

## Peer Review File

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### Review Comments A

#### **Comment 1: Case series more than a retrospective analysis.**

**Reply 1:** Thank you for taking the time to review our manuscript. We agree that our manuscript is most consistent with a case series. As such, we have further specified at multiple points within the text that our retrospective analysis was indeed a case series, as below.

**Changes in the Text:** We have edited the text to reflect that this is a retrospective case series in multiple places: Page 6, Line 102; Page 11, Line 243; Page 13, Lines 303-4; Page 14, Line 323; and Page 15, Line 344.

#### **Comment 2: Clinical endpoint not clear.**

**Reply 2:** Thank you for pointing this out. Our overarching goal is to describe the initial clinical experience treating patients with palliative radiotherapy on the Halcyon linear accelerator, for malignant pleural mesothelioma, and we aimed to achieve this goal by reporting multiple specific clinical endpoints. In the first sentence of the “Data analysis” subheading of the Materials and Methods section, we stated that the primary objective of our analysis was to describe the initial clinical experience treating patients with MPM with palliative RT on Halcyon, in terms of the patients and treatment techniques used, symptomatic palliation, treatment toxicity, dosimetric parameters, couch corrections, and treatment timing. Thus, each of those aspects (patient/treatment variety, symptomatic palliation, RT toxicity, dosimetric constraint achievement, couch correction, and speed of treatment) were our explicit clinical endpoints. In the ensuing text in the “Data analysis” section, we then describe how each clinical endpoint was assessed. We have edited the text to explicitly state that these measures were the specific clinical endpoints assessed.

**Changes in the Text:** We have edited the text to clarify the clinical endpoints. Specifically, we deleted “in terms of” on Page 7, Line 136, and created a separate sentence stating “The specific clinical endpoints assessed were...”

#### **Comment 3: Local control at 2 months from the end of RT does not add any clinically relevant information.**

**Reply 3:** Thank you for this comment. We agree that local control with such a short follow-up interval may have limited clinical relevance. Further, even with extended follow-up since initial submission, three of the four patients were already deceased, and the fourth patient passed away in May 2020, extending his follow-up interval to 7.1 months, still keeping our median follow-up interval at only 2.2 months. As such, we have removed mention of local control from the case series, and instead, remain focused on the symptomatic palliative role of the radiotherapy, and the rapidity and tolerability of the treatment for the frail, elderly population assessed.

**Changes in the Text:** We updated the upper bound of the follow-up interval in multiple places (Page 2, Line 21; Page 9, Line 171). We removed mention of local control as an outcome in multiple places (Page 6, Line 97; Page 7, Line 137; Page 10, Line 199; Page 11, Line 245; Page 12, Line 268; Page 14, Line 327; Page 15, Line 332; and Page 15, Line 346). We added text on Page 15, Lines 336-337 to note a limitation of the short follow-up interval.

#### **Comment 4: The published evidence on IMRT in MPM is already solid.**

**Reply 4:** Thank you for this comment. We certainly agree that there is strong evidence to support the use of IMRT in MPM. The novelty of our case series is not that we describe the use of IMRT to deliver palliative

radiotherapy for patients with MPM. We feel that the novelty of our work and the contribution to the existing foundation of literature, is that we describe the initial clinical experience delivering palliative IMRT for MPM using the Halcyon linear accelerator, which delivers flattening-filter-free RT. This represents not only the initial report of the clinical use of flattening-filter-free RT for MPM, but also represents one of the only reports of the clinical use of the novel Halcyon linear accelerator to date. A major point and potential distinction between IMRT on Halcyon and IMRT on a flattening-filtered linear accelerator is that flattening-filter-free IMRT may result in shortened treatment times, as compared to flattening-filtered IMRT, which may be more tolerable for patients, particularly who may be frail and elderly, as in the studied population. In our case series, we observed mean beam-on, treatment, and approximated total room usage times of 1.6, 1.8, and 9.8 min., respectively, representing short and tolerable treatment times. As such, we add these treatment time data for palliative flattening-filter-free IMRT in MPM to the existing body of literature, which lacks any similar reports in this setting.

**Changes in the Text:** We have added text to Page 6, Lines 95-96, Page 11, Line 244, and Page 15, Lines 345-346, to reinforce the novelty of our work.

**Comment 5: Not clear the difference in dose prescriptions.**

**Reply 5:** Thank you for raising this point. With respect to the dose/fractionation and constraint prescriptions used, we utilized four different palliative regimens (20 Gy in 5 fractions, 30 Gy in 10 fractions, 32 Gy in 8 fractions, and 45 Gy in 15 fractions). The decision as to which regimen to use on each patient was made at the discretion of the treating physician, taking into account the patient's overall prognosis, location of disease (i.e. possible role for higher dose/BED), and logistical considerations of requiring a patient to come in for treatment for a given number of days. We have added text to the "Prescriptions and constraints" subheading to delineate these considerations. With respect to the dose prescriptions, these are presented as a range in the "Prescriptions and constraints" section of the Materials and Methods section, expanded upon in more detail in the "Patient clinico-pathologic and treatment details" section of the Results section, and also listed with patient-specific dosimetric constraints in Table 1. If further description is felt to be beneficial, we would be happy to edit further.

