Reviewer's report

Title: Local control of metastatic lung cancer is worse than that of primary lung cancer in patients treated with stereotactic body radiotherapy

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Reviewer: Oliver Blanck

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Summary: The authors present their long term data from SBRT treatments for primary and secondary lung tumors with various dosing schedules. They found that local control and overall survival is related to dose, tumor size and disease (primary vs. secondary). These findings are not new though the authors present long term data which is relevant for publication and relevant for future SBRT patient selection and dosing schedules. The study is nicely written and presented, but a flaw in the data is the various dose schedules which is then mixed with primary and secondary malignance in the univariate and multivariate analysis. Please see details below.

1. Is the question posed by the authors well defined?
   The question by the authors is well defined as they seek a better prognostic score for better SBRT patient selection.

2. Are the methods appropriate and well described?
   The method is to most extent well described which includes dose schedules and dose calculation algorithms.
   A: However the authors stated they prescribed isocentric with pencil beam and later to 95% coverage with AAA which makes a significant difference as the two dosing schemes are not comparable without further analysis. Statistical analysis may be impacted by the different dose calculations and prescription method resulting in different results. Either transformation from one in the other, re-calculation or comparing mean GTV dose may solve this issue.
   B: Biological equivalent dose (BED) is missing in their analysis rendering the statistical dose analysis somewhat irrelevant (greater and lower than 10Gy per fraction is meaningless without total dose) and as local control is clearly dependent of BED (> 105 BED see Guggenberger et al. 2013).

3. Are the data sound?
   The data is sound to most extent yet the mentioned problems with dose schedule comparisons and missing BED may render the statistical analysis for dose somewhat incorrect. Furthermore, it is unclear how the dose was given for primary and secondary malignancies in detail. I.e. was the BED lower in general for metastases (i.e. because multiple tumors were treated) resulting in lower local control? The reviewer finds it hard to believe that local control is significantly
dependent from disease (primary or secondary tumor) as local control should only be a function of dose and only to some extend be related to tumor type or previous treatments and hypoxia as described in the discussion. This is at least for doses > 100 BED. Surely colorectal metastases seem to be more radioresistant also for doses > 100 BED, yet this can only be proven when the same dose is administered for a larger cohort, which is clearly not the case for the data presented by the authors. The dosing schedules are varying too much in the perspective of the reviewer or they are not presented adequately. Everything else seems sound and obvious.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes, at the time being. Newer standards incorporate BED and mean GTV dose to compare the dosing schedules in a more relevant way.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
No. Discussions on BED is completely missing. Also the presented local control seems to be much lower than other studies (i.e. Guggenberger et al. 2013 for primary and XXX for metastases). This should be discussed in regard to the authors own dose schedules based on BED. To this regard the used dose schedules by the authors seem to be all below 100 BED (tumor edge dose) as the highest BED (3 x 15 Gy isocentric = 112.5 BED) do seem to reflect to only 80 BED (4 x 10 Gy to 95% coverage) and is much lower than the 105 BED (3 x 14,4 to 95% coverage) as defined significant by Guggenberger et al. 2013. The impact of primary versus secondary tumor of overall survival is obvious yet the impact on local control is not as it also may be different with doses greater 105 BED.

6. Are limitations of the work clearly stated?
No. There is a 1:4.5 bias towards primary tumors, meaning for each metastases data for 4.5 primary tumors is presented and used for statistical analysis. This is a clear bias that may strongly influence the statistical results for local control especially when looking at primary versus secondary malignancies. Furthermore, the doses schedules may be unbalanced based on the limited patients treated for metastases.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes. However they do most reflect on Japanese data (and their own) and disregard many of the US and European data which is seen in their discussions.

8. Do the title and abstract accurately convey what has been found?
Yes, it would, if the data would be sound and the limitations of the study (i.e. BED, unbalanced treatments) would not be dominating. The reviewer does believe that the local control may be dependent on BED, but only to minor extend and especially with doses > 100 BED. So with the limited data presented in this paper the title does not seem proven or at least questionable. A matched pair
analysis may be the more proper way to analyze the data for the title given.

9. Is the writing acceptable?
Yes. Minor spell checking may be advised.

Major Compulsory Revisions: The BED, the imbalance of the data and the multiple dosing schemes needs to be addressed.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests