 and this is why multimodality treatment is key. This sentence requires revision, as by your definition of an R1 resection, this is not curative.

Reply 13: We agree with the reviewer's comments and suggestion. Patients undergoing surgery in this study were planned for aggressive multimodality treatment, including complete macroscopic resection. We have removed the term, "curative intent." Majority of surgical patients underwent palliative PD with goal of complete macroscopic resection.
Change in text: Methods section: "Both, EPP and PD operations performed in both study periods consisted of planned gross complete macroscopic resection (R1)." (page 5, lines 22-23)
Discussion section: "One of the main highlights of our regionalization program, was that significantly more eligible patients for multimodality treatment did indeed

undergo optimal treatment compared to pre-regionalization." (page 10, lines 12-14)

10. Page 5, lines 7-15: there are a few comments in this section that I would like to make:

The authors have listed postoperative complications that they wished to explore. Supplemental table 1 outlines the incidence of postoperative complications. However, not all the complications listed in the methods section are not accounted for in supplemental table 1 (bronchopleural fistula, deep vein thrombosis, prolonged air leak, prolonged supplemental oxygen and atelectasis). These need to be added into the table.

It is well-known that BPF is a known complication of EPP and the reader will be very interested to observe the reduction, if any, following the change from EPP to EPD. I would expect this incidence to be higher in the earlier group and non-existent or reduced in the later time group.

I would like to see the rates of re-operation included in the complication table (either due to air leak, bleeding or thoracic duct ligation, for example).

This section requires more explanation of definitions. How were the following complications defined: prolonged intubation, prolonged supplemental oxygen and prolonged air leak?

Bronchopleural fistula appears in the list of complications twice, one of these should be removed.

Reply 14: Thank you for this feedback. We observed no bronchopleural fistulas (BPF) in our early cohort, likely due to the small number of patients undergoing EPP. No BPFs were observed in the later cohort who underwent PD. Similarly, there were no re-operations in either cohort possibly due to relatively small N value.

We chose to remove prolonged air leak, as all of our patients who underwent PD had prolonged air leak, as defined by air leak more than 5 days, before and after regionalization. As part of our routine mesothelioma protocol, we generally keep chest tubes on suction regardless of the extent of air leak for 5 to 7 days minimum in anticipation of allowing more optimal sealing and pleurodesis effect after PD. We further investigated through chart review and found that prolonged air leak did not affect patient's LOS as patients are also sent home with a Blake drain.

We have addressed duplication of terms, updated the supplemental table to reflect listed complications in methods section, and better-defined complications, noted in

supplemental Table 1 below.

Change in text: We have updated our text noting post-operative complications: "Post-operative complications within 30 days of EPP or PD were defined as anemia, atrial fibrillation/atrial flutter, chyle leak, prolonged supplemental oxygen, hypotension, mucous plug, pneumonia, pericardial effusion, remained intubated post-operatively, prolonged initial intubation (>48 hours), stroke, acute respiratory failure, cardiac arrest, empyema, venous thromboembolism, urinary retention, UTI, wound infection, reintubation, pleural effusion, tracheostomy, bronchopleural fistula, and re-operation." (page 5, lines 25-29, page 6, lines 1-2)

We have defined prolonged intubation, prolonged supplemental oxygen and in supplemental Table 1.

We have updated Supplemental Table 1:

Supplemental Table 1. Surgical complications between early and later periods

	Total**	2009-2014 N = 10	*2015-2020 N = 44*
Anemia	5	1	4
Atrial fibrillation/Atrial flutter	16	5	11
Chyle leak	5	0	5
Prolonged supplemental oxygen	3	1	2
Hypotension	9	0	9
Mucous plug	2	0	2
Pneumonia*	5	0	5
Pericardial effusion	1	1	0
Remained intubated post operatively	3	0	3
Prolonged Initial Intubation (>48hrs) *	0	0	0
Stroke	1	0	1
Acute respiratory failure*	2	0	2
Cardiac arrest	2	0	2
Empyema	1	1	0
Venous thromboembolism*	1	1	0
Urinary retention	3	0	3
UTI	1	0	1
Wound infection	1	0	1
Reintubation*	1	0	1
Pleural effusion	1	0	1
Tracheostomy*	1	0	1

Bronchopleural fistula*	0	0	0
Re-operation	0	0	0

**STS complication*
***A patient can have >1 complication. Thus, Total exceeds 33.*
Prolonged initial intubation: initial ventilator support >48 hours (STS complication definition)
Prolonged supplemental oxygen: new home oxygen requirement
Re-operation: re-operation within 30 days

10. Page 5, line 18: The authors have identified adjustment covariables of: age, gender, histology, stage, smoking status and CCI. There is no explanation as to why the authors selected these variables. I agree with the majority of them, but I don't understand why the authors chose to adjust for smoking status? I suggest that this should be removed. Also, did the authors collect information on asbestos exposure? This would be useful to include in the demographic table and also to adjust for.

Reply 15: We agree and have removed adjustment by smoking status. Stage and histology are the strongest prognostic factors for patients with MPM (PMID: 25791825). Other poor prognostic factors include older age and poor performance status (PMID 9515850). Given gender disparities that exist in patients with MPM it is important to adjust for gender (PMID: 24928677). We were unable to ascertain asbestos exposure in all patients.
Change in text:
"We conducted a multivariable logistic regression to examine the associations with receiving any treatment and period with adjustments for age, gender, histology, stage, and Charlson Comorbidity Index (CCI) 8-9 at time of cancer diagnosis." (page 6, lines 10-13)
"We also conducted Cox proportional hazards regression model to examine the associations between overall survival (OS) and period with adjustments for any treatment, age, gender, histology, stage, and CCI at cancer diagnosis." (page 6, lines 17-20)
"Patients in the later period cohort were three times more likely to receive treatment than patients in the early period cohort (Adjusted Odds Ratio 3.33, 95% CI, 2.00-5.57, p <0.0001) after adjusting for age, gender, CCI, histology, stage, and at cancer diagnosis." (page 8, lines 10-13)

11. Page 5, line 22: The authors stated that patients who left our institution prior to the study endpoint were censored from the study. This is the number that would be lost to follow-up. How many patients were lost to follow-up? This

would be important to include. As the timepoint of interest is overall survival, is there no centralised system to be able to search to see if the patient has succumbed to their disease or is still alive. This would reduce the loss to follow-up and strengthen the argument made in this manuscript.

Reply 16: We agree with the reviewer's comment. We found that 10 patients had left Kaiser Permanente Northern California (KPNC) during our study. These patients may have received additional treatment outside of KPNC, so were censored from the study once they left KPNC to avoid misclassification.
KPNC is a large integrated health system of 21 cancer centers over a broad geographic area in Northern California serving a 4.5 million population. Because the health care system is integrated, patients who remain in our health system are well tracked throughout their MPM care. Death data is accurate for our cohort due to the integrated nature of our institution.
Change in text: We have clarified this point in our methodology, "Ten patients who left our institution prior to the study end point were censored from the study." (page 6, lines 16-17).

Results:

1. Page 6, line 2-6: this sentence is too long and needs to be split into two for it to make sense. Please change this.

Reply 17: Thank you for this comment. We have split this sentence into two sentences.
Change in text: "Demographic data showed similar patient characteristics from the early to later periods for the included 368 patients with MPM except for histology and CCI, which was higher in the later period cohort (Table 1). We note the, although difference in CCIs may have been affected by the ICD coding switch from ICD-9 to ICD-10 in September 2015, with the ICD-10 using additional codes." (page 6, lines 27-29, page 7, lines 1-2)

2. Page 6, line 6: "Twelve patients were missing MPM stage". This has already been stated in the methods section and there is no need for it to be repeated here. Please remove this sentence.

Reply 18: We agree with the reviewer's comment and have removed this sentence.
Change in text: "~~Twelve patients were missing MPM stage.~~ There was no missing data for other variables, other than stage." (page 7, line 2-3)

3. Page 6, line 7-10: The authors state that more patients received any MPM-

directed treatment in the later period compared to the early period. Now, this is a surprising result to me. Any treatment includes systemic chemotherapy with Cisplatin/Carboplatin and Pemetrexed chemotherapy in isolation. In 2003, Vogelzang et al., reported that there was a survival advantage of combination chemotherapy and this was widely adopted worldwide as the only evidence-based therapy in existence. I wonder why patients in the earlier time period were not receiving this. Whilst some would have been of poor performance status and not fit enough to receive treatment, I doubt they were all too unfit in this time period. I would like to see a discussion point on this finding in the discussion section as I think that it is a surprising finding.

Reply 19: Many patients in the early cohort received no treatment. Unfortunately, we do not have explicit reasons for all patients who received no treatment. Based on chart review of our cohorts in the early period, we encountered patients receiving no treatment due to age, functional status, comorbidities or patient preference. We also observed that chemotherapy was not often recommended. Despite improvement in OS by 3 months with cisplatin/carboplatin and pemetrexed chemotherapy shown by Vogelzang et al, after consultation with the medical oncologists reviewing risks versus benefits with the patient, the decision was made to forgo chemotherapy. This practice pattern is reflective of a real-world community practice of medical oncologists, many who did not commonly recommend chemotherapy over best supportive care for mesothelioma.
Change in text: We have updated the discussion section: "In the early cohort, we found that over half of patients received no treatment, despite similar age and higher CCI in the later cohort. We suspect that after consultation with the medical oncologist reviewing risks versus benefits with the patients, the decision was made to forgo chemotherapy. This is a practice pattern reflective of a real-world community setting and has been demonstrated in other institutions (18). Our study showed successful implementation and increased use of multimodal therapy within a patient population that is representative of the greater population of California (19)." (page 10, lines 4-9)

4. Page 6, line 17: "…during the later period, $p<0.0001$". In the previous sentence, the reader is directed to Figure 1. I therefore think that after the p-value, it is worth re-directing the reader to the relevant table and so I would add Table 1 in parenthesis after the p-value.

Reply 20: We agree with the reviewer's comment and have added reference to Table 1.
Change in text: "Despite similar age, staging and inclusion of patients with greater CCIs, more patients received any MPM directed treatment in the later period from 2015-2020 (n=124, 63%) compared with those patients in the early period from 2009-2014 (n=75, 44%, $p<0.0001$, Table 1)." (page 7, lines 3-6)

5. Page 6, line 23: ECOG has not been explained before, please expand.

Reply 21: Thank you for this comment. We have updated this sentence to better define ECOG.
Change in text: "The CCIs and ECOG Performance Status Scale (11) were similar in both the early and later surgical cohorts." (page 7, lines 20-21)

6. Page 6, line 24: "CCI was greater than 7 in 29.5% in patients…". This should read: "CCI was greater than 7 in 29.5% of patients". Please change.

Reply 22: Thank you for this comment. We have correctly updated the grammar of this sentence.
Change in text: "CCI was greater than 7 in 29.5% in of patients who received surgery during the later period and 20% of patients who received surgery during the early period." (page 7, lines 21-23)

Discussion:

1. Page 8, line 11: The authors have said that they did not find increases in length of stay nor rates of postoperative complications. It is interesting to note that the one major complication of EPP (BPF) and EPD (prolonged air leak) have not been documented. I suspect once these have been included you might find a difference in complication rates. I am also surprised that with prolonged air leak, a major complication of PD, that there is no increased length of stay. The authors might want to explore this further in the discussion. Why should the rates of air leak be lower?

Reply 23: We did not have any BPFs in our data set although that is a major complication of EPP, only a few EPPs were performed thus probably the small N value is why we did not have any BPF. As for prolonged air leak, all of our patients that underwent PD had prolonged air leaks before and after regionalization. We observed similar LOS before and after regionalization because that was the main reason they stayed was for prolonged air leak. Since all of our patients stayed due to expected prolonged air leak, we did not see this difference, nor did we focus on this complication, as we thought this more of a common side effect from an extensive PD. We discharge all of our patients with a Blake drain as well, as we know the occurrence of prolonged effusion or air leak can occur even two weeks after surgery, thus we proactively prevent this by sending all of our P/D patients home with a drain.

Change in text: We have noted our practice of drain use in the methods section: "Patients are discharged home after surgery with Blake drains to proactively prevent prolonged effusion or complications arising from air leak." (page 5, lines 20-22).

We updated our results: “All patients who underwent PD developed prolonged air leak, air leak lasting for greater than 5 days, that was managed with a Blake drain.” (page 7 line 29, page 8, lines 1-2)

We have updated the discussion section: “Prolonged air leak was not considered a major complication as all of our PD patients before and after regionalization had prolonged air leak as defined by air leak greater than 5 days, thus we considered this more of a normal side effect from PD.” (page 9, lines 17-19)

2. Page 8, line 16: “Through surgical regionalization…early stage, epithelial MPM”. I don’t think that this conclusion can be drawn. The authors are saying owing to surgery, the survival is improved. This has never been proven nor was it examined in this manuscript. I think that authors can state that with the existence of the MDT, patients have been able to access multimodal therapy which may be responsible for the improvement in survival seen in this observational study. This needs to be changed.

Reply 24: We agree with the reviewer’s comment. We believe that increased access to multimodality treatment may be responsible for the improvement in survival, but this finding is limited by the observational nature of this study.
Change in text: “Through surgical regionalization, eligible patients have increased access to specialized surgical care, which may have contributed to the improvement in survival seen in this observational study.” (page 9, lines 23-26)
We have also updated an earlier section of our discussion: “We observed a correlation between patients who received tri- or bi-modality MPM directed therapies in the later period and improved survival. Our findings are consistent with other studies showing a relationship between treatment and improved survival (12).” (page 9, lines 3-6)

3. Page 8, line 25: curative intent is mentioned here again. This cannot be said. No treatment for MPM is currently curative, but palliative. Therefore, one of the main highlights of this study is that a higher proportion of patients could be considered for multimodal therapy and receive it.

Reply 25: We agree with the reviewer’s comments. Unfortunately, optimal treatment is palliative, but can prolong patients’ survivals. Our study shows through bi-disciplinary review optimal treatments could be increased for eligible patients.
Change in text: “One of the main highlights of our regionalization program, was that significantly more eligible patients for multimodality treatment did indeed undergo optimal treatment compared to pre-regionalization.” (page 10, lines 12-14)

4. Page 8, line 29: 45%-65%. In the results section, it was reported that in the early period 44% received any MPM treatment. This needs to be corrected.

Reply 26: We agree with the reviewer's correction.
Change in text: "From the early to the later period, we saw an increase in use of any treatment from 44% to 65%, respectively, despite higher CCIs in the later period cohort." (page 10, lines 16-18)

5. Page 9, line 12: the authors comment here that multidisciplinary review can improve histological diagnosis, assure evidence-based treatment recommendations. I think it is very important to also include that the multidisciplinary review can also improve the recording of the stage of disease. At this point, it can also be discussed why 12 patients have not had a staging.

Reply 27: We agree with the reviewer's comment that the bi-disciplinary review improves the recording of stage of disease. 12 patients were missing staging. Some of these patients due to patient preference, performance status, age or comorbidities did not receive complete staging imaging. Imaging for staging was not obtained due to preference to proceed with supportive care measures, instead of disease directed treatments.
Change in text: "In MPM, bi-disciplinary review can improve histologic diagnosis, increase accurate staging of MPM, assure evidence-based treatment recommendations, and increase enrollment in clinical trials, but improvement in outcomes have yet to be reported." (page 11, lines 15-18)

6. Page 9, line 16: The authors state that the board interacted directly with the pathologists. It might also be worth stating if they also directly interacted with the Radiologist as the staging of the disease is also an important factor.

Reply 28: We appreciate the reviewer's comment. The bi-disciplinary tumor board did interact with the radiologist and pathologist.
Change in text: "In MPM, bi-disciplinary review can improve histologic diagnosis, increase accurate staging of MPM, assure evidence-based treatment recommendations, and increase enrollment in clinical trials, but improvement in outcomes have yet to be reported (22) … The tumor board interacted directly with pathologists and radiologists to determine each patient's histological subtype and staging, leading to a more accurate diagnosis, prognosis, and appropriate treatment plan." (page 10, lines 2-10)
"For 12 patients, imaging for staging was not obtained due to patient preference to proceed with supportive care." (page 11, lines 13-14)

7. Page 9, line 28: The authors comment that because of the rarity and the

difficulty of conducting RCT's, questions remain about the role of surgery in MPM management. The authors should acknowledge the MARS and MARS 2 trials that are two RCT's from the United Kingdom that have looked to answer this exact question. The MARS trial advocated the transition from EPP to EPD and MARS 2 has completed recruitment and will report in time to answer this very important question. Without the inclusion of these studies, it looks as if the authors are not aware of the literature surrounding RCT's in MPM.

Reply 29: We agree with the reviewer's comments and have included additional information on the available and anticipated results of RCTs in MPM.
Change in text: "The MARS trial was a limited, randomized controlled trial that showed no benefit of EPP in MPM (8). Results from the MARS2 trial comparing PD and chemotherapy compared with chemotherapy alone are awaited (24)." (page 11, lines 23-26)

8. Page 10, line 29: "…further work is needed to increase treatment options for older patients, patients with multiple comorbidities, or non-epithelial histology". This is an important point that is made, however, there are recent and powerful studies available now to answer this question: the Checkmate-743 and the CONFIRM trial from the United Kingdom. Both of these trials have shown that immunotherapy can be beneficial. Checkmate-743 highlighted the benefit of combination immunotherapy in the front line driven by non-epithelioid disease and CONFIRM examined single agent immunotherapy in the second line setting. Adding in this information will give credence to this manuscript and show the progress that has been made in the last few years. It also highlights the importance of the MPM MDT meeting as the number of treatments increase.

Reply 30: Thank you for this important comment. It is key to note the additional treatment options that have shown benefit to patient with MPM histologies with historically poorer prognoses with limited response to standard treatment. A multidisciplinary tumor board is essential component of these patient's care to be sure all treatment options are being considered based on a patient's stage and histology.
Change in text: "Checkmate 743 and CONFIRM studies have shown that immunotherapy is beneficial in all patients with MPM, while the benefit appeared to be greater in non-epithelioid histologies (29-30). Our study shows the importance of bi-disciplinary review as treatments to these subgroups increase over time." (Page 13, lines 1-4)

Conclusion:

1. Page 11, line 11: "…leads to an improvement in overall survival". The authors set out to assess whether the MDT would allow eligible patients to receive

increased treatment modalities. The authors have shown that they do, however, they focus on the improvement in overall survival, an outcome that was not consistent with the primary aim. In my opinion this needs to be amended and the focus placed on the fact that the MPM MDT increases the availability and receipt of multimodality treatment approaches. It is this multimodality treatment that may have the potential to improve survival. You cannot conclude that it leads to an improvement in survival.

Reply 31: We agree with the reviewer's feedback. Our study aims to show an increase of multimodality treatment as a result of bi-disciplinary review and regionalization of MPM surgeries. Prior studies have shown the benefit of multimodal therapy for MPM patients.
Change in text: We have updated multiple sections focus on our finding that regionalization and tumor board review increase multimodal treatment, while improved survival outcomes were not proven through this study.

Abstract: "Consolidating mesothelioma surgery to a specialized surgical team and regular bi-disciplinary review of MPM cases to determine appropriate multimodality therapy, increases the incorporation of surgical treatments in the management of patients with MPM." (page 2, lines 26-29)

Discussion: "Regionalization of MPM surgeries and bi-disciplinary review can lead to increased utilization of surgery as part of multimodal therapy in an older population with multiple comorbidities within a large integrated health care system without higher rates of surgical complications. We observed a correlation between patients who received tri- or bi-modality MPM directed therapies in the later period and improved survival. Our findings are consistent with other studies showing a relationship between treatment and improved survival (12)." (page 8, lines 27-28, page 9, lines 1-6)
"Our study shows the importance of bi-disciplinary review as treatments to these subgroups increase over time." (page 13, lines 3-4)

Conclusion: "Our study suggests using expert review of MPM cases and cytoreductive surgery performed by an experienced surgical team leads to increased availability and receipt of multimodality treatment options." (Page 13, Lines 13-16)
Deleted: "With standardized surgical technique and appropriate adjuvant systemic therapy, patients with MPM have improved survival." (Page 13, lines 11-13)
Deleted: "Our results are consistent with prior studies showing that multimodality treatment of MPM improves survival." (page 13, lines 16-18)

Tables and Figures:

1. Table 1: Can the authors divide the BMI groups further. They have combined the underweight and normal weight groups. It is well known that in many

disease types that an obesity paradox exists whereby underweight patients have a worse outcome relative to their normal weight, overweight and obese counterparts. Teasing this apart may demonstrate a difference.

Reply 32: Thank you for this comment. There were only two patients in the underweight category, BMI<18.5, so we grouped patients who were underweight and normal weight together. It was difficult for us to drawn inferences from such a small group of underweight patients. A larger study may be able to demonstrate stronger differences among different weight groupings.

Variables	2009-2014 (N=171)	2015-2020 (N=197)	P Value
BMI			0.455§
<18.5	0	2 (1.0)	
18.5-24.9	76 (44.4)	77 (39.1)	
25.0-29.9	65 (38.0)	84 (42.6)	
>=30	30 (17.5)	34 (17.3)	

Please see below for additional breakdown of BMI groups:

2. Tables 3 and 4: I would strongly encourage the authors to revisit the inclusion of the missing staged patients in the analyses.

Reply 33: We agree with the reviewer's comments and have performed odds ratio analysis and cox proportional hazard models excluding patients with missing stage data.

Change in text: We have updated Tables 3 and 4, excluding patients with missing staging.

Table 3. Factors associated with receiving any treatment

Variables	Adjusted Odds Ratio (95% CI)	P-value
Study period		
2015-2020	3.25 (1.93-5.49)	<.0001
2009-2014	Reference	
Age at Cancer Diagnosis, years		
18-64	Reference	
65-74	1.29 (0.58-2.86)	0.533
75-84	0.32 (0.15-0.65)	0.002
>=85	0.10 (0.04-0.25)	<.0001
Male vs Female	1.77 (1.00-3.14)	0.048
Charlson Comorbidity Index (CCI)		
0-3	Reference	
4-6	0.54 (0.30-0.99)	0.046

7+	0.38 (0.20-0.70)	0.002
Histology		
Epithelial	1.78 (1.08-2.93)	0.023
Biphasic, Sarcomatoid, Other	Reference	
Stage		
I/II	1.04 (0.63-1.70)	0.888
III/IV	Reference	

Table 4. Cox Proportional hazard models in Overall Population

Variables	Adjusted Hazard Ratio (95% CI)	P-value
Study period		
2015-2020	0.99 (0.77-1.26)	0.916
2009-2014	Reference	
Any Treatment vs none	0.57 (0.44-0.73)	<.0001
Age at Cancer Diagnosis, years		
18-64	Reference	
65-74	1.21 (0.84-1.74)	0.308
75-84	1.86 (1.30-2.67)	<.001
>=85	2.33 (1.51-3.59)	<.001
Male vs Female	1.02 (0.78-1.33)	0.893
Charlson Comorbidity Index (CCI)		
0-3	Reference	
4-6	0.86 (0.65-1.14)	0.293
7+	1.27 (0.94-1.71)	0.122
Histology		
Epithelial	0.71 (0.56-0.89)	<.001
Biphasic, Sarcomatoid, Other	Reference	
Stage		
I/II	0.62 (0.49-0.78)	<.0001
III/IV	Reference	

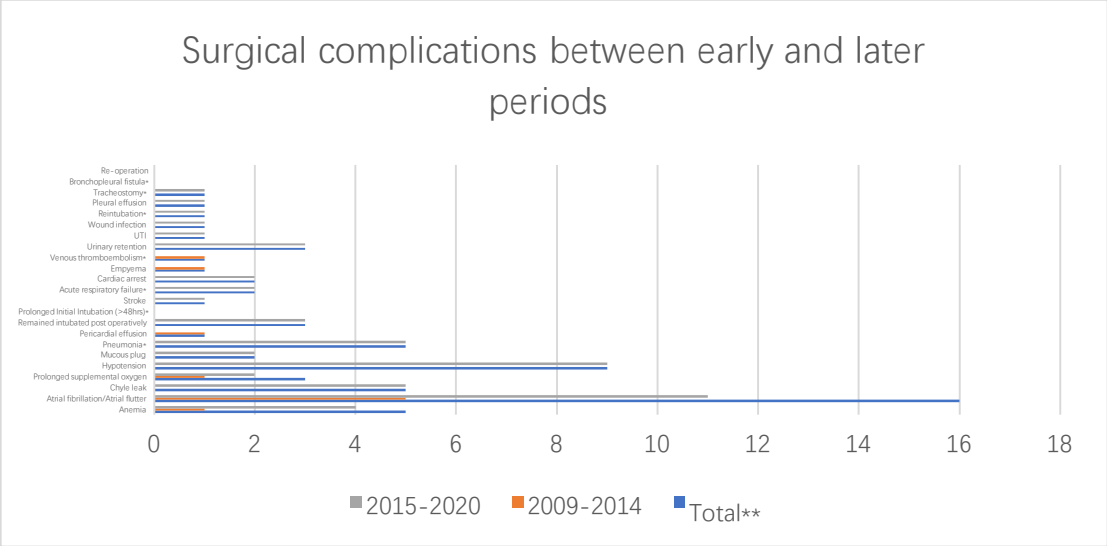
3. Supplemental table 1: Other complications that I have mentioned above (for example, BPF, prolonged air leak, etc) need to be added in here. Also, I think this would be better illustrated as a horizontal cluster bar graph tan a table as it will be much easier to visualise the complication rates between the two time periods. Please amend this accordingly.

Reply 34: Thank you for these comments. We have updated supplemental table 1 to include the additional complications. We have also converted our table to a horizontal

cluster bar graph.

Change in text:

Supplemental Figure 1. Surgical complications between early and later periods



**STS complication*

***A patient can have >1 complication. Thus, Total exceeds 33.*

Prolonged initial intubation: initial ventilator support >48 hours (STS complication definition)

Prolonged supplemental oxygen: new home oxygen requirement

Re-operation: re-operation within 30 days

3. Figures 2A and 2B: The y-axis should read, overall survival and the x-axis should read, time (months). Please amend.

Reply 35: Thank you. We have updated our x- and y- axes.

Change in text: Figure 2 has been updated below.

Figure 2. Survival of All Patients by Treatment Type in Early Period (2009-2014) (A) and Later Period (2015-2020) (B)

1. Multimodality treatment includes surgery and systemic therapy with or without radiation. 2. Systemic only includes systemic treatment with or without radiation. 3. Surgery only includes surgery with or without radiation. 4. No treatments administered.

Figure 2A.

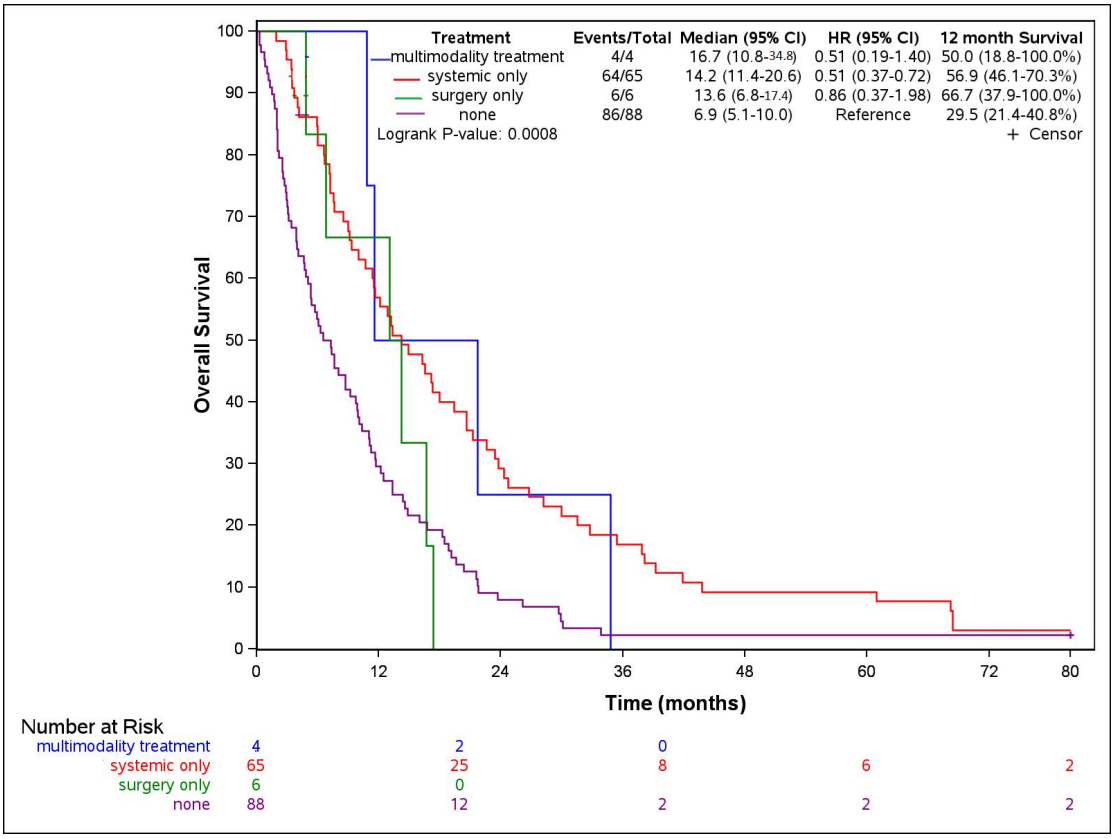
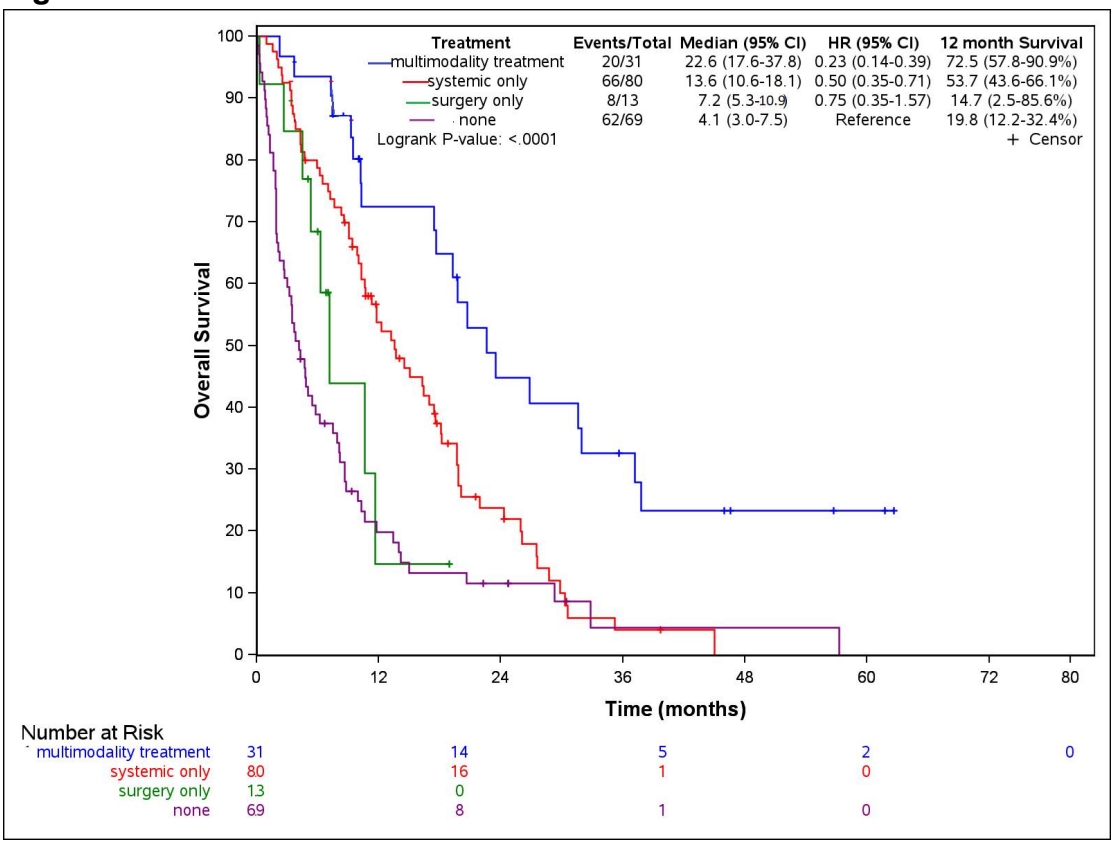