**Changes in the Text:** We have added text to Page 7, Lines 123-124 to delineate the various considerations that went into choosing the dose prescriptions for the patients assessed.

## **Review Comments B**

**Comment 1: The follow-up time is short. The updated description including the outcome of the patients is warranted.**

**Reply 1:** Thank you for raising this point. We agree that the follow-up time is short. Unfortunately, however, this is limited by the fact that each patient's survival was short as well. At the time of the initial draft of the manuscript, 3 of the 4 patients were already deceased. Since the initial review, and at the time of the current revision, all 4 patients now are deceased, due to progressive disease outside of the irradiated fields. As such, we have updated the follow-up data to extend the high-end of the follow-up range to 7.1 months, though this did not change the median follow-up time from 2.2 months. Given that all patients expired, the median follow-up is equal to the median overall survival. We felt that description of the details of patterns of failure and causes of death were beyond the scope of the report of the use of Halcyon to deliver palliative RT, but would be happy to elaborate further if this is felt to be beneficial. We have added one line to the "Palliation" subheading in the Results section to state "All patients expired due to progressive disease outside of the irradiated fields."

**Changes in the Text:** We have edited the text to update the upper bound of the follow-up interval in multiple places (Page 2, Line 21; Page 9, Line 171; and Page 10, Line 200. We have added text on Page 10, Lines 214-215, to reflect that all patients expired due to progressive disease outside of the irradiated fields.

We have added text to Page 11, Lines 249-250 to reflect that palliative responses remained durable through the remainder of the patients' clinical courses, to further clarify the updated outcomes of the patients.

**Comment 2: There are 2 patients who demonstrated symptom relief with the RT. More detailed description of the cases including the time from initiation of RT to symptom relief, and if available, CT images before and after the RT are warranted.**

**Reply 2:** We agree that the manuscript would be strengthened by providing further discussion of the palliative experiences. We further elaborated on and created a figure (Figure 2) to better convey the palliative experiences of two patients. For one patient (presented with worsening dyspnea on exertion with hypoxia requiring home oxygen, nebulizers, and steroid treatments), we provided these further details. In addition, we provided images from RT simulation, which demonstrate the region of right mainstem bronchial compression that accounts for his symptoms. As suggested, we then showed a 1-month interval CT chest after RT, showing tumor regression and reduction in bronchial compression. We then described this in the text and noted that his supplemental oxygen requirement remained stable for the remainder of his clinical course. This is shown pictorially in Figure 2a. We did the same with Figure 2b for the patient who presented with dysphagia. We reported his clinical presentation (multiple weeks of progressive regurgitation and a sense that foods could not be swallowed). We now state explicitly that these symptoms were corroborated by the finding of bulky mediastinal disease compressing his esophagus, and then state at a 3-week interval from completion of mediastinal RT, an interval CT chest showed stable, but necrotic, irradiated disease, with resulting improvement in swallow function to the point that he could eat foods of most consistencies. In Figure 2b, we show the before RT and after RT images, as suggested. For the two patients with painful chest wall lesions requiring narcotics, radiographic correlation of response was not available, however we did add the timeframe from completion of RT to cessation of narcotic use (1-2 weeks between the two patients).

**Changes in the Text:** As described above, we have added text to Page 10, Lines 202-215, to elaborate upon the symptom palliation seen in our patients following RT on Halcyon. We also changed mentions of "Figure 2" to "Figure 3," as the new figure created is now Figure 2. We generated a Figure caption for Figure 2 as well.

**Comment 3: There are a few G1 and G2 toxicities. The association between the toxicities and RT should be discussed.**

**Reply 3:** There were multiple acute Grade 1 and 2 toxicities. While it is difficult to definitively link causation between a single treatment modality and a given toxicity, it is at least possible that radiotherapy contributed to the fatigue, dyspnea, cough, and nausea experienced by the patients assessed. We have edited the text to explain in greater detail how each of the observed toxicities may be at least partially explained by radiotherapy, and also introduced some of the other potentially likely causes.

**Changes in the Text:** We have added text to Pages 12-13, Lines 274-285, to state, "While it is difficult to definitively show causation between a single treatment modality and the toxicities observed, it is likely that RT was at least partially contributory. Fatigue is a common side effect experienced during most RT courses, and most systemic therapy courses, with 3 of our patients receiving some form of systemic therapy concurrently with RT. Dyspnea and cough are symptoms experienced at baseline by many patients with MPM, but could be exacerbated by any local inflammation caused to the tracheobronchial tree and/or esophagus during RT. Further, nausea was observed in a patient who received mediastinal radiotherapy for lymphadenopathy compressing a length of the esophagus and gastroesophageal junction, and in a patient receiving concurrent systemic therapy, which may independently cause nausea."