

Peer Review File

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Reviewer A

The group of Dr Bueno has an impressive experience in the surgical treatment of patients with MPM. Already for many years data on this therapy has been reported in the literature when Dr Sugarbaker was also involved in the Boston clinic.

The paper is well written and confirms the superior survival for women with the epithelial type of MPM and an MCR. Interestingly the authors find more cases of biphasic MPM during surgery compared to the initial diagnosis. This is not unexpected.

The downside of the paper is the retrospective analysis. There is no randomization and there are different treatment schedules used.

Statistics are limited and only the univariate data are reported. In this setting there are to my opinion many biases that cannot be ruled out in this setting.

As stated by the authors in many different tumor types women do better. Whether this is due to a RAS like estrogen inhibiting gene or simply by lesser comorbidity is not answered by this study.

Reply: Thank you for your comments. As mentioned in the discussion paragraph, one of the limitations of this manuscript is the retrospective analysis. Analysis of the data presented in the manuscript demonstrates that females with pleural mesothelioma have better overall survival and recurrence-free survival (new data added in the results section) after pleurectomy decortication compared to males. The reasons for sex being a prognostic factor in this disease are still not clear in the literature.

Reviewer B

This is a manuscript of a retrospective analysis of female patients with pleural mesothelioma who underwent pleurectomy/decortication. The authors concluded that significant prolonged survival was demonstrated for patients with epithelioid subtype those achieved macroscopic complete resection. The manuscript is well written and well organized. The presented data would give important information to readers in the area.

1. The difference between male and females were discussed in the manuscript. It is well known that smoking is not associated with development of mesothelioma, however, smoking might influence the peri or post-operative comorbidities. The possible effect of smoking is warranted to be discussed.

Reply: The smoking habits of PM patients in this manuscript were collected and analyzed. Group of 239 smokers (recent and past smokers) compared to 188 never smokers. No association between perioperative morbidity such as postoperative pneumonia, empyema, or prolonged air leak in the smoking group was seen. In addition, smoking was not found to be a significant negative prognostic factor. In a group of 58 significant smokers defined by at least 20 pack years during the last 15 years, no association with perioperative morbidity or overall survival was seen.

Changes in the text: Supplementary data.

2. The utility of intraoperative heated chemotherapy has not yet been established. The indication and role of the modality should be discussed.

Reply:

We added data regarding relevant clinical trials, our previous experience, and references.

Subsequently, IOHC was performed using Cisplatin at a concentration of 175 mg/m²minute circulated at 42 °C for up to 60 minutes with renal protection measures as previously described(12) (13). This approach, previously shown to be safe, has become a standard practice in our program for achieving local control(12). For patients who did not receive neo-adjuvant therapy and were found to have positive lymph nodes during ePD, advanced T stage, or non-epithelioid histology adjuvant therapy- postoperative chemotherapy (platinum-based chemotherapy and pemetrexed) as part of the multi-modality treatment is recommended following surgical resection.

Changes in the text: Methods lines 89-95

In 2013 Sugarbaker and colleagues conducted a study involving 103 low-risk groups of patients who underwent cytoreductive surgery and IOHC compared to those who underwent cytoreductive surgery alone demonstrating benefits to patients receiving IOHC. Their research revealed that hyperthermic intraoperative pleural cisplatin chemotherapy prolonged the time to recurrence and improved survival among low-risk patients with malignant pleural mesothelioma undergoing surgical macroscopic complete resection(24). The effectiveness and safety of surgical resection and IOHC were evaluated in phase I clinical trial(25) but further investigation through a prospective randomized phase II clinical trial is necessary to elucidate the benefits of these features. It is important to approach the interpretation of our findings regarding IOHC cautiously as a significant proportion of patients in our study were skewed towards receiving IOHC.

Changes in the text: Discussion lines 209-217

3. Abbreviations such as pleural mesothelioma (PM) should be organized. The term ‘epithelial’ should be corrected as ‘epithelioid’ mesothelioma.

Reply: Corrected.

Reviewer C

This paper describes a retrospective analysis of a single-centre cohort of consecutive 124 female patients who underwent pleurectomy/decortication for resectable pleural mesothelioma. This cohort is compared to the male patients who underwent the same surgery for the same cancer in this hospital.

- (1) Given the fact that pericardium and/or diaphragm were (sometimes) removed and reconstructed, I would use extended pleurectomy/decortication to describe the surgical procedure.

Reply: Thank you for suggesting using extended pleurectomy decortication (ePD) instead of pleurectomy decortication (PD). We changed from PD to ePD for all intended extended pleurectomy decortication cases. Corrections were added.

(2) The results are not very attractively presented in long paragraphs. Some editing would improve the manuscript. Some sentences would benefit from less telegraph style.

Reply: The results section was edited.

(3) In table 2 and 3 the T and N descriptors are reported in the univariate and multivariate analysis, but in table 1, these are not reported among patient characteristics. Please add those.

Reply: T and N descriptors are added to Table 1.

(4) Why were patients evaluated for resectability by the surgeons and not by an MDT?

Reply: Patients underwent evaluation by a multidisciplinary team with particular focus on input from the surgeons to assess resectability and ability to achieve the goal of Macroscopic Complete Resection (MCR).

Changes in the text: Methods line 81-82

(5) How many surgeons were involved and was there a uniform protocol for extended pleurectomy/decortication?

Reply: Between 2007 to 2017, a total of 454 consecutive patients underwent thoracotomy with intended ePD for PM applying a uniform protocol. Thirteen surgeons were involved while two of them performed almost ninety percent of the cases.