Treatment
Events/Total
Median (95% CI)
HR (95% CI)
12 month Survival
multimodality treatment 4/4 16.7 (10.8-34.8) 0.51 (0.19-1.40) 50.0 (18.8-100.0%)
systemic only 64/65 14.2 (11.4-20.6) 0.51 (0.37-0.72) 56.9 (46.1-70.3%)
surgery only 6/6 13.6 (6.8-17.4) 0.86 (0.37-1.98) 66.7 (37.9-100.0%)
none 86/88 6.9 (5.1-10.0) Reference 29.5 (21.4-40.8%)
Logrank P-value: 0.0008
+ Censor
Overall Survival
Time (months)
Number at Risk
multimodality treatment 4 2 0
systemic only 65 25 8 6 2
surgery only 6 0
none 88 12 2 2 2

Figure 2B.


Treatment
Events/Total
Median (95% CI)
HR (95% CI)
12 month Survival
multimodality treatment 20/31 22.6 (17.6-37.8) 0.23 (0.14-0.39) 72.5 (57.8-90.9%)
systemic only 66/80 13.6 (10.6-18.1) 0.50 (0.35-0.71) 53.7 (43.6-66.1%)
surgery only 8/13 7.2 (5.3-10.9) 0.75 (0.35-1.57) 14.7 (2.5-85.6%)
none 62/69 4.1 (3.0-7.5) Reference 19.8 (12.2-32.4%)
Logrank P-value: <.0001
+ Censor
Overall Survival
Time (months)
Number at Risk
multimodality treatment 31 14 5 2 0
systemic only 80 16 1 0
surgery only 13 0
none 69 8 1 0

4. Figure 2B: The scale on the x-axis is too long. Scaling this to 80 months would be sufficient and remove redundant space.

Reply 36: Thank you. We have reformatted our x-axis scale.
Change in text: We have updated our scale. See updated Figure 2 in Reply 35.

Overall, I think that this is a valuable piece of work that highlights the importance of the MDT, however, there are major revisions required in order to make this article suitable for publication in the Journal of Thoracic Disease. Namely, the marrying up of the aims and the conclusion of the manuscript and the provision of the complication rates, some of which are missing.

Reviewer C

Intro paragraph 2

a) Multidisciplinary review improves outcomes in patients with testicular and non-small cell lung cancer. 5-7 I am not sure this sentence adds any value

Reply 1: We appreciate the reviewer's comment. Multidisciplinary review in many other malignancies, including NSCLC, has shown to be effective, but there are few studies which examine the impact of multidisciplinary review and guidance of treatment for patients with MPM. We have refined this sentence to better fit with our topic.
Change in text: "Multidisciplinary review and regionalization, the shifting of patient care to designated centers within a certain region, improves outcomes in patients with non-small cell lung cancer (5-7). Little is known about regionalization of MPM surgeries to a specialized surgeon." (Page 3, lines 11-14).

b) Little is known about regionalization of MPM surgeries to a specialized surgeon. I am uncertain what you mean by this especially what you mean by "regionalization" You talk about it more in paragraph 3 but don't explain it well. Do you send all patients to one center? Please clarify. I know you do a bit more in the Methods but it is hard to follow in the Intro as this precedes the methods.

Reply 2: Thank you for this comment. We have defined regionalization in the text of our introduction: shifting of patient care to designated centers within a certain region.
Change in text: "Multidisciplinary review and regionalization, the shifting of patient

care to designated centers within a certain region, improves outcomes in patients with testicular and non-small cell lung cancer. Little is known about regionalization of MPM surgeries to a specialized surgeon." (Page 3, lines 11-14).

Methods
a) You state: More extrapleural pneumonectomies (EPP) were performed during the early 25 period, and more pleurectomy/decortications (PD) were performed in the later period 26 due to changes in practice at our institution. I would like to know more about this as this could be a major confounding factor.

Reply 3: Thank you for this comment. Although limited, the MARS trial was one of the first randomized controlled trials showing no benefit of EPP in the context of multimodality therapy. Due to the results of the MARS trial, our surgical teams shifted to largely performing PD. The surgical team preferred PD due to lower complication rate and morbidity and mortality seen with PD. We overall observed low number of patients undergoing EPP in both cohorts.
Change in text: "More extrapleural pneumonectomies (EPP) were performed during the early period, and more pleurectomy/decortications (PD) were performed in the later period due to changes in practice at our institution, related to influences from the MARS trial results (8)." (page 5, lines 8-11)
"For appropriate surgical candidates, PD was the most utilized surgery in the later period, due to institutional change in practice, given lower mortality with PD compared with EPP (1)." (page 7, lines 16-18)

Reviewer D

Thank you for your research on malignant pleural mesothelioma. I have read it with interest. I agree with your conclusion that multi-modality strategy may improve patients' survival outcomes, although there are some points not stated enough in this manuscript. These points should be added and the authors should organize these data again. First, the authors described details of surgical treatments. On the other hand, other treatments such as chemotherapy regimen and radiotherapy modality were not enough referred. According to recent guidelines, only systematic therapy has been improving mesothelioma outcomes with sufficient evidences. Thus, chemotherapy regimens and the treatment order including neoadjuvant or adjuvant should be described in this study.

Reply 2: We appreciate the reviewer's comments. We have more clearly defined treatment order in our methods section. Our typical pathway involves upfront surgery, followed by adjuvant systemic therapy in patients with epithelial or biphasic histology, stage I or II disease, and ECOG <2. If patients have mediastinal

lymphadenopathy on PET and mediastinoscopy, we consider giving neoadjuvant chemotherapy prior to surgery. Our patients typically receive adjuvant systemic therapy. Neoadjuvant systemic therapy is rarely administered at our institution. One patient received neoadjuvant systemic therapy due to mediastinal lymph node involvement on mediastinoscopy and did go on to receive P/D. Radiation is not commonly administered as a part of adjuvant treatment.
Change in text: "Patient's undergoing surgery, where intended to receive adjuvant systemic therapy, while radiation was not commonly administered as part of adjuvant treatment." (page 5, lines 1-3)

Second, radiotherapy is a controversial topic today due to lung toxicities. The treatment modality, doses, and so on should be referred on this manuscript.

Reply 3: Very few patients received adjuvant radiation in our cohort. Radiation was largely administered for palliation of symptoms and was pursued as per local preference. Two patients in the early cohort received palliative RT for symptom control. One patient in the early cohort received adjuvant radiation and was planned for adjuvant chemotherapy but died prior to starting on chemotherapy.

Third, surgery only cases outcomes seem worse than multimodality therapy in the 2015-2020 period. I wonder if these patients did not receive chemotherapy for surgical complications. In other words, was this classification intention-to-treat? If not, I think, the bias should not be negligible.

Reply 4: We appreciate the reviewer's comments. You are correct, this classification was intent-to-treat. The patients who received surgery only were intended to receive chemotherapy but due to patient characteristics and possible surgical complications were unable to receive systemic therapies. We were not able to ascertain the exact cause of patients being unable to receive subsequent treatments.
Change in text: "Patient's undergoing surgery were intended to receive adjuvant systemic therapy, while radiation was not commonly administered as part of adjuvant treatment." (page 5, lines 1-3)

Finally, the authors should state staging criteria. T4N0M0 cases were categorized Stage IV in TMN 7th edition, while most of them are IIIB in the 8th edition.

Reply 4: Thank you for this comment. We used the AJCC 8th edition TNM staging system.
Change in text: We noted this staging edition in Table 1.