Peer Review File
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Review Comments
Reviewer A
Comment 1: This is a manuscript titled Treatment-associated quality of life in patients with malignant pleural mesothelioma. The authors have reviewed a lot of articles of treatment of malignant mesothelioma; however, it is just a series of article reviews without future perspectives.

Reply 1: Dear Reviewer, thank you for taking the time to review our manuscript and identify areas where it would stand to benefit from. Per your recommendation, we added a new section entitled, "Future perspectives on quality of life in malignant pleural mesothelioma" to discuss ongoing developments in MPM treatment and QoL. This new section can be found on line 1018-1056, pgs 14-15.

Changes in the text:

Future perspectives on quality of life in malignant pleural mesothelioma

Given the heterogeneity of prior studies in assessing outcomes, measuring QoL, patient population/selection, surgical approach, and chemo-, immune-, and radiotherapeutic regimens, among others, efforts have shifted to bring homogeneity to the study of MPM.

From a surgical standpoint, most experts agree that EPP should not be done for MPM and highly favor PD, however, thus far, no randomized controlled trial (RCT) has been completed that has explicitly evaluated the efficacy of pleurectomy decortication itself. The closest trial was MesoVATS, conducted by Rintoul et al., which evaluated video-assisted thoracoscopic partial PD rather than extended PD and thus not comparable as the two approaches have different aims(101). Currently, MARS 2 is an ongoing RCT evaluating the efficacy of PD plus chemotherapy relative to chemotherapy alone in respect to OS with secondary outcomes of health-related QoL, PFS, and adverse events, among others, all while taking into account surgical consistency, patient treatment pathways, QoL measurements (using EORTC QLQ-C30 and EuroQol EQ-5D-5L periodically for 24 months), and chemotherapeutic regimen.

Newer approaches of radiation therapy are being explored in a phase III RCT evaluating the utility of Intensity-Modulated Pleural Radiation Therapy (IMPRINT/IMRT) in patients undergoing PD and chemotherapy with platinum and pemetrexed given the improved safety profile of IMRT implemented by Rimner et al. in their phase II study published in 2016.

The ongoing phase IIa MiST trial is personalizing treatment for MPM in patients that have already undergone chemotherapeutic treatment with

disease progression or in which disease has relapsed using prospective molecular profiling of tumour suppressors BAP1, BRCA1, and p16ink4A and an immune checkpoint inhibitor PDL1. The 4 arms are composed of: (1) Rucaparib, a PARP inhibitor, for BAP1 inactivated/BRCA negative; (2) Abemaciclib, a CDK4/6 inhibitor, for p16ink4a negative, (3) Pembrolizumab, a PD1 inhibitor, and Bemcentinib, an AXL kinase inhibitor, for patients without biomarker specification, and (4) Atezolizumab (anti-PDL1) and Avastin (anti-VEGF) for PDL1 positive(102). So far, arms 1-3 have met the primary endpoint of disease control at 12 weeks. Results of arm 4 have yet to be published(102–105).”

Comment 2: The abstract does not summarize the manuscript, just an explanation of the disease. Conclusion does not conclude the manuscript, just a description of mesothelioma.

Reply 2: Dear Reviewer, thank you for identifying these additional areas where our manuscript can be improved upon to better communicate the overall manuscript in both the abstract and conclusion. We have expanded on both of these sections so that the abstract (lines 43-68, pg 2) does a better job of summarizing the manuscript and the conclusion (lines 1059-1083, pg 16) more aptly concludes it with the intended message. We highlighted in green the sections of conclusion we feel best conclude the manuscript with overall the message intended.

Changes in the text (highlighted in yellow):

“Abstract

The symptomatic burden of malignant pleural mesothelioma (MPM) remains unsurmountable due to not only the insidious nature of its development and abrupt nature of progression, but also due to our relatively limited capabilities to treat it or even slow down its progress and the associated toll such a disease has on an individual’s overall quality of life (QoL). The majority of cases are linked to occupational asbestos exposure and arise after a latency period of up to 40 years. Overall survival (OS) drastically varies across studies and treatments, with pooled analyses approximating 13 months post-diagnosis median survival and 10% 5-year survival. As a result of its very grim prognosis and significant deterioration in QoL, treatment strategies began to incorporate the effects of a particular treatment on a patient’s QoL. Treatment is often multimodal and consists of surgery, chemotherapy, and radiotherapy. Recent investigations have utilized standardized QoL measurement tools, such as Lung Cancer Symptom Scale for mesothelioma and European Organization for Research and Treatment of Cancer Core (EORTC) Quality of Life Questionnaire, to make studies more comparable so treatments and their effects can be better understood and expanded on. Overall, surgery remains the mainstay of therapy with recent studies

finding pleurectomy and decortication leads to improved QoL when compared to extrapleural pneumonectomy. Chemotherapy and immunotherapy are the most rapidly advancing segment of trimodality therapy due to technological advances which have improved development, synthesis, administration, and efficacy. Radiotherapy's impact on QoL continues to be debated despite its significant palliative potential due to a high risk of radiation toxicity even after approach, dose, and timing modifications. Given the complexities in MPM treatment, understanding the standardized data generated by these questionnaires and investigating their generalizability in assessing patient QoL will be crucial in the advancement of MPM treatment."

"**Conclusion**

Malignant pleural mesothelioma is an insidious disease that inevitably becomes aggressive and unforgiving with an invariably grim prognosis. Surgery remains the mainstay of therapy with major advancements made in surgical approach utilized favoring PD given its superiority in terms of post-operative complications, survival, and QoL when compared to EPP. Surgery has also been found to provide opportunities such as intracavitary administration of medications and solutions which have produced significant and consistent improvements in patient quality of life. Chemotherapy and immunotherapy seem to be the most rapidly advancing segment of trimodality therapy in part due to significant technological advances which have allowed for improvements in development, synthesis, and targeting, however, their current, relative superiority and impact remain topics of debate due to the overtly complex and variable physiology of mesothelioma. Nevertheless, recent studies have demonstrated promising results for chemo- and immunotherapeutics used in conjunction with surgery in terms of median survival, symptomatic burden, such as dyspnea and pain, and overall QoL. Radiotherapy currently appears to be the modality in which a breakthrough has yet to be made given the high risk of radiation toxicity that continues to exist despite different approaches, doses, and timing. Nevertheless, radiotherapy's role in the treatment of mesothelioma should not be mitigated given the significant palliative potential it holds for pain. Thus, while current treatments and therapies remain far from ideal, progress throughout the last few decades has been promising and seems to be significantly increasing in pace. The development of standardized quality of life measurement tools established a foundation upon which treatment regimens can now be compared and refined which has resulted in significant improvements in not only progression free or (OS), but also quality of life."

Reviewer B
Comment 1: The purpose of the paper: "Overview Interesting paper; pleural mesothelioma is a challenging problem and this work is very appropriate

Reply 1: Dear Reviewer, we kindly thank you for reviewing our manuscript and very much appreciate your time and efforts.

Changes in the text: n/a

Reviewer C
Comment 1: I appreciate your insightful review, which seems to be a valuable review for all of readers in this journal.
In line 516 hemothoracic should be changed as hemithoracic.

Reply 1: Dear Reviewer, we kindly thank you for your attention in noticing this typo. We have made the suggested correction on line 943, pg 13.

Changes in the text: hemithoracic