Author’s response to reviews

Title: Fractionated palliative thoracic radiotherapy in non-small cell lung cancer - futile or worth-while?

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POINT-BY-POINT RESPONSE LETTER

Dear Editor

We have now revised the manuscript “Fractionated palliative thoracic radiotherapy in non-small cell lung cancer – futile or worth-while?” with manuscript ID (PCAR-D-17-00062) and we hope that you will find the changes satisfactory.

We thank the reviewers for the thorough review and constructive comments, all of which we have now addressed. The review has been done in a professional and critical way which we appreciate.

Detailed response to all the concerns is found below. We have also addressed the technical and declaration comments. We believe that with the changes the manuscript has improved substantially.

Hereunder are point-by-point answers to the comments by the reviewers.

We thank you for your time and look forward to hear from you.
Yours sincerely,

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Reviewer reports:

Joshua Jones (Reviewer 1):

1. The authors describe looking for EGFR mutation status in their paper, but then do not analyze that data. Is there data on EGFR or ALK mutation status? That data should be presented and should be analyzed in the context of symptom relief as well as survival.

Answer: we agree on the importance of EGFR and ALK mutational status. Unfortunately, at our institution, this was not routinely done in 2010-2011 from where the data was generated. Hence, we only have EGFR-mutational status of 13 patients of which one patient had the mutation in exon 19. None were tested for ALK mutational status in the period. This was not sufficient for statistical analysis. We have argued for this in line 134-137.

2. The authors describe "primary treatment" in table 1. That characteristic should be explained. Is this the primary treatment at diagnosis? How is it defined? What was the timing of this primary treatment in relation to timing of palliative radiotherapy?

Answer: We have defined primary treatment as the first treatment given to the patient after diagnosis. The group was heavily pretreated before PTR with 18 patients (11%) who had received > 3 regimes of chemotherapy. We have not noted if a patient received chemotherapy after PTR but PTR was in almost all cases the last treatment that the patient received which can be seen in median OS from time to prescription of PTR to death = 4.2 months. The above has been noted in lines 110-114

3. The authors have a number of patients in their study who could theoretically be candidates for radical radiotherapy (stage I, stage II and a subset of stage III patients). How was the
decision made to proceed with palliative radiotherapy rather than curative radiotherapy in these patients? This deserves some explanation.

Answer: These patients had comorbidity and/or PS not suitable for curative radiotherapy. This has been clarified in lines 114-117.

4. As described in the initial paragraph, the timing of palliative radiotherapy and availability of other treatments could potentially have a significant impact on survival. Was data about prior chemotherapy courses available? The data suggests that a number of patients had >1 and even >3 prior chemotherapy courses. What was the impact of number of prior chemotherapy courses on survival? This data would also be very helpful in thinking about when and how to offer palliative thoracic radiotherapy.

Answer: We agree that this is interesting and important. We have data on prior chemotherapy schedules, duration and change of regime. The variety also consisted of change from e.g. Cisplatin to Carboplatin due to nephrotoxicity, disruption of chemotherapy due to other toxicity, progression or the wish of the patient. Due to this extensively variety, we chose to write down only the number of regimes given as it would otherwise be too confusing. The longer survival, the more regimes.

5. As the authors describe, there is literature that suggests a dose-response relationship with improved overall survival for patients with a good performance status who receive a BED of at least 30 Gy in 10 fractions. The authors present data on survival based on performance status and separate data on dose-fractionation scheme and survival (in supplementary data). If the numbers are not too small, it would be helpful to present data on survival for patients with PS 0-1 based on dose-fractionation scheme as well as PS >2 based on dose-fractionation scheme.

Answer: We agree very much. Only one patient received 10Gy/1F and seven patients received 15 Gy/3F, so these numbers were too small to analyze. Therefore the regimes shown are 30 Gy/10F and 25 Gy/5F. There was no difference in OS for patients in PS 0-1 and PS 2 when stratifying for the two dose-fractionation regimes. Number of patients receiving these two regimes in PS > 2 was 16 and 14 respectively, making these numbers too small for further analysis.

6. With regard to symptom control, the authors describe that only a small number of patients received the suggested dose prescription of 15 Gy in 3 fractions for hemoptysis. Did those
patients have other comorbid symptoms (dyspnea, pain, etc.)? If so, it would suggest these patients might be good candidates for fractionation schemes other than 15 Gy in 3 fractions.

Overall, this report represents an important contribution to the literature, but it will better answer questions about how to offer palliative radiotherapy with responses to the questions above.

Answer: We agree on this point as well. As the reviewer writes, the indication for this scheme was hemoptysis. So even if the patient had another indication less life-threatening than hemoptysis, e.g. pain and dyspnea, this was the scheme we had in our guidelines at that point. The scheme 15 Gy/3F has later on been removed from our guidelines due some of the same reasons as the reviewer points out.

Peiman Haddad (Reviewer 2): Thank you for a practical and useful study.

Answer: we also thank you for taking the time to review our work.