Changes in the text: Results lines 112-114

Patients underwent evaluation by a multidisciplinary team with particular focus on input from the surgeons to assess resectability and ability to achieve the goal of Macroscopic Complete Resection (MCR). The surgical objective was complete removal of parietal and visceral pleura along with excision of the diaphragm and pericardium if found to be involved with tumor either visibly or by frozen section analysis. Reconstruction of the diaphragm and pericardium as deemed necessary by the surgeon was carried out with permanent patches (GorTex with pericardial fenestrations). Lymph nodes were sampled from the mediastinum, hilum, intercostal and mammary vessel. Previous biopsy sites were excised, and the pleural cavity was irrigated with saline, water and peroxide. Additionally, the chest wall and suspected area of remaining visceral pleura were treated with argon beam painting.

Changes in the text: Methods lines 81-89

(6) Why was performance status – a known major prognostic factor – not collected / included in the analysis?

Reply: Unfortunately, we have no data regarding the patients' performance status in this series.

(7) On what basis was the chemotherapy regimen selected (neoadjuvant vs adjuvant)?

Reply: Neoadjuvant therapy was administered to the following groups: 1. Patients with mediastinal nodal metastases detected during cervical mediastinoscopy or endo bronchial ultrasound; 2. patients showing ipsilateral extension through vital structures or chest wall; 3. A few of the patients who were not initially evaluated at our institution. Prior to surgery all these groups underwent restaging and needed to demonstrate treatment response

Changes in the text: Methods lines 75-79

For patients who did not receive neo-adjuvant therapy and were found to have positive lymph nodes during ePD, advanced T stage, or non-epithelioid histology adjuvant therapy-postoperative chemotherapy (platinum-based chemotherapy and pemetrexed) as part of the multi-modality treatment is recommended following surgical resection.

Changes in the text: Methods lines 92-95

(8) Theoretically, the OS could also have been influenced by treatments following relapse. I would like to see data on PFS included in this manuscript.

Reply: Survival outcomes such as progression free survival (PFS) and relapse free survival (RFS) which might be more sensitive to the isolated effect of surgery on PM patients were analyzed. PFS (time from surgery to disease progression or death, whichever comes first) was significantly longer in females (Supplementary Figure1). The median PFS for females was 455 days versus 310 for males (HR=1.5, p=0.001). Median RFS of 468 in females was significantly longer compared to 323 days in males (HR=1.4, p=0.002).

Changes in the text: Results lines 126-131

Reviewer D

Review of the paper entitled: "Prolonged Survival and Novel Prognostic Factors in Women with Pleural Mesothelioma Treated with Pleurectomy Decortication" by Lapidot M, et al. Brigham & Women's Hospital, The International Mesothelioma Program, Harvard, Boston, USA. The authors reported their excellent experience in the treatment of MP focusing in particular on women and they found better OS for women with epithelioid histology, early stage, intraoperative heated chemotherapy (IOCH), adjuvant therapy and macroscopic complete resection (MCR). The numbers and the results are remarkable, but I have some questions and suggestions to improve the paper.

Major issues:

- 1) the paper focused as main result on overall survival. What about the other survival outcomes such as recurrence-free survival (RFS)? RFS could be more sensitive in cancer dynamics than OS and could reflect the different responses to the treatment and corroborate the use of surgery in MP.

Reply: Survival outcomes such as progression free survival (PFS) and relapse free survival (RFS) which might be more sensitive to the isolated effect of surgery on PM patients were analyzed. PFS (time from surgery to disease progression or death, whichever comes first) was significantly longer in females (Supplementary Figure1). The median PFS for females was 455 days versus 310 for males (HR=1.5, p=0.001). Median RFS of 468 in females was significantly longer compared to 323 days in males (HR=1.4, p=0.002).

Changes in the text: Results lines 126-131

2) the details of adjuvant therapies are not mentioned, but I suggest including some sentence or line in a table about it.

Reply: For patients who did not receive neo-adjuvant therapy and were found to have positive lymph nodes during ePD, advanced T stage, or non-epithelioid histology adjuvant therapy-postoperative chemotherapy (platinum-based chemotherapy and pemetrexed) as part of the multi-modality treatment is recommended following surgical resection.

Changes in the text: Methods lines 91-94

3) the paragraph results is too long and it should be reduced deleting some sentences about not significant data that could be reported only in tables.

Reply: The results section was edited and sentences about insignificant data (such as in the MCR paragraph) were deleted.

Minor issues:

1) I suggest inserting a list of complications and their grade

Reply: Postoperative complications were categorized as major including deep venous thrombosis, Chyle leak, empyema, pneumonia, Horner's syndrome, pulmonary embolism, vocal cord paralysis/paresis, surgical site infection, cerebral vascular disease/transient ischemic attack, acute respiratory distress syndrome, seizures, myocardial infarction, epidural abscess, and hemothorax and minor such as prolonged air leak- over 14 days, atrial fibrillation, urinary tract infection, delirium, ileus, and urinary retention (14). These complications were defined as occurring within 90 days of the surgery. Out of the patients, 36 patients (31.6%) did not experience any complications (neither major nor minor), 26 (25.7%) had minor but not major complications, 21(18.4%) had both major and minor complications and 31(27.2%) had major complications without minor. The most frequently observed complications were prolonged air leak (34.2%), deep venous thrombosis (17.5%) pneumonia (8.8%) and Chyle leak (8.7%).
Supplementary table 1

Changes in the text: Results lines 151-160

2) acronyms should be defined at the first appearance even in the abstract (MCR, IOCH)

Reply: Checked and corrected.

3) check the words post op (quite colloquial)

Reply: Corrected.