Peer Review File

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Reviewer A

The major concern of this study is the time frame of drug exposure and small sample size. The authors were trying to identify changes in cell morphology and protein level following 30 minute tissue exposure. From the in vitro data (ref 23), changes in cell growth was observed after 30 minutes but this can be completely different in vivo due to the presence of extracellular matrix and surrounding microenvironment cells. Therefore, the data is insufficient to show that there is no effect of Povidone-Iodine in vivo. A study in animal model with the analysis at later time point would be more suitable. The authors should also investigate other cell death mechanisms as well as changes in the microenvironment that may affect tumor growth eg. immune cell infiltration.

Thanks for your comment. In the study published by Lang Lazdunski et al in mesothelioma patients published in JCTVS in 2015, the duration of the hyperthermic lavage was 15 mins. In order to perform a study in mesothelioma patients we could not increase the time of the procedure more than 30 mins to avoid any increased risk of complications or longer general anesthesia.
The animal model can be used but as seen in other studies where chemotherapy agents or Car T cell were tested in animal model, a good response in animal model does not correspond to the same response in human model. Animal model and humans are very different and this pilot study wanted to assess the feasibility of testing the real response in patients compared to cell line models.

Reviewer B

In this prospective in vivo study you investigate the effects of intrathoracically applied povidone-iodide on MPM cells. I think the topic is interesting and important. Intracavitary therapies are increasingly being investigated as part of multimodal therapy approaches in MPM, most notably hyperthermic intrathoracic chemotherapy (HITOC) with cisplatin. But povidone iodide is also used clinically and has also been studied in-vitro, as described by you in the article. I have the following questions and comments:
1. Your analysis confirms the significantly better OS after surgical resection and multimodal therapy compared to chemotherapy alone. The resection forms the basis, the intracavitary irrigation with whatever is additive after the resection.
You should please formulate this better in the introduction.
Many thanks. We have amended this to emphasise povidone-iodine lavage as an “additive to oncological thoracic resection” in the Introduction section, lines 89-90.

2. You cite data on HITOC, but there are now many more recent studies available, so I would ask you to update the literature. Examples: Klotz LV, Respir. 2021;100(12):1165-1173. doi: 10.1159/000517334. Ried M, Cancers (Basel). 2021 Sep 12;13(18):4580. doi: 10.3390/cancers13184580. Burt, B.M.; Richards, W.G.; Lee, H.S.; Bartel, S.; Dasilva, M.C.; Gill, R.R.; Jaklitsch, M.T.; Johnson, B.E.; Swanson, S.J.; 457 Bueno, R.; et al. A Phase I Trial of Surgical Resection and Intraoperative Hyperthermic Cisplatin and Gemcitabine 458 for Pleural Mesothelioma. J Thorac Oncol 2018; 13 (9): 1400-1409.
Lapidot, M.; Gill, R.R.; Mazzola, E.; Freyaldenhoven, S.; Swanson, S.J.; Jaklitsch, M.T.; Sugarbaker, D.J.; Bueno, R. 463 Pleurectomy Decortication in the Treatment of Malignant Pleural Mesothelioma: Encouraging Results and Novel 464 Prognostic Implications Based on Experience in 355 Consecutive Patients. Ann Surg 2020; 3: Online ahead of print.
Many thanks. We have amended and updated references accordingly – see Discussion section lines 217-218 and corresponding references as suggested.

3. Out of 12 patients, you were only able to include 6 patients for the complete examination. This should

be mentioned as a limitation. More patients are needed to support your initial results.
How long does hyperthermic irrigation with povidone-iodide usually take after tumour resection? 30-60 minutes? HITOC lasts 60, sometimes 90 minutes. Maybe the duration of the irrigation was too short in your analysis?
Many thanks we agree. We have stated small sample size to be a limitation (Discussion section lines 254-255). We also agree that 30 minutes irrigation may not be enough and we have discussed the requirement for a longer exposure time.

4. Intracavitary lavage with cisplatin or povidone-iodide is aimed at microsopic tumour remnants after macroscopic complete resection and not at macroscopic tumour findings in the pleura parietalis. Perhaps this explains the missing apoptosis signs in your study?
It may explain it. This is an excellent comment but unfortunately it will impossible to test the effect the effect of hyperthermic lavage on microscopic disease because they can't be identified and sampled. The idea of this study was to see the effect of betadine on macroscopic viable tumor which can be sampled and processed. As you can see due to a high fibrotic rate of mesothelioma and the requirement for the tissue in order to be processed it was difficult even with macroscopic tumor to have sufficient tissue to perform the analysis

5. In this paper you speak of a pilot study. What further follow-up studies or investigations based on these results are planned? Longer exposure time of the rinse? Do you use the povidone-iodide rinse after surgical cytoreduction? A brief outlook at the end of the discussion would be helpful for the readers.
Thank you. Yes, we do use povidone-iodine rinse after surgical cytoreduction. We plan to further investigate with a larger patient population over a longer period of time (patient cohort study), with longer exposure times of betadine lavage. This was a pilot study to evaluate feasibility, present initial results and to guide further experiments.