Author’s response to reviews

Title: Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for the Treatment of Malignant Mesothelioma

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Version: 2 Date: 23 Mar 2018

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Dear Editor:

Thank you for reviewing our manuscript “Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for the Treatment of Malignant Mesothelioma”. We have addressed all points raised by the reviewers and have changed the manuscript accordingly. Please find attached a detailed point-by-point list with the changes (marked in red color in the manuscript) made to the manuscript.

We hope that the manuscript is now suitable for publication in BMC Cancer.

Sincerely yours,

Urs Pabst, M.D.

Changes made to the manuscript BCAN-D-18-00101R1, entitled: “Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) for the Treatment of Malignant Mesothelioma”
Reviewer I:

1. The number of patients is extremely limited (n = 20 with >2 PITAC treatments) and the patients were rather heterogeneous. It is difficult to fully interpret the data presented given these two factors. Additional cases would be helpful.

The reviewer is correct that the number of cases is limited. However, one has to keep in mind that this disease is very rare with a reported prevalence of 7-40 cases/ million population worldwide (Robinson & Lake 2005). Cases of peritoneal mesothelioma are even rarer and thus it is very difficult to collect large series of such patients. In fact, our case series is one of the largest case series published on patients with peritoneal mesothelioma based on a recent PubMed literature search (search terms: mesothelioma and peritoneal; search date 03-March-2018). We have now added a note of caution to the Discussion section referring to the limited sample size (Discussion, line 387).

2. Only 5 PITAC procedures on a total of 3 patients were performed. The manuscript would perhaps be more streamlined if PITAC was discussed even less prominently or exclude entirely.

Following the reviewer’s suggestion, we have now streamlined the manuscript and have reduced the focus on PITAC (Results, line 291).

3. Table 1. Please include smoking status, EtOH use, asbestos exposure when known, family history of cancer and diagnosis of additional cancers.

As suggested, we have now added patient-specific information as available and have included this information in Table 1. However, only data about alcohol consumption and nicotine abuse were available. Details about patients’ other previous cancer diseases or even family history are missing.

4. Figures 3 and 4 should be move to the supplemental section and the remaining 3 Figures should be combined into one figure.

As suggested by the reviewer, we have now moved Figures 3 and 4 to the supplemental section (Supplementary Figures S1 and S2) and have combined the remaining Figures into one Figure (now termed Figure 1).
5. Figure 1 is very difficult to interpret. Perhaps a waterfall plot/waterfall plots or alternative representation would work better.’

As suggested, we have no re-configurated Figure 1 into a waterfall-style plot (now part of the combined Figure 1 – see above) to make it more vivid for the reader.

6. Discussion. Page 15. Instead of using quantifies such as "more than every second patient" or "every fifth patient" please provide the precise percentage.’

The sentences have been corrected as suggested and the precise numbers are now given (Discussion, lines 328, 362, and 363).

7. Limitations of this study should be extensively discussed and necessary future studies should be proposed.’

As suggested by the reviewer, we have now added a thorough discussion of the limitations of this study as well as proposals for future studies (Discussion, line 387ff).

8. Quality of life should be discussed. Does PIPAC impact quality of life? How? Were any measurements taken?’

We have indeed measured the patients’ quality of life using a standardized EORTC-QLQ 30 questionnaire (now described in the Methods section, line 148). The results of the quality of life assessments have now been included (Figure 1D; Results, line 284). Also, these data are now being discussed appropriately (Discussion, line 373).

9. Page 15. "Based on these observations… we do not recommend complex adhesiolysis…” This is an important conclusion that should be featured more prominently.’

As suggested by the reviewer, we have now added a paragraph discussing this clinical recommendation in more detail (Discussion, line 381).

10. Table 1. The meaning of "dry", "wet" and "mixed" should be explained somewhere.’

As suggested by the reviewer, we now explain these terms appropriately (Table 1; Legend).
Reviewer II:

1. I suggest the authors, if possible, if they can make more evident - maybe through the use of the tables- which are the patients who achieved tumor regression and a longer overall survival.’

As suggested by the reviewer, we have now included the survival times broken down by the degree of tumor regression (Table 2; last 4 lines).

2. …figure 1 in particular is handy but the graph is difficult to read…”

As suggested, we have re-configurated Figure 1 (now part of the combined Figure 1 – see above) to make it more vivid for the reader.